To: 'Higgins, Rosemary (NIH/NICHD) [E]'; McGowan, Elisabeth C
Subject: RE: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)

Hello Rose,

We have also received IRB approval for the Follow-up study. I've attached a pdf of the approval for your records.

Best,
Veronika

Veronika Testa, BSN, RN, CCRC
Project Manager
Tufts Medical Center
800 Washington Street, Box 391
Boston, MA 02111
☎: 617.636.2379 | 🖷: 617.636.8329
✉: vtesta@tuftsmedicalcenter.org

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, January 23, 2012 9:54 AM
To: McGowan, Elisabeth C
Cc: Testa, Veronika
Subject: Re: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)

To me
Thanks
Rose

From: McGowan, Elisabeth C [mailto:emcgowan@tuftsmedicalcenter.org]
Sent: Monday, January 23, 2012 09:35 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Testa, Veronika <vtesta@tuftsmedicalcenter.org>
Subject: RE: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)

Hi Rose,

My administrative assistant will be in mid-week, and we will send the SUPPORT documentation as well as all other renewals. Everything has been completed.

Who should I send to ?

Liz

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, January 20, 2012 3:28 PM
To: McGowan, Elisabeth C
Subject: Fw: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)

Liz
Can you send?
Thanks

Rose

From: Frantz, Ivan [mailto:Ivan.Frantz@childrens.harvard.edu]
Sent: Friday, January 20, 2012 03:24 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: McGowan, Elisabeth C <emcgowan@tuftsmedicalcenter.org>
Subject: RE: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)

Rose: I no longer have access, but Liz should be able to get the items to you.

Ivan

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, January 20, 2012 2:43 PM
To: Frantz, Ivan
Cc: Maddox, Yvonne (NIH/NICHD) [E]; Hirschfeld, Steven (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]
Subject: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)

Ivan
As you are aware the Neonatal Research Network (NRN) continues to support studies under common protocols, but which require individual institutional IRB review prior to the conduct of these studies at each of the NRN sites. This is to inform you that The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), which provided the Federal support to the NRN, has been requested by the Office of Human Subjects Protection, to provide to the Office the most current consent form approved by your IRB and the corresponding IRB approval for the main SUPPORT Study, including any revisions, as soon as possible. As the NICHD Program Director of the NRN, I am requesting that the most recent consent form with IRB approval for your site for SUPPORT be submitted to me as soon as possible, but no later than January 26, 2012. Thank you for your cooperation.

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
6100 Executive Blvd., Room 4B03
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Bethesda, MD 20892
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301-496-3790 (FAX)
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contact the Tufts Medical Center HIPAA Hotline at (617) 636-4422. If the e-mail was sent to you in error but does not contain patient information, please contact the sender and properly dispose of the e-mail.

The information in this e-mail is intended only for the person to whom it is addressed. If you believe this e-mail was sent to you in error and the e-mail contains patient information, please contact the Tufts Medical Center HIPAA Hotline at (617) 636-4422. If the e-mail was sent to you in error but does not contain patient information, please contact the sender and properly dispose of the e-mail.

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Boston, MA 02111

tel 617.636.7502
fax 617 636 8394
http://tnemcirb.tufts.edu

Tufts | Health Sciences

Health Sciences Campus Institutional Review Board

NOTICE OF IRB APPROVAL - CONTINUING REVIEW

Elisabeth McGowan, MD
Box 44
Tufts Medical Center
Boston, MA 02111

IRB #: 7758

Title: Follow-up Study of Extremely Low Birth Weight Infants

Date of IRB Review: 12/16/2011
Date of IRB Approval: 12/16/2011
IRB Approval Valid Until: 12/15/2012

Protocol approved: Version Dated: 31 October 2007 (received 19 September 2011) and the Site-Specific Appendix Version Dated: 14 October 2010 (received 19 September 2011)

- as submitted x

- The above referenced-research was reviewed and approved using expedited review procedures in accordance with 45 CFR 46.110(b)(4).
- Receipt of the revised Health Insurance Portability and Accountability Act (HIPAA) Research Authorization Form (RAF) version dated 16 November 2011 (received 22 November 2011) was acknowledged. The RAF was revised to reflect changes among the research team.
- The ICF was revised to clarify that subjects will be given a gift certificate from Target rather than Wal-Mart Changes among the research team were also reviewed and acknowledged.

Informed Consent Form(s): 1

1. ICF to Participate in Research version dated 16 November 2011 (received 22 November 2011)
   -approved as submitted; validated copy enclosed x

Other Document(s): 6

1. SES at Discharge (NF01) Form dated 01 April 2011 (received 22 November 2011)
2. SES at 18 + 4 Months (NF03) Form dated 01 April 2011 (received 22 November 2011)
3. Medical History (NF04) Form dated 01 April 2011 (received 22 November 2011)
4. Readmission (NF04A) Form dated 01 April 2011 (received 22 November 2011)
5. BITSEA (NF13) Form dated 18 February 2011 (received 22 November 2011)
6. BITSEA (NF13S) Form (Spanish) dated 18 February 2011 (received 22 November 2011)
   -approved as submitted; validated copies enclosed x

Human Protection Form for Funding Agency:

-enclosed x

Regulations regarding your research protocol:

1. The approval is valid for one (1) year from the date of review (unless otherwise stipulated by the IRB).
2. Unanticipated problems are to be reported to the IRB within five (5) business days. Other internal SAEs and any external SAEs requiring protocol and/or ICF changes are to be reported to the IRB within fifteen (15) business days. All other external SAEs and internal non-serious situations may be summarized and submitted at continuing review. Further details may be found in the Unanticipated Problem and Adverse Event Reporting policy on the IRB website.
3. Any changes or modifications in the study protocol or consent form must be reviewed and approved by the IRB prior to implementation.

/CMC

4. You may not use the ICF or any other study document until it has been approved and validated by the IRB.
5. If you are subject to HIPAA, the Security Rule applies to your research. If you create, store, or transmit electronic PHI you must meet institutional Security Rule standards. For more information, please contact your HIPAA Privacy Officer for Research.

THIS NOTICE MUST BE RETAINED WITH YOUR RESEARCH FILES.

12/20/11
Date

Susan Hadley MD
Signature of Chair/Vice-Chair
Institutional Review Board (IRB)

ICMC

OMB No. 0990-0263
Approved for use through 1/31/2012

Protection of Human Subjects
Assurance Identification/IRB Certification/Declaration of Exemption
(Common Rule)

Policy: Research activities involving human subjects may not be conducted or supported by the Departments and Agencies adopting the Common Rule (56FR28003, June 18, 1991) unless the activities are exempt from or approved in accordance with the Common Rule. See section 101(b) of the Common Rule for exemptions. Institutions submitting applications or proposals for support must submit certification of appropriate Institutional Review Board (IRB) review and approval to the Department or Agency in accordance with the Common Rule.

Institutions must have an assurance of compliance that applies to the research to be conducted and should submit certification of IRB review and approval with each application or proposal unless otherwise advised by the Department or Agency.

1. Request Type	2. Type of Mechanism	3. Name of Federal Department or Agency and, if known, Application or Proposal Identification No.
[ ] ORIGINAL [X] CONTINUATION [ ] EXEMPTION	[X] GRANT [ ] CONTRACT [ ] FELLOWSHIP [ ] COOPERATIVE AGREEMENT [ ] OTHER:_____	

4. Title of Application or Activity	5. Name of Principal Investigator, Program Director, Fellow, or Other
Follow-up Study of Extremely Low Birth Weight Infants	**McGowan, Elisabeth MD** **Pediatrics: Newborn** **Tufts MC** **IRB #: 7768**

6. Assurance Status of this Project *(Respond to one of the following)*

[X] This Assurance, on file with Department of Health and Human Services, covers this activity:
Assurance Identification No. **FWA00004449** the expiration date **5/24/2014** IRB Registration No. **IORG0000435**

[ ] This Assurance, on file with *(agency/dept)*_____, covers this activity.
Assurance No._____, the expiration date_____ IRB Registration/Identification No._____ *(if applicable)*

[ ] No assurance has been filed for this institution. This institution declares that it will provide an Assurance and Certification of IRB review and approval upon request.

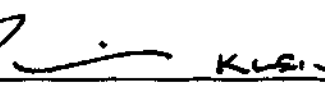
[ ] Exemption Status: Human subjects are involved, but this activity qualifies for exemption under Section 101(b), paragraph_____.

7. Certification of IRB Review (Respond to one of the following IF you have an Assurance on file)

[ ] This activity has been reviewed and approved by the IRB in accordance with the Common Rule and any other governing regulations.
by: [ ] Full IRB Review on (date of IRB meeting) _____ or [X] Expedited Review on (date) **12/16/2011**
[ ] If less than one year approval, provide expiration date _____

[ ] This activity contains multiple projects, some of which have not been reviewed. The IRB has granted approval on condition that all projects covered by the Common Rule will be reviewed and approved before they are initiated and that appropriate further certification will be submitted.

8. Comments

9. The official signing below certifies that the information provided above is correct and that, as required, future reviews will be performed until study closure and certification will be provided.	10. Name and Address of Institution
11. Phone No. *(with area code)* **617.636.7512**	**Tufts Medical Center** **800 Washington Street** **Boston, MA 02111**
12. Fax No. *(with area code)* **617.636.8394**	
13. Email: **AKlein2@tuftsmedicalcenter.org**	
14. Name of Official **Andreas K. Klein, MD**	15. Title **IRB Chair**
16. Signature 	17. Date **12/20/2011**

Authorized for local Reproduction — Sponsored by HHS

ICMC 12/20/11

TUFTS MEDICAL CENTER
DEPARTMENT OF PEDIATRICS, DIVISION OF NEWBORN MEDICINE

INFORMED CONSENT FORM TO PARTICIPATE IN RESEARCH

FOLLOW-UP STUDY: FOLLOW-UP OF HIGH RISK INFANTS

Principal Investigator: ELISABETH MCGOWAN, MD

INTRODUCTION

You are being asked to give permission for your child to take part in a research study about the growth and development of premature babies because your child was born at less than or equal to 26 completed weeks (26 6/7).

The study is conducted by the Tufts Medical Center (Tufts MC) and the National Institute of Child Health and Human Development's (NICHD) Neonatal Research Network. The NICHD Neonatal Research Network consists of multiple hospitals from around the country, and Tufts MC is a member of the network. We need to tell you about the study, so you can decide if you want your child to participate. You need to know why we are doing the study, if there might be risks for your child, and what we will expect from you and your child.

After learning about the study and if you decide that you and your child are willing to participate, you will be asked to sign this consent form and you will receive a signed copy. Being in the study is voluntary. If you choose not to participate in this study, it will not affect your baby's current or future care.

Having your child take part in this study is totally your choice. Please read all of the information carefully. Please ask Dr. McGowan, or her representative, to explain any words, terms, or sections that are unclear to you.

BACKGROUND

As a result of your child's prematurity, follow-up assessments are a part of his/her routine medical care. Follow-up evaluation of your child is important because babies born with a low birth weight are at increased risk for complications of prematurity which may affect their growth and development. Routine follow-up assessments include medical history, physical examination, and neurodevelopment examination. While your infant is in the NICU, regardless of whether you choose to participate in the study, your nurses and doctors will discuss the Follow-Up Clinic with you and arrange your baby's first appointment prior to discharge.

PURPOSE OF STUDY

The goal of this follow-up study is to learn more about the growth and development of children who were born at less than or equal to 26 completed weeks (26 6/7). This research study is a nationwide survey of such children when they are 18 months old, adjusted for prematurity. We estimate that the Neonatal Research Network will enroll 1200 babies per year for this study and 85 of these babies will be from Tufts-MC. This study begins when your baby is ready to be discharged from our hospital with a parent interview and ends at the follow-up visit occurring between 18-22 months of age corrected for prematurity.

STUDY PROCEDURES

At discharge from the hospital:

- Obtain family's social history: The mother/primary caretaker/informed household member will be asked questions about the family's social history (for example, home environment, what you do for a living, and level of education obtained).
- Obtain contact information for family: The family will be asked to provide their contact information as well as contact information of relatives and friends of the family so that we can contact the family if the family moves.

After discharge from the hospital until 18-month Follow-up visit:

- To be contacted by mail and/or telephone calls 4 times per year in order to track contact information in case it changes from that collected at discharge from the hospital to the time of the18-month follow-up visit

At the 18-month Follow-up visit:

- Obtain infant's medical history, social history, utilization of special child services, and assessment of infant behavior: As the parent/legal guardian, you will be asked to answer questions about your child's medical history and utilization of special services, the family's social history, and your child's behavior.
- Physical and neurodevelopmental examination: Your child will have his/her growth measured, such as weight, height and head circumference, and a neurodevelopmental examination (to evaluate for tone, strength, coordination and how your child gets around). Infants will also be screened to identify social/emotional behavior using standardized questionnaires. The follow-up visit should take no longer than a total of one and one half to two hours, the usual amount of time required for an 18 month follow-up assessment.
- To grant permission for release of medical information from your child's medical records at Tufts MC, primary care or specialist physician's office, and community hospitals in which your baby received medical care such that results of tests (such as eye examinations or

hearing tests) and data that pertain to your baby can be confidentially documented. They will be kept secure with other study records.

EXPECTED RISKS AND DISCOMFORTS

Your child will not experience any additional risks or discomforts because you and he/she participate in this study. The study procedures do not increase the risk for you or your baby. There are no blood tests related to the study. No experimental procedures, therapies, or medicines are involved in this study.

BENEFITS

Your baby will receive no direct benefit for participation in this study.
Potential benefits to society and future premature babies: We hope that the information which we gain from this study will teach doctors about the development of premature infants after they leave the NICU. This information will help us to alter care to potentially decrease complications and to provide better counseling to parents in the future.

You will be informed of any new findings developed during the course of this research study that may affect your willingness to continue to participate in this study.

ALTERNATIVES TO PARTICIPATION

You may choose not to take part in this study. Your child will receive the same follow up care regardless of participation in the study.

COSTS

There is no charge to you or your child for participating in this research. Either you or your health insurance will be responsible for the costs of medical care that is medically necessary or indicated for your infant's care.

PAYMENT FOR PARTICIPATION

A gift certificate to Target for $20.00 will be provided per child at the 18-month follow-up visit as an appreciation payment for your child's participation. You will also be reimbursed reasonable travel expenses to get to the appointment.

VOLUNTARY PARTICIPATION/WITHDRAWAL

If you agree to allow your child to be in this study, you are free to change your mind at any time. If you withdraw your child from the study, your child will continue to have access to health care at Tufts MC and you baby's care at the NICU follow-up clinic will not change. If you do decide to withdraw your child, we ask that you contact Dr. Elisabeth McGowan. Dr. McGowan can be reached via telephone through the Tufts MC Paging Operator: (617) 636-5114 or Tufts MC NICU (617) 636-5008. Her mailing address is 800 Washington Street, Tufts MC #44, Boston, MA 02111. Information that has been collected before your withdrawal from the study will be confidential. Your child may be removed from the study without your consent if we are unable to check on your child regularly or if other administrative reasons occur. If the study doctor thinks it is in your child's best interest to stop being in the study, your child may also be removed from this study.

CONFIDENTIALITY

Extensive efforts are made to treat all research information confidentially. Specifically, access to information about your child is restricted to the Tufts MC Clinical Research staff that is involved in this study. Clinical and research information with respect to this study is maintained in a research file separate from hospital medical records and will not be placed in the official Tufts MC medical record by research staff. All medical information about your baby is coded with a unique number. The key linking the code number with your baby's identity will be kept secure at Tufts MC clinical research office. Information, such as name or medical record number, which directly identifies your baby to study data, will not leave Tufts MC. Research data from which your child may be identified will not be disclosed to third parties except with your written permission or as may be required by law. If research results from this study are reported in a professional setting, such as in a medical journal or at a scientific meeting, the identity of research subjects taking part in the study is withheld.

CONTACT INFORMATION

If you have any questions about the study or concerns during the study, you may contact the investigator (Dr. McGowan) or her designees via the Tufts MC Paging Operator: (617) 636-5114 or Tufts MC NICU (617) 636-5008.

If you have questions about your rights as a research study subject, call the Tufts Medical Center and Tufts University Health Sciences Institutional Review Board at 617-636-7512. The Institutional Review Board is a group of doctors, nurses, and non-medical people who review human research subjects for safety and protection of human subjects.

PARENT'S STATEMENT

I have read this consent form and have discussed with Dr. McGowan or her representative the procedures described above. I have been given the opportunity to ask questions, which have been answered to my satisfaction. I understand that any questions that I might have will be answered verbally or, if I prefer, with a written statement.

I understand that I will be informed of any new findings developed during the course of this research study that may affect my willingness to continue to participate.

I understand that participation in this research study is voluntary. I understand that I/my child may refuse to participate in this study. I also understand that if, for any reason, I/my child wishes to discontinue participation in this study at any time, I/my child will be free to do so, and this will have no effect on his/her future care or treatment by his/her physicians or this hospital.

I understand that in the event my child becomes ill or is injured as a result of participating in this research study, medical care will be provided to him/her. However, such medical care will not be provided free of charge, even if the injury or illness is a direct result of this research study. I understand that no funds to provide financial compensation for research-related injury or illness are available.

If I have any questions concerning my child's rights as a research subject in this study, I may contact the Tufts Medical Center and Tufts University Health Services Institutional Review Board at (617) 636-7512.

I have been fully informed of the above-described study with its risks and benefits, and I hereby consent to the procedures set forth above. I have received a signed copy of this consent form.

I understand that as a participant in this study my child's identity and medical records and data relating to this research study will be kept confidential, except as required by law, and except for inspections by the study sponsor.

_____ _____

One Parent/Legal Representative Signature Date

I have fully explained to _____ (Parent) the nature and purpose of the above-described study and the risks that are involved in its performance. I have answered all questions to the best of my ability.

_____ _____

Principal Investigator or Representative's Signature Date

July 7, 2006, Nov 13, 2007, Dec.7, 2007, 4/21/2008, 9/24/08, 6/23/10, 11/16/11

From: Vaucher, Yvonne
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: NEJM website
Date: Friday, March 02, 2012 6:04:49 PM

Hope so, too.

Yvonne

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]
Sent: Friday, March 02, 2012 11:21 AM
To: 'Das, Abhik'; Finer, Neil; 'Wally Carlo, M.D.'; Vaucher, Yvonne; 'Myriam Peralta, M.D.'
Subject: NEJM website

01618

Neurodevelopmental Outcome of Extremely Preterm Infants in a Trial of Two Different Oxygen Saturation Targets
[View Submission<https://pedsmail.pediatrics.ucsd.edu/OWA/UrlBlockedError.aspx>]

09-Feb-2012

09-Feb-2012

With the Editor

Under Internal Review

-01547

Early CPAP versus Surfactant in Extremely Preterm Infants: Neurodevelopmental Outcomes in Early Childhood
[View Submission<https://pedsmail.pediatrics.ucsd.edu/OWA/UrlBlockedError.aspx>]

08-Feb-2012

08-Feb-2012

With the Editor

Under Internal Review

I looked at the NEJM website today to see the status of the SUPPORT FU papers. I am hoping the internal review is the in-house statistician!!!!

Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
6100 Executive Blvd., Room 4B03
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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Testa, Veronika"; "McGowan, Elisabeth C"
Cc: "Gonsalves, John"; "Peterson, Theresa"
Subject: RE: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)
Date: Friday, March 02, 2012 9:36:00 AM

Thanks and yes we have the other emails.
Thanks For your patience.

Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
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301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Testa, Veronika [mailto:vtesta@tuftsmedicalcenter.org]
Sent: Friday, March 02, 2012 9:14 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; McGowan, Elisabeth C
Cc: Gonsalves, John; Peterson, Theresa
Subject: FW: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)

Hello Rose,

Here is the IRB approval for the NRN Follow up Study.

Back on January 24th and February 14th I had sent you a total of 4 emails containing various IRB approvals.

Please let me know that you had received these emails. If not, I'd be happy to resend them to you for your files.

Best regards,
Veronika

Veronika Testa, BSN, RN, CCRC
Project Manager
Tufts Medical Center
800 Washington Street, Box 391
Boston, MA 02111
☎: 617.636.2379 | 🖷: 617.636.8329
✉: vtesta@tuftsmedicalcenter.org

From: Testa, Veronika
Sent: Tuesday, January 24, 2012 11:53 AM
To: 'Higgins, Rosemary (NIH/NICHD) [E]'; McGowan, Elisabeth C
Subject: RE: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)

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Hi Rose,

My administrative assistant will be in mid-week, and we will send the SUPPORT documentation as well as all other renewals. Everything has been completed.

Who should I send to ?

Liz

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Sent: Friday, January 20, 2012 03:24 PM
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Cc: McGowan, Elisabeth C <emcgowan@tuftsmedicalcenter.org>
Subject: RE: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)

Rose: I no longer have access, but Liz should be able to get the items to you.

Ivan

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Sent: Friday, January 20, 2012 2:43 PM
To: Frantz, Ivan
Cc: Maddox, Yvonne (NIH/NICHD) [E]; Hirschfeld, Steven (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]
Subject: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)

Ivan
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Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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From: Finer, Neil
To: jmd3@case.edu
Cc: Richard Martin; Michele Walsh; Rich, Wade; Wrage, Lisa Ann; Wally Carlo; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik
Subject: RE: IH vs target range manuscript - J Peds Reviewer response
Date: Monday, February 27, 2012 11:52:39 AM

Great Good luck
Neil

-----Original Message-----
From: Juliann Di Fiore [mailto:jmd3@case.edu]
Sent: Monday, February 27, 2012 6:51 AM
To: Finer, Neil
Cc: Richard Martin; Michele Walsh; Rich, Wade; Wrage, Lisa Ann; Wally Carlo; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik
Subject: Re: IH vs target range manuscript - J Peds Reviewer response

Thanks Neil! I will work on the conclusion to tighten that up.
Although your thoughts on neurodevelopmental impairment are important,
from Wally suggestion regarding the main paper, we will leave that out.
Great eye on the figure legend. I went back to the original tif files
and they are clearly distinguishable. Somehow when I pasted them into
Word the format changed. I will verify them once more when I upload them
to the journal.

Take Care!

Julie

On 2/27/2012 9:23 AM, Finer, Neil wrote:
> Hi Julie
> I think your responses are appropriate
> In the conclusions you state that 2 clinical trials have shown an association between low SpO2 targets and death. Stensons letter to the NEJM describes a combined interim analysis for the UK Australia and New Zealand Boost 2 trials - so perhaps a better way of saying this is that preliminary results from three other trials also supports this association (between low target SpO2 and death) None of these studies has been presented in depth or published - their primary outcomes were to be determined at follow-up and none will be at that point till 2014
> The concern about IH is the possible association with neurodevelopment and cognition
> We have now presented the follow-up for both arms of SUPPORT at Hot Topics
> Would it be appropriate in the discussion to note that we did not find any difference in cognitive or neurodevelopmental outcomes between the 2 target SpO2 groups - I am asking this of Rose and Wally as well.
> While we do have differences in this study cohort of< 10% of the trial, the overall trial found no differences and this to me is a major proposed clinical implication of increased IH events.
> The manuscript looks very detailed and complete
> I am still unclear about the potential etiologies for the differences in IH in Phase 3 - I am reassured by the follow-up data
> The legends describing the actual groups - ie solid line and hatched line do not appear different to me on the figures - they both look solid to me. This is clear on the legends in the manuscript but not on the actual figures.
> Thanks for all of your amazing efforts.
> Be well
> Neil
>
> -----Original Message-----
> From: Juliann Di Fiore [mailto:jmd3@case.edu]
> Sent: Thursday, February 23, 2012 8:56 AM

> To: Richard Martin; Michele Walsh; Finer, Neil; Rich, Wade; Wrage, Lisa Ann; Wally Carlo
> Cc: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik
> Subject: IH vs target range manuscript - J Peds Reviewer response
>
> Hi Everyone,
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> RE: Low Oxygen saturation target range is associated with increased incidence of IH- reviewer response from J Peds
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> Attached are the reviewers' comments, my response, the modified figures and manuscript for your review. I have deleted the 4th figure and pasted the remaining 3 in a word file to make them easier for viewing. Please look these documents over and give me any of your comments. Please note that we are under significant restraints as I have had to add ~500 words to an already lengthy manuscript to respond to the reviewers.
>
> I would like to get this wrapped up by the end of next week if possible and would appreciate receiving your comments by then.
>
> Thanks!
>
> Julie
>
> --
> Juliann Di Fiore
> Research Engineer
> Case Western Reserve University
> Rainbow Babies& Children's Hospital
> Division of Neonatology, room 3100
> 11100 Euclid Ave
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>
>

--
Juliann Di Fiore
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by law.

From: Phelps, Dale
To: "Wrage, Lisa Ann"; "Kennedy, Kathleen A"; Higgins, Rosemary (NIH/NICHD) [E]
Cc: "Das, Abhik"; "Gantz, Marie"
Subject: RE: ROP Natural History update
Date: Saturday, February 25, 2012 9:38:50 PM

Oh, and did I forget to mention: ONE OUT OF EVERY 10 infants who needed laser had been discharged home before needing treatment !
Thank you for digging that out for us Lisa.

half empty glass or half full, that is an ENORMOUS medico-legal risk. A very important point for the poster.

Dale

PS: I think there is a typo problem in Table 5:
Please report Zones in Roman numerals (I, II, III)
The second time you say "Lowest zone of vessels = II and no ROP" I'm pretty sure you really meant

"Lowest zone of vessels = III and no ROP"

From: Phelps, Dale
Sent: Saturday, February 25, 2012 2:59 PM
To: 'Wrage, Lisa Ann'; Kennedy, Kathleen A; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik; Gantz, Marie
Subject: RE: ROP Natural History update

Hi Lisa and Kathleen,
I enjoyed reading carefully through the materials for the ROP Natural History update. (also thought the data were useful for my thinking about the inositol protocol too, thanks!) Just 2 concerns/questions, then some minor notes.

Item:
In Table 1, as it was expanded, the goal of the percentages in the boxes changed, but the calculations did not, so I had to get my calculator out to learn what I wanted... (and almost missed it).

For the first 4 columns (up to "all outcomes") we are looking down the columns, asking how those with final outcomes differ from those who don't have them.
In the last 3 columns, however, we are looking to see how the severity of ROP is affected by the subgroups going across the table.
What the columns tell me now is the % of "No ROP infants" that were black, white, Hispanic or other.

But what I can use is "What % of Black infants had no ROP?" What % of White infants had no ROP?" What Percent of Hispanic infants had no ROP?"

It's s different question. I can calculate it myself from the data in the table, but I don't think most readers would pick this up, and you cannot complete a sentence about what you observed

from the percentages in the table. (Same for "Did the % of males with severe ROP differ from the % of females? " The table shows what % of severe ROP subjects were male)

I'm not sure of the best solution, but it might require 1 table to describe the population that have outcomes, and a different table to describe the characteristics of the infants with those various outcomes. There has to be some way to do this. Put these items into Table 2?

In Table 3

I cannot tell how you treated infants with Type 1 ROP on their first examination(footnote 5). Were there any? a lot? excluded? If I compare the 128 here, to Table 1 where there are 138, there are 10 not represented. Maybe you could satisfy the curious and 'bean counters" by adding in the footnote #5 that xx infants had Type 1 ROP on their first examination so that the time of onset is not known, or something similar to describe what actually was done. It actually is important to know how early they might have been when trying to determine when first examinations should be done. Were these 10 <31 weeks PMA at first exam? (current screening guidelines). If it turns out these 10 were all first examined after 31 weeks (because too sick to do sooner or some other presumed reason), it is not worrisome that they do not show up in Table 3, or probably) in the accumulation curves that follow.

And some minor thoughts.

In the flow sheet (which might also appear on a poster), As read the first box of 4369 born, it might be good to put in this box that 3536 were assessed for eligibility. (optional) In footnote 2 of the flow chart, you might better say "2 of these had a good outcome..." because "a positive outcome" was at first ambiguous to me (like a positive blood culture.. definitely NOT good)

In Table 1, do you want to add a column after enrolled for the number that died before the first examination? (it's probably covered in the flow sheet).

Thank you very much.
I really enjoyed and studied the figures. There is a lot of information in them. Kathleen, you're going to have fun picking the reduced numbers you want for the poster. :-)

Dale

From: Wrage, Lisa Ann [mailto:wrage@rti.org]
Sent: Friday, February 24, 2012 11:13 AM
To: Kennedy, Kathleen A; Phelps, Dale; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik; Gantz, Marie
Subject: ROP Natural History update

Hello,
I have attached an update to the ROP Natural History analysis. The updates are summarized in the header and include an edit to the top number in the flow chart, addition of some information about

the adjudication, addition /edits of some figures as well as other clarifications in response to recent comments I received from Kathleen.

Kathleen:

Please note that on the timing of maturity graphs I compressed the upper end of the x-axis where the outliers are so that they are still in the figure but in such a way that allows the data to be better spread out, so let me know if something like this will be ok (this was in response to your comment that the graphs might look better if the x-axis was decreased, and keep in mind that I could compress more of the upper end of the x-axis if preferred).

And regarding the Type II information -- please note that in the December update I added the median age of onset for Type I ROP for those without a Type II ROP exam vs. those with one (see the yellow highlighted info after the last footnote in Table 3). A while back you had mentioned that if Type I onset for the group with no Type II exam was much quicker than for those with a Type II exam then we might still have usable information even though we have no Type II information for a large proportion of infants with Type I. So take a look at that, the medians are a week apart, I don't know if that is truly 'much quicker' or 'different' but we might want to look at the whole curve just to be sure.

Thanks, and I hope you all have a great weekend.
Lisa

Lisa Wrage, MPH
Research Statistician
Statistics & Epidemiology
RTI International
wrage@rti.org
919-220-2653

From: Juliann Di Fiore
To: Wally Carlo, M.D.
Cc: Richard Martin; Michele Walsh; Neil Finer; Wade Rich; Wrage, Lisa Ann; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik
Subject: Re: IH vs target range manuscript - J Peds Reviewer response
Date: Friday, February 24, 2012 8:59:43 AM

Thanks for catching that!

On 2/23/2012 8:52 PM, Wally Carlo, M.D. wrote:
> Hi Julie:
> You did an excellent job with the responses. You missed changing 90% to
> 91% in the Abstract. You may want to add the reviewers' comments to your
> responses in the same letter (alternating them) to make it easier for
> the Editor and reviewers.
>
> Wally
>
> Wally Carlo, M.D.
> Edwin M. Dixon Professor of Pediatrics
> University of Alabama at Birmingham
> Director, Division of Neonatology
> Director, Newborn Nurseries
> 1700 6th Avenue South
> 176F Suite 9380R
> Birmingham, AL 35233-7335
> Phone: 205 934 4680
> FAX: 205 934 3100
> Cell: 205 (b)(6)
>
>
> -----Original Message-----
> From: Juliann Di Fiore [mailto:jmd3@case.edu]
> Sent: Thursday, February 23, 2012 10:56 AM
> To: Richard Martin; Michele Walsh; Neil Finer; Wade Rich; Wrage, Lisa
> Ann; Wally Carlo, M.D.
> Cc: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik
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>
> I would like to get this wrapped up by the end of next week if possible
> and would appreciate receiving your comments by then.
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> Thanks!
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> Julie
>
> --
> Juliann Di Fiore
> Research Engineer
> Case Western Reserve University
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From: Juliann Di Fiore
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Cc: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik
Subject: IH vs target range manuscript - J Peds Reviewer response
Date: Thursday, February 23, 2012 11:56:40 AM
Attachments: figures.docx
Response to reviewers.docx
Final effect of low target range on the incidence of IH RESPONSE TO REVIEWERS.docx
Table New.doc
Reviewer comments.docx

Hi Everyone,

RE: Low Oxygen saturation target range is associated with increased incidence of IH- reviewer response from J Peds

Attached are the reviewers' comments, my response, the modified figures and manuscript for your review. I have deleted the 4th figure and pasted the remaining 3 in a word file to make them easier for viewing. Please look these documents over and give me any of your comments. Please note that we are under significant restraints as I have had to add ~500 words to an already lengthy manuscript to respond to the reviewers.

I would like to get this wrapped up by the end of next week if possible and would appreciate receiving your comments by then.

Thanks!

Julie

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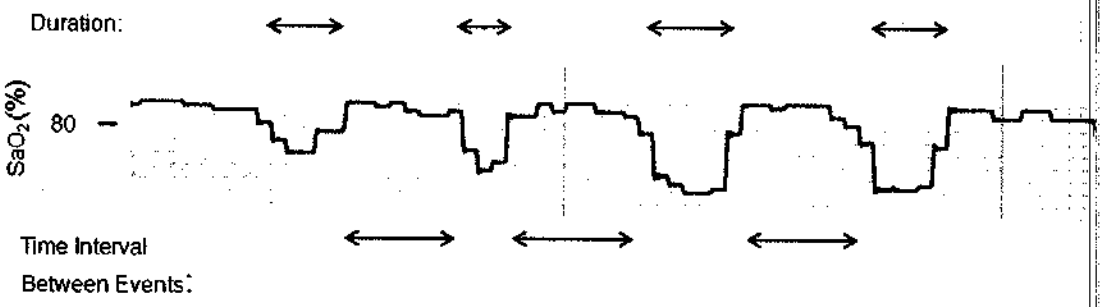
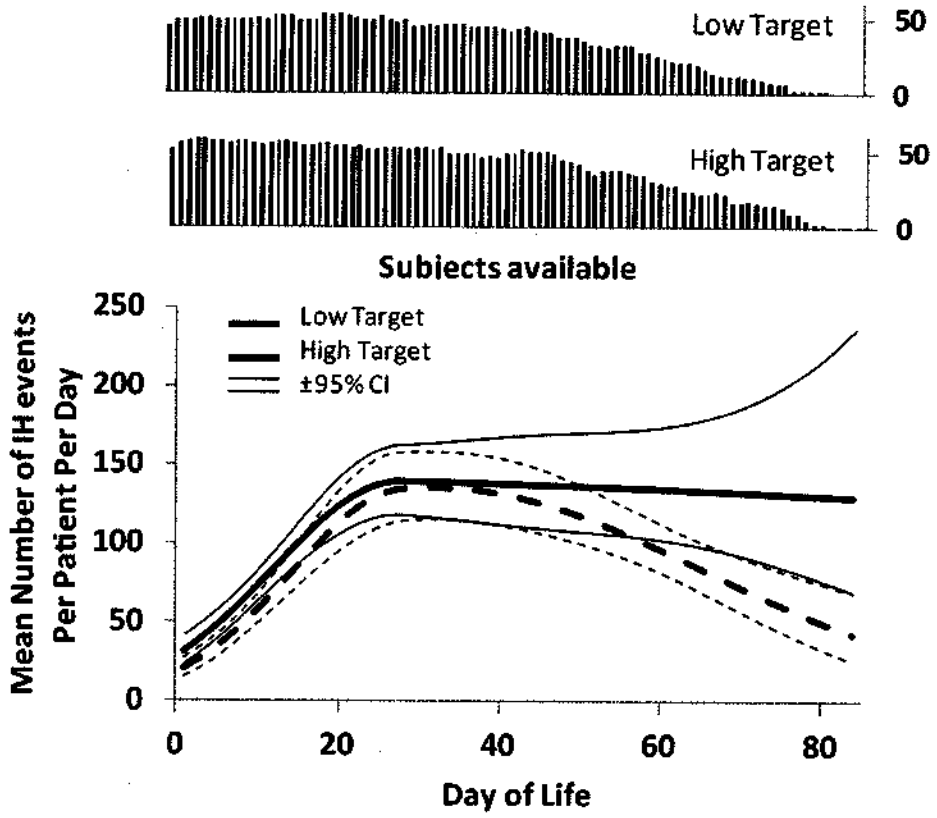


fig 1

A



B

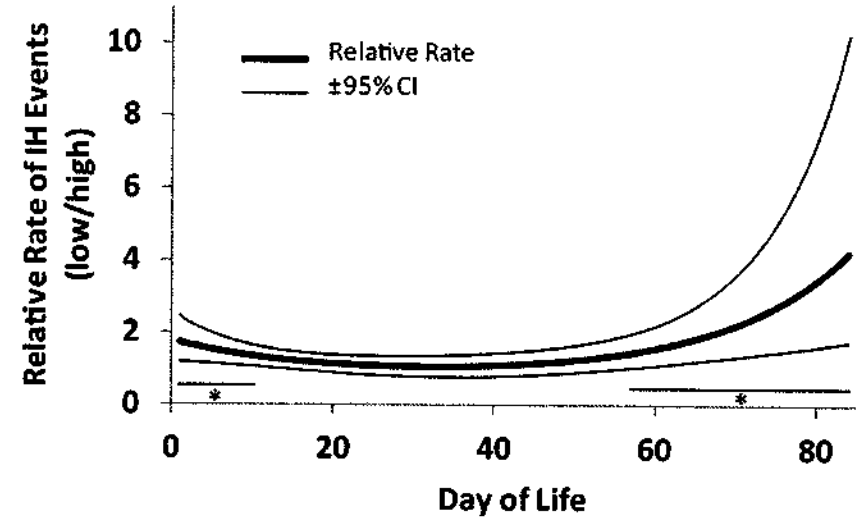
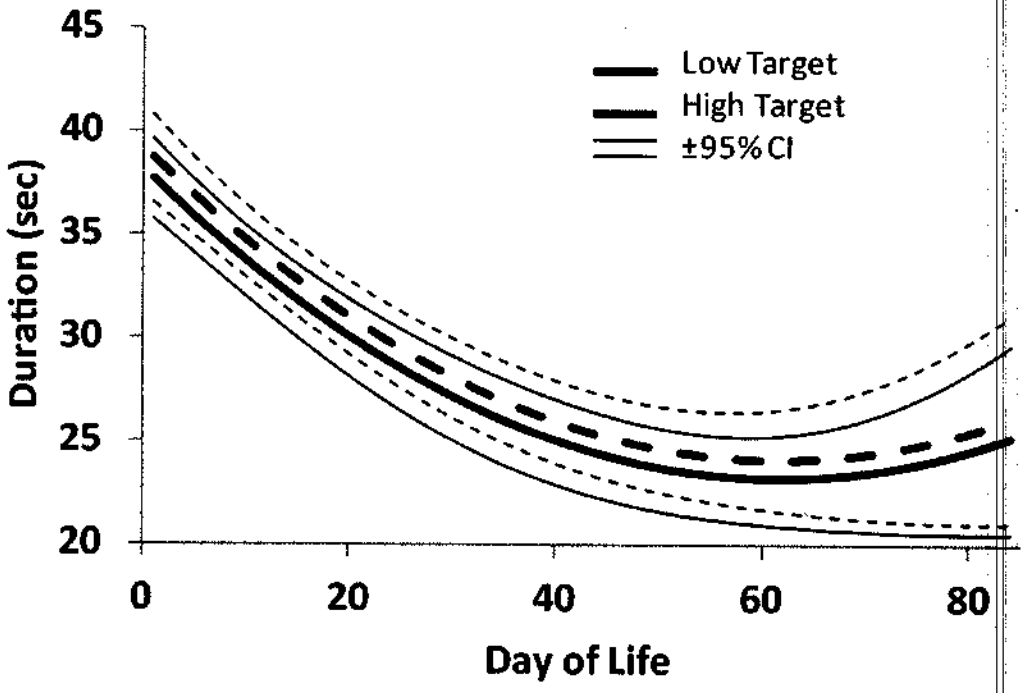


fig 2

A



B

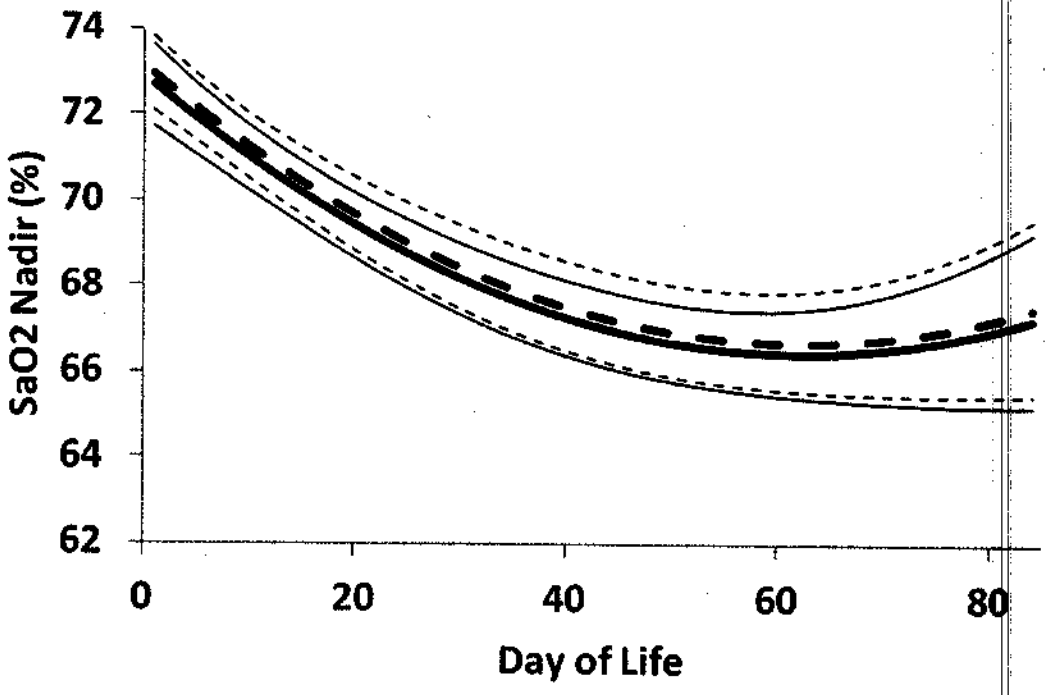


fig 3

Low oxygen saturation target range is associated with increased incidence of intermittent hypoxemia

Juliann M. Di Fiore, BSEE[1], Michele Walsh, MD[1], Lisa Wrage, MPH[2], Wade Rich, RRT[3], Neil Finer,MD[3], Waldemar A. Carlo, MD[4], Richard J. Martin, MD[1], and the SUPPORT Study Group of the NICHD Neonatal Network

[1] Division of Neonatology, Department of Pediatrics, Rainbow Babies & Children's Hospital, Case Western Reserve University, Cleveland, Ohio

[2] Statistics and Epidemiology Unit, RTI International, Research Triangle Park, NC

[3] Division of Neonatology, Department of Pediatrics, University of California, San Diego, California

[4] Division of Neonatology, University of Alabama at Birmingham, Birmingham, Alabama

Financial Assistance:

Supported by the National Institute of Child Health and Human Development Cooperative Multicenter Neonatal Research Network (Grant HD021364-23)

Juliann Di Fiore wrote the first draft of the manuscript.

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Keywords: preterm infants, hypoxemia

The authors state no conflicts of interest

Abstract:

Objective:

To test the hypothesis that preterm infants randomized to a low versus high ~~O_2~~ oxygen saturation target range have a higher incidence of intermittent hypoxemia (IH).

Study Design:

A subcohort of 115 preterm infants with high resolution pulse oximetry enrolled in the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) ~~trial~~, were randomized to low (85-89%) or high (90-95%) oxygen saturation target ranges. Oxygen saturation was monitored until 36wks postmenstrual age or until the infant was breathing room air without respiratory support for ≥72hrs.

Results:

The low target oxygen saturation group had a higher rate of IH events (≤80% for ≥10 sec and ≤3 min) prior to 12 days and beyond 57 days of life ($p<0.05$). The duration shortened ($p<0.0001$) and the severity increased ($p<0.0001$) with increasing postnatal age with no differences between target saturation groups. The higher rate of IH events in the low target group was associated with a time interval between events of <1min.

Conclusion:

A low oxygen saturation target was associated with an increased rate of IH events that was dependent on postnatal age. The duration and severity of events was comparable between target groups. Further investigation is needed to assess the role of IH events and their timing on neonatal morbidity.

Background:

Intermittent hypoxemia (IH) may be associated with morbidity in preterm infants. In newborn animal models, administered IH paradigms have been shown to impair dopamine signaling[1], contribute to neurological handicap[1-3], and exacerbate retinal neovascularization[4]. Although, IH events are common in preterm infants, data relating to the prevalence of these events have been limited. Pulse oximetry technology has enabled non-invasive recording of spontaneous intermittent hypoxemic events in preterm infants over prolonged periods of time. This has allowed for accurate documentation of the temporal changes in the incidence of IH events over the first few months of life. Recent data in a previous cohort of preterm infants of 24-28 weeks gestation have shown relatively few IH events over the first week of life, a progressive increase in events until approximately 5 weeks post natal age followed by a decline thereafter[5].

The multi-center Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) ~~trial~~ examined the role of high versus low oxygen (O_2) saturation target ranges on retinopathy of prematurity. Following randomization to lower (85-89%) or higher (91-95%) oxygen saturation target ranges, infants in the lower target group were found to have a lower incidence of severe ROP. This was associated with an unexpected higher mortality in infants targeted to low baseline oxygen saturation in two separate clinical trials[6,7]. The effect of these oxygenation target ranges on the occurrence of intermittent hypoxemia (IH) is unknown. As a lower baseline oxygen saturation target may increase hypoxic vulnerability and the likelihood of IH, we prospectively designed this study to test the hypothesis that infants randomized to a

low compared to high O_2 saturation target range would have an increase in the incidence of intermittent hypoxemia.

Methods:

The study population included a new subcohort of 115 preterm infants enrolled in the multi-center SUPPORT study from two sites: Rainbow Babies & Children's Hospital, Cleveland, and University of California San Diego. Enrollment criteria for the main trial included infants who were born between 24 weeks 0 days and 27 weeks 6 days of gestation for whom a decision had been made to provide full resuscitation. Infants born in other hospitals and those known to have major anomalies were excluded. Using a permuted-block randomization design, with stratification according to study center and gestational age (24 weeks 0 days to 25 weeks 6 days or 26 weeks 0 days to 27 weeks 6 days), infants were randomized to a low (85-89%) or high (91-95%) oxygen saturation target group within two hours of birth. Infants who were part of multiple births were randomly assigned to the same group.

Electronically altered pulse oximeters (Radical SET, Masimo, Irvine, CA) were used to blind the staff to the randomization group. The nursing response was dictated by the individual caregiver and center. The clinical staff was blinded as to the randomization group and instructed to maintain infants in an oxygen saturation range of 88-92%, with altered monitors showing target levels of 88-92% with a maximum offset of 3%. For example a displayed value of 90% corresponded to an actual oxygen saturation value of 87% in the low target group and 93% in the high target group[6]. Actual values were displayed when the oxygen saturation values were $\leq$85% or $\geq$95% in both treatment groups. Limits of 85% and 95% that would trigger a monitor

alarm were suggested, but they could be changed for individual patients. Centers received quarterly feedback for compliance in time spent in target range.

Due to the massive file sizes, storage and analysis costs only 2 centers from the main trial collected data with the highest resolution of 2 sec averaging and 2 sec sample rate needed for this data analysis (main SUPPORT study settings: 16 sec averaging and 10 sec sample rate). These files included up to 3.6 million oxygen saturation values per subject. Targeting of oxygen saturation and high resolution data collection began within 2 hours after birth and continued until 36 wks postmenstrual age or until the infant was breathing air without respiratory support for ≥ 72 hours, whichever came first. Respiratory support was defined as high frequency ventilation, conventional mechanical ventilation, nNasal SIMV, CPAP, nasal cannula, or hood~~,~~ ~~for ≥ 72 hours, whichever came first~~. . If the infant was off respiratory support for <72 hours and then support was re-administered, monitoring would have continued throughout that period. Infants weaned to room air for >72 hours but re-administered supplemental oxygen were returned to the original randomization group~~.~~

The study was approved by the Institutional Review Board at each site and by RTI Internatinal, which is the independent data coordinating center for the Neonatal Research Network. Written informed consent was obtained from the parent or guardian of each child before delivery. Additional approval and informed consent included permission to perform secondary analysis of de-identified data.

Respiration and apnea were not recorded for this study. We defined an IH event as a fall in oxygen saturation to ≤80% for ≥10sec and ≤3min. To eliminate periods of fluctuations around

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the threshold point but include rapid cycles of hypoxia as can occur with periodic breathing, the minimal time interval between events was set to 4 seconds. Events were identified by custom software. The software output was verified by hand scoring of events in 4-1hr segments in 5 randomly chosen infants. Events were~~We~~ then characterized ~~these events~~ by their duration and the time interval between each event (Figure 1). The time interval between each event was calculated as the time between the end of the IH event (designated by the return of oxygen saturation above 80%) and the beginning the next IH event (designated by a fall below 80%). The severity, or nadir, of each event was also documented. For each postnatal day for each subject a calculation was made of the total number, duration and time interval between IH events. These values were then used in the model.

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Demographic and clinical variables were compared between high and low SaO_2 target groups using t-tests or Generalized Estimating Equation (GEE) regression models, adjusting for SUPPORT study stratification variables site and gestational age group, where appropriate. Variables for gestational age group and center were included as they were stratification factors for the SUPPORT study. Due to sparse data a Fisher's exact test was used to evaluate death prior to 36 weeks. To model counts of intermittent hypoxemia events a GEE regression model assuming a negative binomial distribution was used. The pre-specified GEE model, including SpO_2 target group and time variables, provided robust standard error estimates which take into account the correlations within multiple-birth clusters, including correlations between repeated measurements. Variables included in the final model for IH events were treatment group, linear and quadratic terms for postnatal age, interactions between treatment group and postnatal age variables, gestational age group, and respiratory support (yes or no, per day). An

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additional quadratic term which allowed the quadratic relationship of postnatal age and IH events to vary before and after 28 days was also included; this spline regression approach provided a better fit than simpler models[8]. Also considered were interactions between GA group and postnatal age, between GA group and treatment group, and between the additional quadratic term and treatment group, as well as variables for gender, race, center, CPAP versus surfactant treatment group (an additional randomization of the main SUPPORT trial protocol), and caffeine use. Because the sample size was small in comparison to the main trial, ~~E~~each of these additional terms considered were not significant and thus were not included in the final model. Similar models for the subsets of IH events that occurred with a time interval of <1 minute and 1 to 20 minute between events were run using the same final set of variables as the overall model. Additional models were run to model duration and severity of IH events. These models included variables for treatment group, linear and quadratic terms for age, gestational age group, and center.

Results:

The population of 115 infants had a mean birth weight of 830±181gm and gestational age of 25.8 ±1.0wks. There were 50 infants in the gestational age range of 24 to 25 weeks 6 days and 65 infants in the gestational age range of 26 to 27 weeks 6 days range. Fifty one percent of the infants were male and 35% were non-Hispanic white. Characteristics of infants randomized to the high (n=62) and low (n=53) target group are presented in Table 1. There were no differences between groups in birth weight, gestational age, incidence of bronchopulmonary dysplasia, ~~or~~ severe retinopathy of prematurity (ROP), or death before discharge. In this small

cohort, there was a trend towards a higher mortality at 36 weeks in the low target group (p=.09), mirroring the finding in the main trial, but this did not reach statistical significance. Caffeine use occurred on approximately 80% of days during the monitoring period in both infant groups. There were no differences between low and high target groups with respect to use of postnatal steroids (5.7% vs. 4.8%), proportion discharged on diuretics (14.3% vs. 14.0%), or inhaled bronchodilators (2% vs. 3.5%). Infants in the low target group received respiratory support for 86% of the monitoring period compared with 92% in the high target group (adjusted RR low versus high target, .93, 95% CI 0.86-0.99, p=.029). The median baseline SpO_2 during days receiving oxygen supplementation was comparable to the main trial with a median SpO_2 of 92 (IQR: 91 to 94) and 94 (IQR: 93 to 94) in the low and high target groups, respectively.

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The model based estimates showed an increase in IH events over the first 3 weeks of life in both infant groups followed by a decrease in IH events in the high target group compared to a plateau in the low target group (Figure 2a). The adjusted relative rate of IH events (RR), (the ratio of the adjusted mean number of IH events in the low target group/ the adjusted mean number of IH events in the high target group, per day), revealed a significantly higher rate of IH events prior to 12 days, and beyond 57 days of age in the low target group ($p<0.05$, Figure 2b). Higher rates of IH events were associated with lower gestational age, (adjusted RR 1.24, 95% CI 1.01-1.5, p=.032), and respiratory support, adjusted (RR 1.85, 95% CI 1.52-2.49, p<.0001).

The mean duration of IH events shortened ($p<.0001$) and the severity worsened ($p<.0001$) with increasing day of life (Figure 3). However, there were no differences in duration or severity between infant groups.

There was a wide range in the time interval between sequential IH events both within and between infants. To address the association between the timing of IH events and the oxygen saturation target group, the number of IH events was documented for three time interval ranges 1) <1 minute, 2) 1-20 minutes and, 3) >20 minutes between IH events. The highest incidence of events occurred with a time interval between events of <1 min, followed by a time interval of 1-20 minutes between events. There were relatively few IH events that occurred with a time interval of >20 minutes between events (Figure 4). IH events occurring with a time interval between events of <1 minute were associated with a significantly higher relative rate of IH events in the low target group at <15 and >54 days of life ($p<0.05$). After 65 days of life, there were a significantly higher number of IH events with a time interval of 1-20 minutes between events in the low target group ($p<.05$) with no differences between groups for IH events with a time interval of >20 minutes between events.

The above analysis examined the number and characteristics of IH events by increasing postnatal age. In addition, the effect of post menstrual age on the occurrence of IH events was also assessed.The number of IH events was not significantly different by treatment group, at any postmenstrual age, indicating that postnatal rather than postmenstrual age is the major determinant of the incidence of IH.

Discussion:

This study showed an association between a low oxygen saturation target range and an escalation in the incidence of IH events that changed with increasing day of life. Infants in the low target range had a higher number of IH events during the first two weeks and after 57 days of life but followed a similar trajectory as the high saturation target group between these time periods. IH events became shorter and more severe with increasing post natal age, however, there were no differences in duration or severity between infant groups. Lastly, the higher incidence of IH events in the low target group was predominantly associated with a time interval between IH events of <1minute in duration.

Intermittent hypoxemic events are ubiquitous in preterm infants, both ventilated[9,10] and spontaneously breathing[11]. Nonetheless, the precise incidence of these events has not been well documented. This is important in order to address their potential pathophysiological consequences. This study showed a higher incidence of IH in the low target group which is consistent with McEvoy et al[12] showing a relationship between oxygen levels and IH in former preterm infants with chronic lung disease. Although these events are thought to be a consequence of immature respiratory control, this study and previous data in a similar infant cohort[5] suggest that other developmentally regulated pathological mechanisms may be contributing. There were relatively few IH events during the 1st week of life regardless of the level of oxygen exposure with a slight but significantly higher incidence of IH events in the low target group. We speculate that the higher incidence of IH events in the low target group during this early time period may be a reflection of hypoxic depression compounded with the peripheral chemoreceptor inhibition of breathing that is known to occur during the transition from fetal to neonatal life. This early phase was followed by a linear increase in IH events

through weeks two to three of life that did not significantly differ between ~~was not affected by~~ the oxygen saturation target ranges. The third phase of IH events began after four weeks of age with a plateau in IH events. After this time group differences emerge with a decline in events in the high target group while remaining relatively constant in the low target group. The increased incidence in IH events in the third phase ~~is~~ may be due to a low baseline alveolar PO_2 in the low target group which, in a model based analysis, has been shown to cause early onset of desaturation[13]. It remains unclear why this low reserve did not consistently result in a higher number of IH events during the ~~at~~ earlier ~~post natal ages~~phases. It is also possible that the higher IH events >57 days in the low target group is due to relatively well infants coming off of the low target monitors earlier thus comparing ill infants in the low target group with relatively well infants in the high target group during this time period. However, there were no differences in severity of illness parameters such as caffeine use, postnatal steroids, incidence of BPD and proportion discharged on diuretics or inhaled bronchodilators between target groups.

Caffeine use and respiratory support are the main clinical therapies for apnea and accompanying desaturation. Although caffeine has been shown to decrease apnea[14], interestingly, it has been shown to have little if any effect on desaturation episodes[15] although this is based on a single small series. Both infant groups spent a high percentage of the monitoring period on caffeine therapy with no significant difference in caffeine usage between infant groups, therefore, it is unlikely that caffeine use affected the results of this study. Respiratory support was associated with a higher incidence of IH events within each treatment

group. However, with the high target group having a higher percentage of time receiving respiratory support, this cannot explain the increased incidence of IH in the low target infants.

Both groups showed a comparable decrease in duration and increase in severity of IH events during the first four weeks of life with no further changes throughout the study monitoring period. Previous data have suggested that convalescing preterm infants, of 30 wks gestation, with increased spontaneous apnea have an augmented ventilatory response to acute hypoxia[16]. Thus, although infants in the low target group may have been more susceptible to initiation of a hypoxic event, they may have been able to rally a compensatory ventilatory response and recover as well as infants in the high target group.

The lower incidence of severe ROP in the main trial is in contrast to our previous findings of an association between IH and severe ROP[5]. This discrepancy may relate to the fact that the initial hyperoxia induced inhibition of angiogenesis is enhanced in the high oxygen target group at a time when IH episodes are not prominent. Time interval between IH events may also play a role. Previous data in animal models have suggested that the timing of patterns of IH events is important and may affect morbidity. In response to hypoxic exposure, measurements of reactive oxygen species have shown an increase in superoxide anion concentration during the recovery phase, with a delayed response of several minutes[17]. Current preterm infant data from our group suggest that ROP is associated with a time interval between events of 1-20 min potentially consistent with the ability to initiate an increase in reactive oxygen species (ROS). In contrast, the higher number of IH events in the low target group predominantly occurred with a time interval between events of less than 1 minute which may have limited the ROS response.

The effect of the duration of recovery time between IH events on the resultant oxidative stress response has yet to be determined and merits further investigation.

There are limited data on the long term consequences of IH events in preterm infants[18]. A history of apnea of prematurity during hospitalization[19] and cardiorespiratory events in the home[20] have been associated with neurodevelopmental impairment. These studies have focused on apnea rather than the accompanying hypoxemic events. The only study to address the latter issue is the observation that mean oxygen saturation during apnea has been shown to predict motor scores[21]. Further analysis is ongoing to assess the relationship between IH events and neurodevelopmental outcome in this infant cohort.

As this was an intention to treat study design with two dichotomous groups, ~~T~~this study was limited by the known challenge of keeping infants in a designated oxygen saturation target range[22,23]. The median SpO_2 for each target group was comparable to the main SUPPORT trial. However, similar to this study, ~~T~~the main SUPPORT trial revealed overlap in the median level of oxygen saturation between target groups with actual median oxygen saturation levels slightly higher than targeted levels in both treatment groups[6]. This may have affected the number of IH events as lowering the median baseline saturation and increasing the time in the actual low target level may have resulted in an even higher incidence of IH events. In addition, the data used in this analysis were collected via pulse oximeters which remained in use from birth up to 36 weeks postmenstrual age (PMA), but only during times when the infants were receiving respiratory support and during the three days after respiratory support was discontinued. Thus, data do not exist for time points four or more days after discontinuation of respiratory support,

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transfer to a non-study hospital, discharge, or 36 weeks PMA (whichever came first). The GEE models used in this analysis assume that any missing data are missing completely at random. This assumption may be violated by these data, because infants who dropped out of the data due to a poor outcome such as death, or a favorable outcome such as discharge or being able to breathe room air without support, are likely to differ from those who remained on respiratory support through 36 weeks PMA. Thus, this should be considered a conditional analysis; that is, it is conditioned upon being alive and on respiratory support, and the results provided by the GEE model for any given point in time should be interpreted as applying only to the subset of infants who were alive and on respiratory support at that time. Lastly, enrollment for this study was limited by the low pulse oximeter settings (16 sec averaging and 10 sec sample rate) per the main SUPPORT trial protocol. Due to memory storage and analysis costs only 2 sites acquired data at a high enough resolution to adequately detect IH events.

In conclusion, a low oxygen saturation target range is associated with an increased incidence of intermittent hypoxemic events that is dependent on postnatal age. These events tend to occur less than one minute apart but are of comparable duration and severity regardless of level of oxygen exposure. Two clinical trials have now demonstrated a potential association between low oxygen targets and increased mortality. While the etiology of such a mortality increase is unknown at this time, we speculate that the association between a low oxygen saturation target and increasing incidence of IH might provide insight to unraveling underlying pathophysiology. Describing the dynamic changes in incidence and timing of events with increasing age is important as it may add insight into the contribution of multiple factors that influence both central and peripheral respiratory control during the transitional phase of fetal to neonatal respiration.

Further studies are needed to assess the contribution of timing of IH events on neonatal morbidity. We speculate that, to minimize episodes of IH, the optimal O_2 saturation target may need to be adjusted by postnatal age.

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Acknowledgements

The National Institutes of Health, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), and the National Heart, Lung, and Blood Institute (NHLBI) provided grant support for the Neonatal Research Network's SUPPORT Trial.

Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Drs. Abhik Das (DCC Principal Investigator) and Marie Gantz (DCC Statistician) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study. The following investigators, in addition to those listed as authors, participated in this study:

NRN Steering Committee Chairs: Alan H. Jobe, MD PhD, University of Cincinnati (2003-2006); Michael S. Caplan, MD, University of Chicago, Pritzker School of Medicine (2006-present).

Case Western Reserve University, Rainbow Babies & Children's Hospital (U10 HD21364, M01 RR80) – Avroy A. Fanaroff, MD; Nancy S. Newman, RN; Bonnie S. Siner, RN; Arlene Zadell RN.

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Eunice Kennedy Shriver National Institute of Child Health and Human Development – Rosemary D. Higgins, MD; Stephanie Wilson Archer, MA.

RTI International (U10 HD36790) – Abhik Das, PhD; W. Kenneth Poole, PhD; Marie G. Gantz, PhD; Margaret Cunningham, BS; Betty K. Hastings; Jeanette O'Donnell Auman, BS; Carolyn Petrie Huitema, MS; James W. Pickett II, BS; Dennis Wallace, PhD; Kristin M. Zaterka-Baxter, RN BSN.

University of Alabama at Birmingham Health System and Children's Hospital of Alabama (U10 HD34216, M01 RR32) – Monica V. Collins, RN BSN MaEd; Shirley S. Cosby, RN BSN. Vivien A. Phillips, RN BSN.

University of California – San Diego Medical Center and Sharp Mary Birch Hospital for Women (U10 HD40461) – Maynard R. Rasmussen, MD; Paul R. Wozniak, MD; Kathy Arnell, RNC; Renee Bridge, RN; Clarence Demetrio, RN.

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Figure Legends:

Figure 1

A raw SaO_2 waveform with the duration of the event, denoted by arrows above, and the time interval between events, denoted by ~~the~~ arrows below.

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Figure 2

A) The model based estimates showed an increase in IH events over the first 3 weeks of life in both infant groups followed by a decrease in IH events in the high target group (- - -)compared to a plateau in the low target group (—) . B) The relative rate of IH events (RR), (the ratio of the adjusted mean number of IH events in the low target group/ the adjusted mean number of IH events in the high target group, per day), revealed a higher rate of IH events from <12 days, and >57 days of age in the low target group (* $p<0.05$).

Figure 3

IH event duration decreased and severity worsened with increasing postnatal age in both the low and high target groups with no differences between groups.

Figure 4

A) The number of IH events was documented for three time interval ranges; <1 minute, 1-20 minutes and, >20 minutes between IH events. The highest incidence of events occurred with a time interval between events of <1 min, followed by a time interval of 1-20 minutes. There were relatively few IH events that occurred with a time interval of >20 minutes between

events. B) IH events occurring with a time interval between events of <1 minute were associated with a significantly higher relative rate of IH events in the low target group at <15 and >54 days of life ($p<0.05$). IH events occurring with a time interval of 1-20 minutes between event had a higher relative rate of IH events >65 days of life ($p<0.05$). IH events occurring >20 min apart were comparable between target groups with a relative rate of approximately one throughout the monitoring period.

Editors comments:

1. The response by the clinical staff has been clarified in the methods section. The nursing response was dictated by the individual caregiver and center. The clinical staff (b)(4) (b)(4) (b)(4) This has been clarified in the methods

2. (b)(4) has been added to Figure 2.

3. We acknowledge the reservation that it is possible that the (b)(4) (b)(4) (b)(4) This has been added to the discussion.

4. The reference format has been corrected with issue numbers deleted.

Reviewer #1:

(b)(4)

(b)(4)

Reviewer #2:

(b)(4)

Reviewer #3

(b)(4)

(b)(4)

Ref.: Ms. No. 20111857
Low oxygen saturation target range is associated with increased incidence of intermittent hypoxemia
The Journal of Pediatrics

Dear Mrs. Di Fiore,

Your manuscript has been evaluated by the Editors and independent reviewers whom we consider to be experts in the field. The manuscript was not accepted for publication in its current form. However, we will review a revised version that satisfactorily addresses editorial criteria, issues raised in this letter, and comments of the reviewers, which are appended below. We cannot guarantee, even with revision, that the manuscript will achieve a high enough priority for publication.

In addition to the important concerns addressed in the reviews, please clarify whether the nursing response was dictated by the trial or individual caregivers; it should be clear whether (b)(4)

(b)(4)

Please make your revision as short as possible; focus the Discussion and remove all redundancy between sections of text and between illustrations and text. Make sure that your Abstract is <250 words. For an Original Article, the Abstract must be structured as explained in our Guide for Authors (http://www.jpeds.com/authorinfo). Because The Journal adheres to Vancouver style, all issue numbers in parentheses must be deleted.

Be sure that figures, if any, are submitted in TIFF, BMP, JPEG, GIF, PNG, EPS, PPT, or DOC format. Line art (black lines on a white background) must be created at 1,000 dpi. Combination line art (eg, line art with gray fill patterns) must be created at 1,200 dpi. Black and white or color photographs must be created at 300 dpi.

Because we have severe page limitations for the print version of The Journal, we need to limit the number of graphics in the print version to a total of 4. Therefore, if more than 4 figures and tables are retained in your revision, please choose an appropriate number for online only publication; no more than 4 graphics should appear in the print version. A reference to the electronic material will appear in the print version.

Submit figures and tables for online publication "as usual" through EES. Indicate what should be published online only in: (1) your point-by-point response; (2) EES, type "Figure x; online only" in the file description field when you upload the files; and (3) manuscript text, add behind the reference to the figure or table going online only "(Table x; online)." Do not renumber online only tables and figures or label them as "supplemental." Thank you for your understanding of our page limitations.

Include with your revision a cover letter listing your responses to the comments from the Editors, as well as those from the reviewers (appended below). Detail the changes made to satisfy each comment or, if you do not agree with a criticism, include a rebuttal. Further consideration will be possible only if you send point-by-point responses to the reviewers and the Editors; changes should not be tracked or highlighted in the manuscript.

Please submit your revision within three months of the date of this letter. To submit a revision, go to http://ees.elsevier.com/jpeds/ and log in as an Author. Your submission record can be found by clicking on "Submissions Needing Revision."

Thank you for submitting your paper to The Journal of Pediatrics. We look forward to receiving your revision.

Sincerely,

Clyde Wright, M.D.
Guest Editor

/mlh

Reviewers' comments:

Reviewer #1: (b)(4)

(b)(4)

Reviewer #2:

(b)(4)

Discussion:

(b)(4)

References- No comment

Figures- No comment

Reviewer #3: (b)(4)

(b)(4)

(b)(4)

(b)(4)

	Low Target (53)	High Target (62)	p value*
Birth Weight (gm), mean(SD)	855(191)	808(171)	0.16
Gestational Age (wk), mean(SD)	25.8(1.1)	25.8(1.0)	0.75
BPD (O_2 @ 36 wk), n/N(%)	14/50(28%)	24/62(39%)	0.45
Death before 36 wk PMA, n(%)	3 (6%)	0 (0%)	0.09
Death before discharge, n(%)	4(7.5%)	3(4.8%)	0.70
Severe ROP, n/N(%)	8/49(16%)	13/58(22%)	0.41
Death or Severe ROP, n/N(%)	12/53 (22.6%)	15/60 (25%)	0.64
Caffeine, n/N(%) of monitored days	2245/2838 (79%)	2757/3417 (81%)	0.87
Respiratory Support[t], n/N(%) of monitored days	2451/2849 (86%)	3085/3369 (92%)	0.03

*p values from: t-tests for BW and GA; GEE models, adjusting for stratification factors (study center and gestational age group) and familial clustering for BPD, ROP, Death or ROP, caffeine, respiratory support; Fisher's exact tests for death.

[t]High frequency jet ventilation, CPAP, conventional ventilation, nasal cannula, Nasal SIMV, or hood

From: Navarrete, Cristina
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Duara, Shahnaz
Subject: Request for additional info for presentaion and manuscript
Date: Thursday, February 23, 2012 9:04:21 AM
Attachments: Pending_analyses_for_SUPPORT_Growth_Sec.docx
PAS 2012 - Growth Outcome SUPPORT.pdf

Good morning Dr. Higgins!
It's wonderful to have the opportunity to present our findings in the upcoming meeting. I am working on the platform presentation and the manuscript simultaneuosly. In order to best deliver, it would be most helpful to have additional information, especially the results of the other requested analyses as outlined before. Please find attached, a copy of the pending analyses.
Thank you, Cristina

SUPPORT: GROWTH SECONDARY STUDY

Remaining analysis needed for presentation and manuscript: (as highlighted)

Abstract: see attached

Hypotheses:

1. **Low O_2saturation infant group less death or <10%ile for weight (=poor growth) at 36wk or discharge and at 18-22m follow-up.**
   Just a few additional descriptors are missing:
   a. *Information on gender (known to affect weight, we need to show balance between groups)*
   b. *BPD according to severity (infants with severe BPD also have growth derangements; desirable to have balance in severity between groups)*
   c. *Absolute mean values of all anthropometrics (wt, L, HC) with SD and n at each time point (for creation of graphs and to disclose changes in n over time due to missing values or death)*
   d. *<10%ile values of all anthropometrics at each time point (to demonstrate progression of growth failure over time, if any)*
   e. *Values for c and d stratified by GA*
   f. *RR for growth failure according to AGA, SGA status at birth*
2. **Low O_2saturation infant group better in-hospital growth trajectory.**
   Very important analysis that is still pending, because time between 28days and 32 weeks is variable by baby (depending on GA at birth, as much as 4 weeks for the 24weeker and as little as 1 week for the 27 weeker). The split in the average weight trend starting at 14 days of age in the less mature babies (see below) suggests different trajectories.

TABLE 1: POPULATION CHARACTERISTICS

Characteristic[1]	Low Sat n=402	High Sat n=408
Gestational age, weeks	26.2 (1.1)	26.2 (1.1)
Birth weight, g.	838.6 (186)	839.9 (191)
Birth weight < 10th %ile[3]	40/402 (10.0)	53/408 (13.0)
HC at birth	23.5 (1.8)	23.6 (1.9)
HC at birth < 10th %ile[3]	41/396 (10.4)	53/398 (13.3)
Length at birth	33.4 (2.9)	33.3 (2.9)
Length at birth <10th %ile[3]	50/396 (12.6)	57/400 (14.3)
Non-hispanic black	179/402 (44.5)	159/408 (39.0)
Multiple birth	90/402 (22.4)	112/408 (27.5)
Antenatal steroids	390/402 (97.0)	389/407 (95.6)
Vaginal delivery	138/402 (34.3)	147/408 (36.0)
Mother's education: HS grad	69/311 (22.2)	90/313 (28.8)
Gender**		

[1] presented as mean (SD) for continuous variables, n/N (%) Yes for categorical variables, except where noted.
[3] based on 10th percentile weight for GA, by gender, from Olsen growth tables
** a balanced gender distribution is important in growth outcome

TABLE 2: CLINICAL CHARACTERISTICS (GDB and SUPPORT data)

Characteristic[1]	Low Sat n=402	High Sat n=408	p-value[2]
Death by 36 weeks PMA	69 (17.2)	60 (14.7)	0.32
BPD, physiological	136/333 (40.8)	146/348 (42.0)	0.84
BPD, oxygen at 36 weeks PMA	132/333 (39.6)	158/348 (45.4)	0.10
~~BPD, Moderate/Severe (?)~~			
BPD, moderate (<30% oxygen suppl at 36wk)			
BPD, severe (≥30% oxygen suppl or on vent at 36wk)			
Postnatal steroids for BPD	33/394 (8.4)	39/399 (9.8)	0.46
# days on ventilator[4], median, mean(SD), n	n=329 9,21.0 (25.6)	n=344 14.5,22.7 (24.7)	0.17
# days supplemental oxygen[4], median, mean(SD), n	n=329 47,53.1 (37.6)	n=344 60,60.6 (36.6)	0.0094**
Severe IVH	58/391 (14.8)	60/396 (15.2)	0.84
PVL	16/392 (4.1)	20/397 (5.0)	0.59
NEC	51/397 (12.9)	48/404 (11.9)	0.63
Late onset sepsis	144/397 (36.3)	139/404 (34.4)	0.70
PDA	181/397 (45.6)	200/403 (49.6)	0.29

BPD based on consensus definition: moderate <30% O2 and severe ≥30%O2 at 36 weeksPMA.
*Important because the infants with severe BPD have the most difficulty with growth.

TABLE AND/OR FIGURE: GROWTH IN-HOSPITAL AND AT 18-22m FOLLOW-UP (Overall)

WEIGHT	Absolute numbers (g) mean (SD), n			≤10th%ile, n/N (%)		
	LOW Sat	HIGH Sat	p	LOW Sat	HIGH Sat	p
Birth	838.6 (186), 402	839.9 (191), 408		40/402 (10.0)	53/408 (13.0)	
Day 7						
Day 14						
Day 21						
Day 28						
32wk PMA						
36wk PMA				155/333 (46.6)	172/342 (50.3)	
18-22m FU				48/296 (16.2)	45/313 (14.4)	
LENGTH	LOW Sat	HIGH Sat	p	LOW Sat	HIGH Sat	p
Birth	33.4 (2.9), 402	33.3 (2.9), 408		50/396 (12.6)	57/400 (14.3)	
Day 7						
Day 14						
Day 21						
Day 28						
32wk PMA						
36wk PMA						
18-22m FU						
HEAD Circ	LOW Sat	HIGH Sat	p	LOW Sat	HIGH Sat	p
Birth	23.5 (1.8), 402	23.6 (1.9), 408		41/396 (10.4)	53/398 (13.3)	
Day 7						
Day 14						
Day 21						
Day 28						
32wk PMA						
36wk PMA						
18-22m FU						

TABLE AND/OR FIGURE: GROWTH IN-HOSPITAL AND AT 18-22m FOLLOW-UP (Stratified by GA: 24-25wks)

WEIGHT	Absolute numbers (g) mean (SD), n			<10th%tile, n/N (%)		
	LOW Sat	HIGH Sat	p	LOW Sat	HIGH Sat	p
Birth						
Day 7						
Day 14						
Day 21						
Day 28						
32wk PMA						
36wk PMA				71/131 (54.2)	85/133 (63.9)	
18-22m FU				24/112 (21.4)	29/121 (24.0)	
LENGTH	LOW Sat	HIGH Sat	p	LOW Sat	HIGH Sat	p
Birth						
Day 7						
Day 14						
Day 21						
Day 28						
32wk PMA						
36wk PMA						
18-22m FU						
HEAD Circ	LOW Sat	HIGH Sat	p	LOW Sat	HIGH Sat	p
Birth						
Day 7						
Day 14						
Day 21						
Day 28						
32wk PMA						
36wk PMA						
18-22m FU						

TABLE AND/OR FIGURE: GROWTH IN-HOSPITAL AND AT 18-22m FOLLOW-UP (Stratified by GA: 26-27wks)

WEIGHT	Absolute numbers (g) mean (SD), n			<10th%tile, n/N (%)		
	LOW Sat	HIGH Sat	p	LOW Sat	HIGH Sat	p
Birth						
Day 7						
Day 14						
Day 21						
Day 28						
32wk PMA						
36wk PMA				84/202 (41.6)	87/209 (41.6)	
18-22m FU				24/184 (13.0)	16/192 (8.3)	
LENGTH	LOW Sat	HIGH Sat	p	LOW Sat	HIGH Sat	p
Birth						
Day 7						
Day 14						
Day 21						
Day 28						
32wk PMA						
36wk PMA						
18-22m FU						

HEAD Circ	LOW Sat	HIGH Sat	p	LOW Sat	HIGH Sat	p
Birth						
Day 7						
Day 14						
Day 21						
Day 28						
32wk PMA						
36wk PMA						
18-22m FU						

PRIMARY OUTCOME:

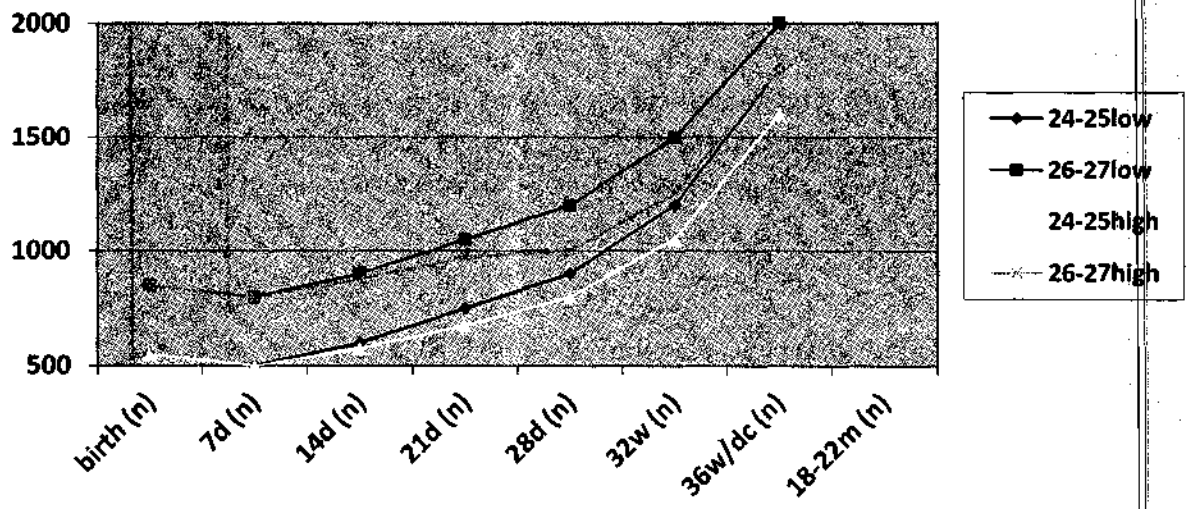
According to AGA and SGA status at birth

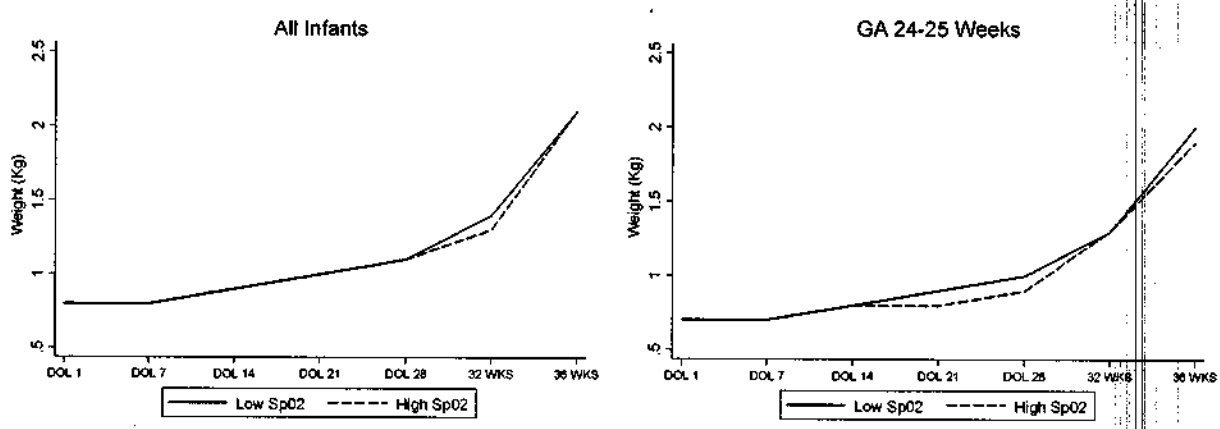
AGA:		LOW Sat	HIGH Sat	RR (95% CI)
36wk PMA	Death or wt<10^{tho}%ile			
	Wt <10^{tho}%ile			
18-22m F/U	Death or wt<10^{tho}%ile			
	Wt <10^{tho}%ile			
SGA:		**LOW Sat**	**HIGH Sat**	**RR (95% CI)**
36wk PMA	Death or wt<10th%ile			
	Wt <10th%ile			
18-22m F/U	Death or wt<10th%ile			
	Wt <10th%ile			

LONGITUDINAL GROWTH ANALYSIS <u>of survivors</u> (by hierarchical modeling and trajectory analysis) (Multilevel-regression analysis) similar to NICHD Ehrenkranz 1999 where weight is first analyzed over time and then by exposure. (FIGURE with plots of change in wt/time for each time period)

Trajectory analysis** **(Patel's exponential method, Pediatrics 2005)**, needs censoring method to analyze missing data from death cases, especially that there are more number of deaths in the low saturation group in the main trial

MOCK GRAPH:





In summary, in order to complete the presentation and the manuscript, we need the following:

1. A few more descriptive information
    a. Gender
    b. BPD severity
    c. Mean and SD values, 'n' for each time period (overall group and stratified)
    d. $<10^{th}$ percentile values for each time period (overall group and stratified)
2. Relative risk analysis according to AGA and SGA status at birth
3. Longitudinal growth analysis of survivors
    a. Hierarchical modeling analysis
    b. Trajectory analysis by exponential method

Please select Print from the file menu to print your Abstract.

First Author: Cristina T Navarrete, MD
Responsible Author: Cristina T Navarrete, MD
Presenting Author: Cristina T Navarrete, MD
Contact Person: Cristina T Navarrete, MD

Filename: 752262

2012 PAS Annual Meeting

Subspecialty: Neonatology - General
Theme: Neonatal Medicine: Clinical Trials

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Responsible Author Declaration: As the responsible author, I confirm that the individual listed as the sponsor has been contacted and given the opportunity to review the abstract and has subsequently agreed to sponsor this abstract.

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QUESTIONNAIRE INFORMATION

Eastern Society for Pediatric Research: No, Do not consider this abstract for the Eastern SPR
Pediatric Hospital Medicine: No, Do not consider this abstract for presentation at the Pediatric Hospital Medicine, July 19-22, 2012
Research Type: Clinical
Presentation Sabbath Conflict on: N/A
APA Special Interest Groups, Committees or Regions: None

AWARDS APPLIED FOR:

No awards selected

SPONSOR INFORMATION

Sponsoring Member for PAS/ASPR abstract:
Sponsor Name: Shahnaz Duara, MD
Email: sduara@med.miami.edu
Is the Sponsor an Author? Yes
Sponsoring Societies:
American Academy of Pediatrics

Society for Pediatric Research

Title: Growth Outcomes of Preterm Infants Exposed to Different Oxygen Saturation Target Ranges from Birth

Cristina T Navarrete, MD[1], Shahnaz Duara, MD[1] and Rosemary D Higgins, MD[2]. [1]University of Miami, Miami, FL, United States and [2]the SUPPORT Subcommittee of the NICHD Neonatal Research Network, Rockville, MD, United States

Background: Post-natal growth restriction is a major morbidity in preterm infants. Perturbations in oxygenation may influence somatic growth; a recent study showed that infants exposed to higher oxygen saturation (SpO_2) targets experience poorer growth (Tin, Arch Child Dis FN 2001). The Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial (SUPPORT) showed that a lower target range of SpO_2 from birth, as compared with a higher range, resulted in less retinopathy of prematurity in survivors but an increase in mortality (Carlo, NEJM 2010).

Objective: To test the hypotheses that infants kept in the low SpO_2 target range from birth will have better growth trajectories and better growth at 36 weeks and at 18-22 months corrected age (fewer babies <10th %ile for weight).

Design/Methods: A sub-cohort of 810 preterm infants enrolled in SUPPORT (n=1,316), randomized at birth to low (85-89%, n=402, GA 26.2 ± 1.1wks, BW 838.6 ± 186 gm) or high (91-95%, n=408, GA 26.2 ± 1.1wks, BW 839.6 ± 191gm) SpO_2 target range was studied. Anthropometric measures were obtained at birth, postnatal days 7, 14, 21, and 28, 32 and 36 weeks post-menstrual age, and at 18-22 months corrected age. Longitudinal growth trajectories were constructed for each target group using the means of each measure per time point. Poor growth (weight, length, head circumference <10th %ile) at 36 weeks and 18-22 months was analyzed using robust Poisson regression.

Results: Growth trajectories for Wt, L, and HC showed no differences in growth between the low and high SpO_2 assignment groups. There was no difference in mortality by 36 weeks and the rate of poor growth at 36 wks and at 18-22 month was not different for any measure.

Growth Outcomes by Assigned Groups

	Low SpO2 (n=402)	High SpO2 (n=408)	p-value
n (%) death by 36wk	69 (17.2)	60 (14.7)	0.32
n /N(%) with Wt <10th %ile at 36wk	155/333 (46.6)	172/342 (50.3)	0.30
n /N(%) with Wt <10th %ile at 18-22m	48/296 (16.2)	45/313 (14.4)	0.49
n /N(%) with L <10th %ile at 36wk	203/314 (64.7)	218/315 (69.2)	0.21
n /N(%) with L <10th %ile at 18-22m	79/296 (26.7)	98/313 (31.3)	0.28
n /N(%) with HC <10th %ile at 36wk	124/319 (38.9)	130/325 (40.0)	0.87
n /N(%) with HC <10th %ile at 18-22m	46/296 (15.5)	49/313 (15.7)	0.92

Conclusions: Early oxygen saturation target assignment did not impact on growth in a large subgroup of infants enrolled in the SUPPORT Trial.

Other Previews:

Abstract Disclosure Info: Disclosures

Close Window

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Blaisdell, Carol (NIH/NHLBI) [E]; Gail, Dorothy (NIH/NHLBI) [E]
Subject: RE: Breathing Outcomes PAS 2-21-2012.pdf - Adobe Acrobat Professional
Date: Wednesday, February 22, 2012 3:23:00 PM
Attachments: SUPPORT ABSTRACTS.docx

And here is the schedule of the SUPPORT PAS abstracts

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From: Blaisdell, Carol (NIH/NHLBI) [E]
Sent: Wednesday, February 22, 2012 3:21 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Gail, Dorothy (NIH/NHLBI) [E]
Subject: RE: Breathing Outcomes PAS 2-21-2012.pdf - Adobe Acrobat Professional

Thanks for sharing this Rose,
Tim Stevens Breathing Outcomes survey was adapted for PROP (our prematurity and respiratory outcomes program (Tim is a co-I on Gloria Pryhuber's grant). So, it is nice to know that (b)(5)
(b)(5)

Carol

Carol J. Blaisdell M.D.
Medical Officer
Lung Development and Pediatrics
Lung Biology and Diseases Branch
Division of Lung Diseases
NHLBI, NIH
301-435-0222

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, February 22, 2012 2:49 PM
To: Blaisdell, Carol (NIH/NHLBI) [E]; Gail, Dorothy (NIH/NHLBI) [E]
Subject: Breathing Outcomes PAS 2-21-2012.pdf - Adobe Acrobat Professional

Hi
I have attached a late breaker abstract from the breathing outcomes secondary study which is being submitted to PAS.

I will send out SUPPORT abstract schedule for PAS in a separate email.

Thanks
Rose

Susan Hintz	Brain MRI and Outcomes at 18–22 Months in Extremely Preterm Infants: The Neuroimaging and Neurodevelopmental Outcomes (NEURO) Cohort	Platform	1670 – Neonatal – Patient–Oriented Research: Neonatal Neurology	Saturday, April 28 2:45 PM	Ballroom B (Hynes Convention Center)	1670.1
Susan Hintz	Early and Late Cranial Ultrasound (CUS) To Predict 18–22 Month Outcomes in Extremely Preterm Infants: The Neuroimaging and Neurodevelopmental Outcomes (NEURO) Cohort	Platform	1670 – Neonatal – Patient–Oriented Research: Neonatal Neurology	Saturday, April 28 3:15 PM	Ballroom B (Hynes Convention Center)	1670.3
Cristina Navarrete:	Growth Outcomes of Preterm Infants Exposed to Different Oxygen Saturation Target Ranges from Birth	Platform	2755 – Neonatal – Patient–Oriented Research: Neonatal Nutrition	Sunday, April 29 2:00 PM	Ballroom B (Hynes Convention Center)	2755.5
Kathleen Kennedy	Evaluating Retinopathy of Prematurity (ROP) Screening Guidelines for 24–27 Week Gestational Age (GA) Infants	Sunday Poster session				
Yvonne Vaucher	Neurodevelopmental Outcome of Extremely Premature Infants Enrolled in the SUPPORT Trial: Early CPAP Versus Intubation with Surfactant Administration	Platform	4630 – Neonatal Medicine: Clinical Trials	Tuesday May 1 2:00 PM	Ballroom B (Hynes Convention Center)	4630.1
Myriam Peralta-Carcelen	Neurodevelopmental Outcome of Extremely Preterm Infants in a Trial of Different Oxygen Saturation Targ	Platform		Tuesday May 1 2:15 PM		4630.2

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Blaisdell, Carol (NIH/NHLBI) [E]; Gail, Dorothy (NIH/NHLBI) [E]
Subject: Breathing Outcomes PAS 2-21-2012.pdf - Adobe Acrobat Professional
Date: Wednesday, February 22, 2012 2:48:00 PM
Attachments: Breathing Outcomes PAS 2-21-2012.pdf

Hi
I have attached a late breaker abstract from the breathing outcomes secondary study which is being submitted to PAS.
I will send out SUPPORT abstract schedule for PAS in a separate email.

Thanks
Rose

Draft Preview of Late Breaking Abstract #450038
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First Author: Timothy P Stevens, MD, MPH
Responsible Author: Timothy P Stevens, MD, MPH
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Filename: 450038

2012 PAS Annual Meeting

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QUESTIONNAIRE INFORMATION

Research Type: Clinical
Reason why the November deadline could not be met:
Analysis had not been completed.

Title: Respiratory Outcomes of The NICHD SUPPORT Trial

Timothy P Stevens, MD, MPH[1] and for the Neonatal Research Network (NRN)[2]. [1]Pediatrics (Neonatology), Univ. of Rochester, Rochester, NY, United States and [2]The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), Bethesda, MD, United States.

Background: The NICHD SUPPORT Trial, a randomized trial using a 2x2 factorial design, compared initial therapy with either prophylactic surfactant or nasal CPAP (Surf v. CPAP) and low (85-89%) or high (91-95%) oxygen saturation targets (Low v. High Sat). Primary outcomes were reported in 2010.

Objective: The Breathing Outcomes Study (BOS), a secondary study to SUPPORT, tested the hypotheses that treatment with CPAP v. Surf or Low v. High Sat reduces the incidences of recurrent wheezing and chronic cough at 18-22m CA.

Design/Methods: Patients 24-27 6/7 wks gestation who were enrolled in SUPPORT were eligible to consent to the BOS. For each BOS patient, a validated questionnaire of respiratory symptoms, medication use and healthcare utilization was administered verbally to the subject's caregiver at 6, 12 and 18-22m CA. Questionnaire responses are reported as unadjusted results according to the primary treatment assignment of SUPPORT: Surf v. CPAP and Low v. High Sat.

Results: Of 1316 patients enrolled in SUPPORT, 1079 survived to hospital discharge and, of these, 922 (85.4%) consented to participate in BOS. Survey response rates exceeded 94% at each of the 6, 12 and 18-22m time points. As in SUPPORT, there were no differences between either Surf v. CPAP or Low v. High Sat in the incidence of either traditional BPD (oxygen at 36 wks) or physiologic BPD among pts in BOS. However, at 6m CA, patients treated with Low v. High Sat targets were less likely to have parental report of wheezy breathing (27.8% v. 36.4%, p< 0.04), documented wheezing (36.3% v. 43.4%, p<0.05) or use a home nebulizer (1.2% v. 3.9%, p<0.02). Differences in these outcomes or in incidence of chronic cough were not seen in the Surf v. CPAP groups at 6m or between either the Surf v. CPAP or Low v. High Sat groups at 12 or 18-22m CA. Hospitalization, physician visit and emergency department visit rates, overall and for respiratory conditions, were similar between the Surf v. CPAP and Low v. High Sat groups at each time point.

Conclusions: Preterm infants managed with Low compared with High Sat targets were less likely to have wheezing or use a home nebulizer at 6m CA. Differences in these outcomes were not seen at 12 and 18-22m CA. Based upon the finding of greater mortality with Low vs. High Sat targets seen in SUPPORT, the benefit of reduced wheezing and nebulizer use at 6m CA does not justify Low Sat targets in patients 24 - 27 6/7 wks gestation.

Analyses to adjust for baseline group differences are ongoing and may affect results.

Other Previews:

Abstract Disclosure Info: **Disclosures**

Print

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: Revised PAS Late Breaker - Breathing Outcomes Study
Date: Wednesday, February 22, 2012 2:44:00 PM
Attachments: Breathing Outcomes PAS 2-21-2012.pdf

Here is Tim's late breaker

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From: Stevens, Timothy [mailto:Timothy_Stevens@URMC.Rochester.edu]
Sent: Wednesday, February 22, 2012 1:56 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: Revised PAS Late Breaker - Breathing Outcomes Study

Hi Rose,

What steps must be taken before the abstract is approved for submission?

Thanks

Tim

From: Stevens, Timothy
Sent: Monday, February 20, 2012 12:09 PM
To: 'Higgins, Rosemary (NIH/NICHD) [E]'
Subject: RE: Revised PAS Late Breaker - Breathing Outcomes Study

Hi Rose,

I received 3 suggestions based on the second version of the abstract and have attempted to address them in a 3rd draft (attached).

As for your suggestion, I added to the conclusion "Analyses to adjust for baseline group differences are ongoing and may affect results". I also made the changes that Yvonne and Wally suggested.

I gained the space by being more parsimonious with the text and modifying the abbreviations.

Thanks

Tim

Rose
You need to state up front "unadjusted"
How about a statement in the conclusions that adjustment could affect results

Yvonne
Looks great, Reads very well.
Question: Should "Low v High Sat 'and' CPAP v Surf" in the Objective and Design sections be "Low v High Sat 'or' CPAP v Surf"? Although babies were assigned to both, the abstract doesn't explore any interaction. The use of 'and' may be confusing to the reader.

Wally
I think it is best to change the title from "Study" to "Trial".
You may want to spell out CA the first time you use the abbreviation.

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, February 17, 2012 3:13 PM
To: Stevens, Timothy
Subject: RE: Revised PAS Late Breaker - Breathing Outcomes Study

How about a statement in the conclusions that adjustment could affect results/
Thanks
Rose

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From: Stevens, Timothy [mailto:Timothy_Stevens@URMC.Rochester.edu]
Sent: Friday, February 17, 2012 10:16 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Revised PAS Late Breaker - Breathing Outcomes Study

I changed the sentence to this:

Questionnaire responses are reported as unadjusted results according to the primary treatment assignment of SUPPORT: Surf v. CPAP and Low v. High Sat.

Is this clear?

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, February 17, 2012 10:11 AM

To: Stevens, Timothy
Subject: RE: Revised PAS Late Breaker - Breathing Outcomes Study

NO
You need to state up front "unadjusted"

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From: Stevens, Timothy [mailto:Timothy_Stevens@URMC.Rochester.edu]
Sent: Friday, February 17, 2012 9:56 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Revised PAS Late Breaker - Breathing Outcomes Study

Hi Rose

In the version that you circulated, I attempted to address Abhik's suggestion with the following phrase:

"Questionnaire responses are reported here, without adjustment, according to the primary treatment assignment of SUPPORT: ....."

Is this strong enough?

Thanks

Tim

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, February 16, 2012 4:47 PM
To: Stevens, Timothy
Subject: RE: Revised PAS Late Breaker - Breathing Outcomes Study

Tim
I sent this through clearance. I also don't see that you specified these as unadjusted results as per Abhik's suggestion – please add this

Thanks
Rose

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From: Stevens, Timothy [mailto:Timothy_Stevens@URMC.Rochester.edu]
Sent: Thursday, February 16, 2012 3:10 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Revised PAS Late Breaker - Breathing Outcomes Study

Hi Rose,

Here is a revision of the Breathing Outcomes abstract for submission to PAS as a late breaker. In the revised version, I have attempted to address each of the comments that I received on the original draft (summarized below).

Can you please forward to the SUPPORT Subcommittee for review?

Thanks

Tim

Comments Received and Addressed

Neil Finer

- I would calculate the percent of survivors that you have in the BOC and add that number and state the actual number of infants in your study

- Also I would, for clarity, in the conclusion or somewhere indicate the increased death in the Low Sat arm to help make your final point

Wally Carlo

- I think it may be best to highlight the pulmonary benefits but add that despite these, low saturation targetting is not recommended because of the higher mortality.

- The first sentence of the Conclusion probably should address the respiratory outcomes in lower vs. higher sats groups better. You now state there was no difference but in the Results section address the differences. I agree with the final sentence saying lower sats cannot be recommended, obviously.

Roger Faix

- I would suggest taking the primary outcomes from the end of the Design/Methods section and

incorporating them into the Objective.

- I agree that the Results section is a bit difficult to unravel on the first reading. It may be better to begin Sentence 3 of the results with the report of no significant differences betweeen surf/CPAp groups at 6 months OR between surf/CPAP groups or hi/low sat groups at 12 or 18-22 months, THEN adding the brief observation of differences only at 6 months and only between the lo/hi sat groups.

Abbot Laptook

- Can the objective be used to state the original hypotheses?

Yvonne Vaucher

- In Results: Myriam's and my paper state a different total number of enrolled patients "1316 extremely preterm infants (24 weeks 0 days to 27 weeks 6 days) born between February 2005 and February 2009 at 20 centers..... The abstract states that " 1323 patients enrolled in SUPPORT...."

- Also- the sentence reading "..However, at 6 mo.....pts treated with low vs. high sat....might be a bit clearer as "...pts treated with low sat....were less likely to report less wheezing, etc.....compared to those treated with high sat.

Abhik Das

- These are all unadjusted analyses and the results may be subject to change upon adjustment, so I think that needs to be somewhere acknowledged in the abstract.

Draft Preview of Late Breaking Abstract #450038
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First Author: Timothy P Stevens, MD, MPH
Responsible Author: Timothy P Stevens, MD, MPH
Presenting Author: Timothy P Stevens, MD, MPH

Filename: 450038

2012 PAS Annual Meeting

Contact Author: Timothy P Stevens
Suffix: MD, MPH
Department/Institution/Address: Pediatrics (Neonatology), Univ. of Rochester, Golisano Children's Hospital, Box 651, 601 Elmwood Ave, Rochester, NY, 14642, United States
Phone: 585-275-2972 **Fax:** **E-mail:** timothy_stevens@urmc.rochester.edu

Reponsible Author: Timothy P Stevens, MD, MPH
Suffix: MD, MPH
Department/Institution/Address: Pediatrics (Neonatology), University of Rochester, Golisano Children's Hospital, Box 651, 601 Elmwood Ave, Rochester, NY, 14642, United States
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Phone: 585-275-2972 **Fax:**
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The presenting author is member of these Alliance Societies:
Is Presenting Author a Trainee? No, Not a Trainee
Presenter Copyright Declaration:

I certify that any material I will use, display, distribute, reproduce or have reproduced or distributed in connection with my above noted presentation for which I do not have permission to use, is my original work and/or is public information or another type of material which does not require securing permission from another party to use, display, distribute, reproduce or have reproduced or distributed.

QUESTIONNAIRE INFORMATION

Research Type: Clinical
Reason why the November deadline could not be met:
Analysis had not been completed.

Title: Respiratory Outcomes of The NICHD SUPPORT Trial

Timothy P Stevens, MD, MPH[1] and for the Neonatal Research Network (NRN)[2]. [1]Pediatrics (Neonatology), Univ. of Rochester, Rochester, NY, United States and [2]The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), Bethesda, MD, United States.

Background: The NICHD SUPPORT Trial, a randomized trial using a 2x2 factorial design, compared initial therapy with either prophylactic surfactant or nasal CPAP (Surf v. CPAP) and low (85-89%) or high (91-95%) oxygen saturation targets (Low v. High Sat). Primary outcomes were reported in 2010.

Objective: The Breathing Outcomes Study (BOS), a secondary study to SUPPORT, tested the hypotheses that treatment with CPAP v. Surf or Low v. High Sat reduces the incidences of recurrent wheezing and chronic cough at 18-22m CA.

Design/Methods: Patients 24-27 6/7 wks gestation who were enrolled in SUPPORT were eligible to consent to the BOS. For each BOS patient, a validated questionnaire of respiratory symptoms, medication use and healthcare utilization was administered verbally to the subject's caregiver at 6, 12 and 18-22m CA. Questionnaire responses are reported as unadjusted results according to the primary treatment assignment of SUPPORT: Surf v. CPAP and Low v. High Sat.

Results: Of 1316 patients enrolled in SUPPORT, 1079 survived to hospital discharge and, of these, 922 (85.4%) consented to participate in BOS. Survey response rates exceeded 94% at each of the 6, 12 and 18-22m time points. As in SUPPORT, there were no differences between either Surf v. CPAP or Low v. High Sat in the incidence of either traditional BPD (oxygen at 36 wks) or physiologic BPD among pts in BOS. However, at 6m CA, patients treated with Low v. High Sat targets were less likely to have parental report of wheezy breathing (27.8% v. 36.4%, $p< 0.04$), documented wheezing (36.3% v. 43.4%, $p<0.05$) or use a home nebulizer (1.2% v. 3.9%, $p<0.02$). Differences in these outcomes or in incidence of chronic cough were not seen in the Surf v. CPAP groups at 6m or between either the Surf v. CPAP or Low v. High Sat groups at 12 or 18-22m CA. Hospitalization, physician visit and emergency department visit rates, overall and for respiratory conditions, were similar between the Surf v. CPAP and Low v. High Sat groups at each time point.

Conclusions: Preterm infants managed with Low compared with High Sat targets were less likely to have wheezing or use a home nebulizer at 6m CA. Differences in these outcomes were not seen at 12 and 18-22m CA. Based upon the finding of greater mortality with Low vs. High Sat targets seen in SUPPORT, the benefit of reduced wheezing and nebulizer use at 6m CA does not justify Low Sat targets in patients 24 - 27 6/7 wks gestation.

Analyses to adjust for baseline group differences are ongoing and may affect results.

Other Previews:

Abstract Disclosure Info: **Disclosures**

Print

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Stevens, Timothy"
Subject: RE: Revised PAS Late Breaker - Breathing Outcomes Study
Date: Wednesday, February 22, 2012 2:00:00 PM

You should submit thanks
rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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From: Stevens, Timothy [mailto:Timothy_Stevens@URMC.Rochester.edu]
Sent: Wednesday, February 22, 2012 1:56 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: Revised PAS Late Breaker - Breathing Outcomes Study

Hi Rose,

What steps must be taken before the abstract is approved for submission?

Thanks

Tim

From: Stevens, Timothy
Sent: Monday, February 20, 2012 12:09 PM
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Is this clear?

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- These are all unadjusted analyses and the results may be subject to change upon adjustment, so I think that needs to be somewhere acknowledged in the abstract.

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Das, Abhik"
Subject: FW: Revised PAS Late Breaker - Breathing Outcomes Study
Date: Wednesday, February 22, 2012 1:56:00 PM
Attachments: Breathing Outcomes PAS 2-21-2012.pdf

Are you ok with this?

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From: Roger Faix
To: timothy_stevens@urmc.rochester.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: Most recent draft of Late-breaker abstract
Date: Tuesday, February 21, 2012 1:36:26 PM

Hi Tim!

I misspelled your name on the e-mail address on my first attempt to send you the message below. Mea culpa! I hope this second attempt is successful.

Roger

From: Roger Faix
Sent: Tuesday, February 21, 2012 11:33 AM
To: timothy_stephens@urmc.rochester.edu
Cc: higginsr@mail.nih.gov
Subject: Most recent draft of Late-breaker abstract

Hi Tim!

I had the chance to review the most recent draft of your late-breaker abstract this past weekend, and would like to offer the following comment:

Maybe it's just me, but it was not obvious to me for a while that you were comparing the incidence of recurrent wheezing and chronic cough at 18-22 mos. CA in two ways: 1) low vs high sat, and 2) CPAP vs surf. For some reason, I initially thought that you were comparing the outcome between the two arms. As I read further, it became evident that I was incorrect and what you actually did became evident. I might suggest that you consider changing the wording of the Objective to make it more clear what was being done in the analysis.

Again, I realize this response may merely reflect my own issues, but I thought you may want to hear it in any event. The work will clearly be a worthwhile contribution to the literature!

Roger

From: Vaucher, Yvonne
To: Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; "Wally Carlo, M.D."; Kurt Schibler [kurt.schibler@cchmc.org]; Michele Walsh; Roger.Faix@hsc.utah.edu; "alaptook@wihri.org"; "Myriam Peralta, M.D."; Abhik Das; Gantz, Marie; nancy newman; Rich, Wade
Cc: "Stevens, Timothy"
Subject: RE: URGENT REQUEST: Revised PAS Late Breaker - Breathing Outcomes Study
Date: Saturday, February 18, 2012 12:44:03 AM

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Sent: Thursday, February 16, 2012 1:22 PM
To: Finer, Neil; 'Wally Carlo, M.D.'; Kurt Schibler [kurt.schibler@cchmc.org]; Michele Walsh; Roger.Faix@hsc.utah.edu; 'alaptook@wihri.org'; Vaucher, Yvonne; 'Myriam Peralta, M.D.'; Abhik Das; Gantz, Marie; nancy newman; Rich, Wade
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Cc: "Stevens, Timothy"
Subject: Re: URGENT REQUEST: Revised PAS Late Breaker - Breathing Outcomes Study
Date: Friday, February 17, 2012 12:34:41 PM
Importance: High

This looks very good
Nice work Tim
Neil

From: Rosemary Higgins <higginsr@mail.nih.gov<mailto:higginsr@mail.nih.gov>>
Date: Thu, 16 Feb 2012 13:22:44 -0800
To: Neil Finer <nfiner@ucsd.edu<mailto:nfiner@ucsd.edu>>, Wally Carlo <wcarlo@peds.uab.edu<mailto:wcarlo@peds.uab.edu>>, "kurt.schibler@cchmc.org<mailto:kurt.schibler@cchmc.org>" <kurt.schibler@cchmc.org<mailto:kurt.schibler@cchmc.org>>, Michele Walsh <mcw3@cwru.edu<mailto:mcw3@cwru.edu>>, Roger Faix <Roger.Faix@hsc.utah.edu<mailto:Roger.Faix@hsc.utah.edu>>, Abbot Laptook <ALaptook@WIHRI.org<mailto:ALaptook@WIHRI.org>>, Yvonne Vaucher <yvaucher@ucsd.edu<mailto:yvaucher@ucsd.edu>>, "'Myriam Peralta, M.D.'" <MPeralta@peds.uab.edu<mailto:MPeralta@peds.uab.edu>>, Abhik Das <adas@rti.org<mailto:adas@rti.org>>, Marie Gantz <mgantz@rti.org<mailto:mgantz@rti.org>>, nancy newman <nxs5@case.edu<mailto:nxs5@case.edu>>, Wade Rich <wrich@ucsd.edu<mailto:wrich@ucsd.edu>>
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For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov<mailto:higginsr@mail.nih.gov>

From: Stevens, Timothy [mailto:Timothy_Stevens@URMC.Rochester.edu]
Sent: Thursday, February 16, 2012 3:10 PM
To: Higgins, Rosemary (NIH/NICHD) [E]

Subject: Revised PAS Late Breaker - Breathing Outcomes Study

Hi Rose,

Here is a revision of the Breathing Outcomes abstract for submission to PAS as a late breaker. In the revised version, I have attempted to address each of the comments that I received on the original draft (summarized below).

Can you please forward to the SUPPORT Subcommittee for review?

Thanks

Tim

Comments Received and Addressed

Neil Finer

* I would calculate the percent of survivors that you have in the BOC and add that number and state the actual number of infants in your study

* Also I would, for clarity, in the conclusion or somewhere indicate the increased death in the Low Sat arm to help make your final point

Wally Carlo

* I think it may be best to highlight the pulmonary benefits but add that despite these, low saturation targetting is not recommended because of the higher mortality.

* The first sentence of the Conclusion probably should address the respiratory outcomes in lower vs. higher sats groups better. You now state there was no difference but in the Results section address the differences. I agree with the final sentence saying lower sats cannot be recommended, obviously.

Roger Faix

I would suggest taking the primary outcomes from the end of the Design/Methods section and incorporating them into the Objective.

I agree that the Results section is a bit difficult to unravel on the first reading. It may be better to begin Sentence 3 of the results with the report of no significant differences betweeen surf/CPAp groups at 6 months OR between surf/CPAP groups or hi/low sat groups at 12 or 18-22 months, THEN adding the brief observation of differences only at 6 months and only between the lo/hi sat groups.

Abbot Laptook

* Can the objective be used to state the original hypotheses?

Yvonne Vaucher

* In Results: Myriam's and my paper state a different total number of enrolled patients "1316 extremely preterm infants (24 weeks 0 days to 27 weeks 6 days) born between February 2005 and February 2009 at 20 centers..... The abstract states that " 1323 patients enrolled in SUPPORT...."

* Also- the sentence reading "..However, at 6 mo.....pts treated with low vs. high sat....might be a bit clearer as "...pts treated with low sat....were less likely to report less wheezing, etc.....compared to those treated with high sat.

Abhik Das

* These are all unadjusted analyses and the results may be subject to change upon adjustment; so I think that needs to be somewhere acknowledged in the abstract.

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Das, Abhik"
Subject: FW: Revised PAS Late Breaker - Breathing Outcomes Study
Date: Friday, February 17, 2012 10:26:00 AM

Is this acceptable?>

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
6100 Executive Blvd., Room 4B03
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For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Stevens, Timothy [mailto:Timothy_Stevens@URMC.Rochester.edu]
Sent: Friday, February 17, 2012 10:16 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Revised PAS Late Breaker - Breathing Outcomes Study

I changed the sentence to this:

Questionnaire responses are reported as unadjusted results according to the primary treatment assignment of SUPPORT: Surf v. CPAP and Low v. High Sat.

Is this clear?

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, February 17, 2012 10:11 AM
To: Stevens, Timothy
Subject: RE: Revised PAS Late Breaker - Breathing Outcomes Study

NO
You need to state up front "unadjusted"

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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higginsr@mail.nih.gov

From: Stevens, Timothy [mailto:Timothy_Stevens@URMC.Rochester.edu]
Sent: Friday, February 17, 2012 9:56 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Revised PAS Late Breaker - Breathing Outcomes Study

Hi Rose

In the version that you circulated, I attempted to address Abhik's suggestion with the following phrase:

"Questionnaire responses are reported here, without adjustment, according to the primary treatment assignment of SUPPORT: ....."

Is this strong enough?

Thanks

Tim

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, February 16, 2012 4:47 PM
To: Stevens, Timothy
Subject: RE: Revised PAS Late Breaker - Breathing Outcomes Study

Tim
I sent this through clearance. I also don't see that you specified these as unadjusted results as per Abhik's suggestion – please add this

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Stevens, Timothy [mailto:Timothy_Stevens@URMC.Rochester.edu]
Sent: Thursday, February 16, 2012 3:10 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Revised PAS Late Breaker - Breathing Outcomes Study

higher sats groups better. You now state there was no difference but in the Results section address the differences. I agree with the final sentence saying lower sats cannot be recommended, obviously.

Roger Faix

- I would suggest taking the primary outcomes from the end of the Design/Methods section and incorporating them into the Objective.

- I agree that the Results section is a bit difficult to unravel on the first reading. It may be better to begin Sentence 3 of the results with the report of no significant differences betweeen surf/CPAp groups at 6 months OR between surf/CPAP groups or hi/low sat groups at 12 or 18-22 months, THEN adding the brief observation of differences only at 6 months and only between the lo/hi sat groups.

Abbot Laptook

- Can the objective be used to state the original hypotheses?

Yvonne Vaucher

- In Results: Myriam's and my paper state a different total number of enrolled patients "1316 extremely preterm infants (24 weeks 0 days to 27 weeks 6 days) born between February 2005 and February 2009 at 20 centers..... The abstract states that " 1323 patients enrolled in SUPPORT...."

- Also- the sentence reading "..However, at 6 mo.....pts treated with low vs. high sat....might be a bit clearer as "...pts treated with low sat....were less likely to report less wheezing, etc.....compared to those treated with high sat.

Abhik Das

- These are all unadjusted analyses and the results may be subject to change upon adjustment, so I think that needs to be somewhere acknowledged in the abstract.

From: Walsh, Michele
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Stevens, Timothy
Subject: RE: URGENT REQUEST: Revised PAS Late Breaker - Breathing Outcomes Study
Date: Thursday, February 16, 2012 4:46:16 PM

Looks great Tim. I think we are supposed to use the term PMA rather than CA. Otherwise, maybe add the word "transient" to The concludions- .... The transient reduction in wheezing, and nebulizer at 6m,....

Michele Walsh, MD
Chief, Division of Neonatology
216.844.3759

It's not what you look at that matters, it's what you see. Thoreau

---

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, February 16, 2012 4:23 PM
To: nfiner@ucsd.edu; 'Wally Carlo, M.D.'; Kurt Schibler [kurt.schibler@cchmc.org]; Michele Walsh; Roger.Faix@hsc.utah.edu; 'alaptook@wihri.org'; 'Vaucher, Yvonne'; 'Myriam Peralta, M.D.'; Abhik Das; Gantz, Marie; nancy newman; wrich@ucsd.edu
Cc: 'Stevens, Timothy'
Subject: URGENT REQUEST: Revised PAS Late Breaker - Breathing Outcomes Study
Importance: High

Here is the updated PAS late breaker from breathing outcomes as well as the comments previously received.

Please send comments back to Tim Steven's (Cc'd) by Monday Feb 20. The abstract must be submitted by Friday, Feb. 24

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "nfiner@ucsd.edu"; "Wally Carlo, M.D."; "Kurt Schibler [kurt.schibler@cchmc.org]"; "Michele Walsh"; "Roger.Faix@hsc.utah.edu"; "alaptook@wihri.org"; "Vaucher, Yvonne"; "Myriam Peralta, M.D."; "Abhik Das"; "Gantz, Marie"; "nancy newman"; "wrich@ucsd.edu"
Cc: "Stevens, Timothy"
Subject: URGENT REQUEST: Revised PAS Late Breaker - Breathing Outcomes Study
Date: Thursday, February 16, 2012 4:22:00 PM
Attachments: Breathing Outcomes PAS 2-16-2012.pdf
Importance: High

Here is the updated PAS late breaker from breathing outcomes as well as the comments previously received.

Please send comments back to Tim Steven's (Cc'd) by Monday Feb 20. The abstract must be submitted by Friday, Feb. 24

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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From: Stevens, Timothy [mailto:Timothy_Stevens@URMC.Rochester.edu]
Sent: Thursday, February 16, 2012 3:10 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
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Neil Finer

- I would calculate the percent of survivors that you have in the BOC and add that number and state the actual number of infants in your study

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Abhik Das

- These are all unadjusted analyses and the results may be subject to change upon adjustment; so I think that needs to be somewhere acknowledged in the abstract.

Draft Preview of Late Breaking Abstract #450038
THIS COPY IS A DRAFT ONLY. YOUR FINAL PRINTOUT WILL BE AVAILABLE AT TIME OF SUBMISSION

First Author: Timothy P Stevens, MD, MPH
Responsible Author: Timothy P Stevens, MD, MPH
Presenting Author: Timothy P Stevens, MD, MPH

Filename: 450038

2012 PAS Annual Meeting

Contact Author: Timothy P Stevens
Suffix: MD, MPH
Department/Institution/Address: Pediatrics (Neonatology), Univ. of Rochester, Golisano Children's Hospital, Box 651, 601 Elmwood Ave, Rochester, NY, 14642, United States
Phone: 585-275-2972 **Fax:** **E-mail:** timothy_stevens@urmc.rochester.edu

Reponsible Author: Timothy P Stevens, MD, MPH
Suffix: MD, MPH
Department/Institution/Address: Pediatrics (Neonatology), University of Rochester, Golisano Children's Hospital, Box 651, 601 Elmwood Ave, Rochester, NY, 14642, United States
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Responsible Author E-mail: timothy_stevens@urmc.rochester.edu

Presenting Author: Timothy P Stevens, MD, MPH
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Department/Institution/Address: Pediatrics (Neonatology), University of Rochester, Golisano Children's Hospital, Box 651, 601 Elmwood Ave, Rochester, NY, 14642, United States
Phone: 585-275-2972 **Fax:**
Presenting Author E-mail: timothy_stevens@urmc.rochester.edu
The presenting author is member of these Alliance Societies:
Is Presenting Author a Trainee? No, Not a Trainee
Presenter Copyright Declaration:
I certify that any material I will use, display, distribute, reproduce or have reproduced or distributed in connection with my above noted presentation for which I do not have permission to use, is my original work and/or is public information or another type of material which does not require securing permission from another party to use, display, distribute, reproduce or have reproduced or distributed.

QUESTIONNAIRE INFORMATION
Research Type: Clinical
Reason why the November deadline could not be met:
Analysis had not been completed.

Title: Respiratory Outcomes of The NICHD SUPPORT Study

Timothy P Stevens, MD, MPH[1] and for the Neonatal Research Network (NRN)[2]. [1]Pediatrics (Neonatology), Univ. of Rochester, Rochester, NY, United States and [2]The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), Bethesda, MD, United States.

Background: The NICHD SUPPORT Trial, a randomized trial using a 2x2 factorial design, compared initial respiratory therapy with either prophylactic surfactant or nasal CPAP (Surf v. CPAP) and low (85-89%) or high (91-95%) oxygen saturation targets (Low v. High Sat). Primary outcomes were reported in 2010.

Objective: The Breathing Outcomes Study (BOS), a secondary study to SUPPORT, sought to test the hypotheses that treatment with Low v. High Sat and CPAP v. Surf reduces the incidences of recurrent wheezing and chronic cough at 18-22 m. CA.

Design/Methods: Patients 24-27 6/7 wks gestation who were enrolled in SUPPORT were given the option to consent to the BOS. For each BOS patient, a validated questionnaire of respiratory symptoms, medication use and healthcare utilization was administered verbally to the subject's parent or caregiver at 6, 12 and 18-22 m. CA. Questionnaire responses are reported here, without adjustment, according to the primary treatment assignment of SUPPORT: Surf v. CPAP and Low v. High Sat.

Results: Of 1316 patients enrolled in SUPPORT, 1079 survived to hospital discharge and, of these, 922 (85.4%) consented to participate in BOS. Survey response rates exceeded 94% at each of the 6, 12 and 18-22 m. time points. As seen in SUPPORT, there were no differences between either Surf v. CPAP or Low v. High Sat in the incidence of either traditional BPD (oxygen at 36 wks) or physiologic BPD among pts in BOS. However, at 6 m. CA, patients treated with Low v. High Sat targets were less likely to have parental report of wheezy breathing (27.8% v. 36.4%, p< 0.04), documented wheezing (36.3% v. 43.4%, p<0.05) or use a home nebulizer (1.2% v. 3.9%, p<0.02). Differences in these outcomes or in incidence of chronic cough were not seen in the Surf v. CPAP groups at 6 m. or between either the Surf v. CPAP or Low v. High Sat groups at 12 or 18-22 m. CA. Hospitalization, physician visit and emergency department visit rates, overall and for respiratory conditions, were similar between the Surf v. CPAP and Low v. High Sat groups at each time point.

Conclusions: Extremely preterm infants managed with Low compared with High Sat targets were less likely to have wheezing or use a home nebulizer at 6 months CA. Differences in these outcomes were not seen at 12 and 18-22 m. CA. Based upon the finding of greater mortality with Low vs. High Sat targets seen in SUPPORT, the benefit of reduced wheezing and nebulizer use at 6 m. CA does not justify low oxygen saturation targets in patients 24 - 27 6/7 wks gestation.

Other Previews:

Abstract Disclosure Info: **Disclosures**

Print

From: Roger Faix
To: Laptook, Abbot; Wally Carlo, M.D.; Finer, Neil; Archer, Stephanie (NIH/NICHD) [E]; adas@rti.org; Bradley Yoder; kzaterka@rti.org; kurt.schibler@cchmc.org; mgantz@rti.org; mcw3@cwru.edu; nxs5@cwru.edu; Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade; wacarlo@uab.edu
Cc: Timothy_Stevens@URMC.Rochester.edu; Myriam Peralta, M.D.; Vaucher, Yvonne
Subject: RE: PAS Late-Breaker Abstract | SUPPORT Breathing Outcomes
Date: Wednesday, February 15, 2012 11:36:11 AM

Hi all!

Congrats on your productive hard work, Tim!

I agree with the statements made previously by Abbot, Neil, Wally and Yvonne.

I would suggest taking the primary outcomes from the end of the Design/Methods section and incorporating them into the Objective.

I agree that the Results section is a bit difficult to unravel on the first reading. It may be better to begin Sentence 3 of the results with the report of no significant differences betweeen surf/CPAp groups at 6 months OR between surf/CPAP groups or hi/low sat groups at 12 or 18-22 months, THEN adding the brief observation of differences only at 6 months and only between the lo/hi sat groups.

I believe the conclusions are appropriate and not at all confusing.

Best of luck!!

Roger

From: Laptook, Abbot [ALaptook@WIHRI.org]
Sent: Thursday, February 09, 2012 3:41 PM
To: Wally Carlo, M.D.; Finer, Neil; Archer, Stephanie (NIH/NICHD) [E]; adas@rti.org; Bradley Yoder; kzaterka@rti.org; kurt.schibler@cchmc.org; mgantz@rti.org; mcw3@cwru.edu; nxs5@cwru.edu; nxs5@cwru.edu; Roger Faix; Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade; wacarlo@uab.edu
Cc: Timothy_Stevens@URMC.Rochester.edu; Myriam Peralta, M.D.; Vaucher, Yvonne
Subject: RE: PAS Late-Breaker Abstract | SUPPORT Breathing Outcomes

Tim
Very nice abstract. Can the objective be used to state the original hypotheses? Otherwise agree with Neal and Wally. Tx, AL

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Thursday, February 09, 2012 3:14 PM
To: Finer, Neil; Archer, Stephanie (NIH/NICHD) [E]; Laptook, Abbot; adas@rti.org; Bradley.yoder@hsc.utah.edu; kzaterka@rti.org; kurt.schibler@cchmc.org; mgantz@rti.org; mcw3@cwru.edu; nxs5@cwru.edu; nxs5@cwru.edu; roger.faix@hsc.utah.edu; Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade; wacarlo@uab.edu
Cc: Timothy_Stevens@URMC.Rochester.edu; Myriam Peralta, M.D.; Vaucher, Yvonne
Subject: RE: PAS Late-Breaker Abstract | SUPPORT Breathing Outcomes

Hi Tim:

Excellent job drafting the abstract. The first sentence of the Conclusion probably should address the respiratory outcomes in lower vs. higher sats groups better. You now state there was no difference but in the Results section address the differences. I agree with the final sentence saying lower sats cannot be recommended, obviously.

Wally

From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Thu 2/9/2012 9:39 AM
To: Archer, Stephanie (NIH/NICHD) [E]; Abbot Laptook (alaptook@wihri.org); Abhik Das (adas@rti.org); 'Brad Yoder (Bradley.yoder@hsc.utah.edu)'; Kristin Zaterka-Baxter (kzaterka@rti.org); Kurt Schibler (kurt.schibler@cchmc.org); Marie Gantz (mgantz@rti.org); 'Michele Walsh (mcw3@cwru.edu)'; 'Nancy Newman (nxs5@cwru.edu)'; Nancy Newman (nxs5@cwru.edu); Roger Faix (roger.faix@hsc.utah.edu); Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade; 'Wally Carlo (wacarlo@uab.edu)'
Cc: Tim Stevens (Timothy_Stevens@URMC.Rochester.edu); Myriam Peralta, M.D.; Vaucher, Yvonne
Subject: RE: PAS Late-Breaker Abstract | SUPPORT Breathing Outcomes

Hi Tim
This looks good
I would calculate the percent of survivors that you have in the BOC and add that number and state the actual number of infants in your study
You do state the number consented – is this the same as the number who participated- If so you are only missing about 46 infants – I would include the actual number in your study and the number as a percent of survivors – that N = 990 in follow-up out of a total of 1058 survivors - beside your N – it looks to me like you have >95% of survivors and I think this is important
Also I would, for clarity, in the conclusion or somewhere indicate the increased death in the Low Sat arm to help make your final point
Nice work Tim and Thanks for leading this study
Be well
Neil

From: Archer, Stephanie (NIH/NICHD) [E] [mailto:archerst@mail.nih.gov]
Sent: Thursday, February 09, 2012 7:12 AM
To: Abbot Laptook (alaptook@wihri.org); Abhik Das (adas@rti.org); 'Brad Yoder (Bradley.yoder@hsc.utah.edu)'; Kristin Zaterka-Baxter (kzaterka@rti.org); Kurt Schibler (kurt.schibler@cchmc.org); Marie Gantz (mgantz@rti.org); 'Michele Walsh (mcw3@cwru.edu)'; 'Nancy Newman (nxs5@cwru.edu)'; Nancy Newman (nxs5@cwru.edu); Finer, Neil; Roger Faix (roger.faix@hsc.utah.edu); Higgins, Rosemary (NIH/NICHD) [E]; Archer, Stephanie (NIH/NICHD) [E]; Rich, Wade; 'Wally Carlo (wacarlo@uab.edu)'
Cc: Tim Stevens (Timothy_Stevens@URMC.Rochester.edu); Myriam Peralta-Carcelen (MPeralta@peds.uab.edu); Vaucher, Yvonne
Subject: PAS Late-Breaker Abstract | SUPPORT Breathing Outcomes

Attached is Tim Stevens Pulmonary Outcomes abstract that he would like to submit as a late-breaker to PAS.

Please send any comments back to Tim, Myriam, and Yvonne by **February 15, 2012**.

Thank you,

Stephanie

Stephanie Wilson Archer
The Eunice Kennedy Shriver
National Institute of Child Health and Human Development
Pregnancy & Perinatology Branch
6100 Executive Boulevard, Room 4B03

Rockville, MD 20852

Tel. 301-496-0430
Fax 301-496-3790
archerst@mail.nih.gov

From: Stevens, Timothy [mailto:Timothy_Stevens@URMC.Rochester.edu]
Sent: Wednesday, February 08, 2012 08:40 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Breathing Outcomes

Hi Rose

Here is a first draft of a late breaker abstract for the Breathing Outcomes Study. The abstract is at 99.38% of the allowed length.

Can you please forward to the SUPPORT subcommittee?

Thank you

Tim

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)
Date: Tuesday, February 14, 2012 9:26:00 AM
Attachments: IRB Approval SUPPORT 2012 Tufts.pdf

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
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301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Testa, Veronika [mailto:vtesta@tuftsmedicalcenter.org]
Sent: Tuesday, February 14, 2012 9:20 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: McGowan, Elisabeth C
Subject: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)

Hello Rose,

We have received IRB approval for 2012 for the above-mentioned study. I've attached a pdf copy for your files.

Best,
Veronika

Veronika Testa, BSN, RN, CCRC
Project Manager
Tufts Medical Center
800 Washington Street, Box 391
Boston, MA 02111
☎: 617.636.2379 | 🖷: 617.636.8329
✉: vtesta@tuftsmedicalcenter.org

800 Washington Street, Box 817
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tel 617.636.7512
fax 617.636.8394
http://tnemcinb.tufts.edu

Tufts | Health Sciences

Health Sciences Campus Institutional Review Board

NOTICE OF IRB APPROVAL - CONTINUING REVIEW

Elisabeth McGowan, MD
Box 44
Tufts Medical Center
Boston, MA 02111

IRB #: 7856

Title: The Surfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT) in Extremely Low Birth Weight Infants

Date of IRB Review: 02/02/2012
Date of IRB Approval: 02/02/2012
IRB Approval Valid Until: 02/01/2013

Protocol approved: An Antenatal Screening and Consent in a Research Network Model Version Dated: 06 October 2005, Breathing Outcomes Study Protocol Version Dated: 06 December 2005; Neuroimaging and Neurodevelopmental Outcome Version Dated: 17 June 2005; Post-natal Growth of Infants Enrolled in the NICHD Neonatal Network Oxygen Saturation (SUPPORT) Study Version Dated: 26 January 2006; Follow-Up Study Version Dated: 31 October 2007 (all received 20 December 2011)

-as closed to subject enrollment x

- The above referenced-research was reviewed and approved using expedited review procedures in accordance with 45 CFR 46.110(b)(8)(c).
- Receipt of grant documentation, *Notice of Award* issued 10 October 2006 (received 20 December 2011) was acknowledged.

Informed Consent Form(s): N/A

Human Protection Form for Funding Agency:
-enclosed x

Regulations regarding your research protocol:

1. The approval is valid for one (1) year from the date of review (unless otherwise stipulated by the IRB).
2. Unanticipated problems are to be reported to the IRB within five (5) business days. Other internal SAEs and any external SAEs requiring protocol and/or ICF changes are to be reported to the IRB within fifteen (15) business days. All other external SAEs and internal non-serious situations may be summarized and submitted at continuing review. Further details may be found in the Unanticipated Problem and Adverse Event Reporting policy on the IRB website.
3. Any changes or modifications in the study protocol or consent form must be reviewed and approved by the IRB prior to implementation.
4. You may not use the ICF or any other study document until it has been approved and validated by the IRB.
5. If you are subject to HIPAA, the Security Rule applies to your research. If you create, store, or transmit electronic PHI you must meet institutional Security Rule standards. For more information, please contact your HIPAA Privacy Officer for Research.

THIS NOTICE MUST BE RETAINED WITH YOUR RESEARCH FILES.

2/9/12
Date

Susan Hadley MD
Signature of Chair/Vice-Chair
Institutional Review Board (IRB)

/CMC

OMB No. 0990-0263
Approved for use through 11/30/2008

Protection of Human Subjects
Assurance Identification/IRB Certification/Declaration of Exemption
(Common Rule)

Policy: Research activities involving human subjects may not be conducted or supported by the Departments and Agencies adopting the Common Rule (56FR28003, June 18, 1991) unless the activities are exempt from or approved in accordance with the Common Rule. See section 101(b) of the Common Rule for exemptions. Institutions submitting applications or proposals for support must submit certification of appropriate Institutional Review Board (IRB) review and approval to the Department or Agency in accordance with the Common Rule. Institutions must have an assurance of compliance that applies to the research to be conducted and should submit certification of IRB review and approval with each application or proposal unless otherwise advised by the Department or Agency.

1. Request Type	2. Type of Mechanism	3. Name of Federal Department or Agency and, if known, Application or Proposal Identification No.
[ ] ORIGINAL [X] CONTINUATION [ ] EXEMPTION	[X] GRANT [ ] CONTRACT [ ] FELLOWSHIP [ ] COOPERATIVE AGREEMENT [ ] OTHER:_____	

4. Title of Application or Activity	5. Name of Principal Investigator, Program Director, Fellow, or Other
The Surfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT) in Extremely Low Birth Weight Infants	**McGowan, Elisabeth MD** **Pediatrics: Newborn** **Tufts MC** **IRB #: 7856**

6. Assurance Status of this Project *(Respond to one of the following)*

[X] This Assurance, on file with Department of Health and Human Services, covers this activity:
Assurance Identification No. **FWA00004449** the expiration date **5/24/2014** IRB Registration No. **IORG0000435**

[ ] This Assurance, on file with *(agency/dept)*_____, covers this activity.
Assurance No._____, the expiration date_____ IRB Registration/Identification No._____ *(if applicable)*

[ ] No assurance has been filed for this institution. This institution declares that it will provide an Assurance and Certification of IRB review and approval upon request.

[ ] Exemption Status: Human subjects are involved, but this activity qualifies for exemption under Section 101(b), paragraph_____.

7. Certification of IRB Review (Respond to one of the following IF you have an Assurance on file)

[ ] This activity has been reviewed and approved by the IRB in accordance with the Common Rule and any other governing regulations.
by: [ ] Full IRB Review on (date of IRB meeting) _____or [X] Expedited Review on (date) **2/2/2012**
[ ] If less than one year approval, provide expiration date _____

[ ] This activity contains multiple projects, some of which have not been reviewed. The IRB has granted approval on condition that all projects covered by the Common Rule will be reviewed and approved before they are initiated and that appropriate further certification will be submitted.

8. Comments

9. The official signing below certifies that the information provided above is correct and that, as required, future reviews will be performed until study closure and certification will be provided.	10. Name and Address of Institution
11. Phone No. *(with area code)* **617.636.7512**	**Tufts Medical Center** **800 Washington Street** **Boston, MA 02111**
12. Fax No. *(with area code)* **617.636.8394**	
13. Email: **AKlein2@tuftsmedicalcenter.org**	
14. Name of Official **Andreas K. Klein, MD**	15. Title **IRB Chair**
16. Signature [signature]	17. Date **2/3/2012**

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AP 2/3/12

From: Stevens, Timothy
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Late Breaker Submission - 2012 PAS Annual Meeting
Date: Monday, February 13, 2012 7:01:32 PM

Yes, I'll have it to you by Thursday

Thanks

Tim

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, February 10, 2012 2:10 PM
To: Stevens, Timothy
Cc: 'adas@rti.org'; Archer, Stephanie (NIH/NICHD) [E]
Subject: Fw: Late Breaker Submission - 2012 PAS Annual Meeting

This is sooner than I thought - can we get a revision late next week for nichd clearance?
Thanks
Rose

From: PAS Central Office [mailto:info@pas-meeting.org]
Sent: Friday, February 10, 2012 01:09 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Late Breaker Submission - 2012 PAS Annual Meeting

PAS Program Office
3400 Research Dr., Suite B7
The Woodlands, TX 77381
Phone: 281.419.0052
Email: info@pas-meeting.org
URL: www.pas-meeting.org

CALL FOR LATE-BREAKING ABSTRACT SUBMISSIONS

The Pediatric Academic Societies is pleased to announce a call for Late-Breaking Abstracts for the 2012 PAS Annual Meeting in Boston, Massachusetts, April 28 - May 1. **The deadline for submissions is Friday, February 24, 2012, 4:00pm Central Time.**

The PAS Program Committee invites investigators to submit the results of their research for consideration for presentation at a special Late-Breaker session. The purpose of the Late-Breaker Session is to ensure that the results of very recent, important clinical trials and scientific discoveries are presented at the 2012 Pediatric Academic Societies Annual Meeting.

To qualify for presentation at a Late-Breaker Session, a clinical trial described in an abstract should be a major one that is likely to have a significant impact on clinical practice and for which the data were not available by the regular abstract deadline of November 17, 2011. Similarly, a scientific discovery described in an abstract submitted for a Late-Breaker Session should represent a major advance in its field with the critical experiment(s) performed after the regular abstract deadline of November 17, 2011.

To assist the reviewers in determining that abstracts qualify for a Late-Breaker Session, submitting authors are required to provide information documenting why their work qualifies using the criteria note above.

All abstracts will undergo peer review and scoring similar to other abstracts, and the PAS Program Committee reserves the right to decide whether the abstracts are appropriate for inclusion in the Late-Breaker Session. We anticipate that the acceptance rate for Late-Breaker Sessions will be lower than that for regular submissions. The Program Committee reserves the right to decide, based on the number, quality, and potential impact of the submissions and the space available in the Convention Center, whether to hold one or more Late-Breaker Sessions.

Visit the PAS website to begin your online submission. A fee of $50.00 is required for each submission. Notification of abstract acceptance status will be on or before April 1st.

Contact the PAS at info@pas-meeting.org or 281-419-0052 if you have any questions.

From: Higgins, Rosemary (NIH/NICHD) [E]
To: JF126@notes.duke.edu
Cc: goldb008@mc.duke.edu; Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin (kzaterka@rti.org)
Subject: FW: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)
Date: Monday, February 13, 2012 3:48:00 PM
Importance: High

Joanne
Both Stephanie and Kris had told me you asked for information regarding the OHRP request for the SUPPORT consent forms – below is the documentation that we have sent out.

Let me know if there are any other questions.

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, January 20, 2012 2:48 PM
To: 'GOLDB008@MC.DUKE.EDU'
Cc: Maddox, Yvonne (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Hirschfeld, Steven (NIH/NICHD) [E]
Subject: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)

Ron

As you are aware the Neonatal Research Network (NRN) continues to support studies under common protocols, but which require individual institutional IRB review prior to the conduct of these studies at each of the NRN sites. This is to inform you that The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), which provided the Federal support to the NRN, has been requested by the Office of Human Subjects Protection, to provide to the Office the most current consent form approved by your IRB and the corresponding IRB approval for the main SUPPORT Study, including any revisions, as soon as possible. As the NICHD Program Director of the NRN, I am requesting that the most recent consent form with IRB approval for your site for SUPPORT be submitted to me as soon as possible, but no later than January 26, 2012. Thank you for your cooperation.

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: SUPPORT renewal
Date: Monday, February 13, 2012 3:46:00 PM

I sent a request for their consent form. (b)(5) I will reforward the email to them and copy you

Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
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301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Archer, Stephanie (NIH/NICHD) [E]
Sent: Monday, February 13, 2012 3:42 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT renewal

I think she may be talking about the (b)(5) I thought you mentioned at the (b)(5)
(b)(5)

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Monday, February 13, 2012 3:37 PM
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: SUPPORT renewal

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tuesday, February 07, 2012 12:33 PM
To: 'Zaterka-Baxter, Kristin'
Subject: RE: SUPPORT renewal

They are free to send the email request to their IRBs.

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Tuesday, February 07, 2012 12:30 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: SUPPORT renewal

Hi Rose,

Please see below; let me know if I can do anything.

Thanks,
Kris

Kris Zaterka-Baxter, RN, BSN, CCRP
RTI International
Res Clinical Study Specialist

3340 Cornwallis Rd
Research Triangle Park, NC 27709
Phone: 919-485-7750
Fax: 919-485-7762

From: Joanne Finkle, J.D. [mailto:j.finkle@duke.edu]
Sent: Tuesday, February 07, 2012 11:43 AM
To: Zaterka-Baxter, Kristin

Subject: SUPPORT renewal

Kris,

It is time for me to submit continuing review renewal for SUPPORT study. I wanted to double check to see if there is something I need to submit with this in reference to the request that was made to review that consent forms. I thought Dr. Higgins mentioned sending something out to us to submit to IRB. If you know of anything, please let me know.

Thanks, Joanne

Joanne Finkle, RN, JD
Clinical Research Associate II
Dept of Pediatrics/Neonatology
2424 Erwin Road suite 504
DUMC 2739
Durham, NC 27705
Work: 919-681-4911
Fax: 919-681-4868

From: Luc Brion
To: bpoindex@iupui.edu
Cc: Martin Keszler (mkeszler@wihri.org); dwallace@rti.org; Higgins, Rosemary (NIH/NICHD) [E]; Pablo Sanchez; carl_danglo@urmc.rochester.edu; kwatterberg@salud.unm.edu
Date: Friday, February 10, 2012 11:17:17 AM
Attachments: Secondary - predicting ext success - Revised (2) 02-07-2012.docx
Watterberg. Hydrocortisone. 02-07-2012 rev.xlsx
Secondary - predicting ext success - Revised (2) 02-07-2012 clean.docx
SBT response 10 Feb 2012 LPB revised clean.doc

Brenda:

Thanks a lot for your comments and those of the protocol review committee.

I attach the itemized response to the comments of the committee, a revised budget, and a revised proposed protocol (full version with itemized changes and clean copy).

If you have any question or suggestion please let me know.

Best regards,

Luc

Luc P. Brion, MD
Professor of Pediatrics
Director, Fellowship Training Program in Neonatal-Perinatal Medicine
University of Texas Southwestern Medical School Program
The University of Texas Southwestern Medical Center at Dallas
5323 Harry Hines Boulevard, STOP 9063
Dallas, TX 75390-9063
Office: (214) 648-3903
Fax: (214) 648-2481
luc.brion@utsouthwestern.edu

PREDICTING SUCCESS OF EXTUBATION DURING HYDROCORTISONE THERAPY IN PRETERM INFANTS < 30 WEEKS OF GESTATIONAL AGE~~AND THE EFFECT OF DIFFERENT MODES OF SYNCHRONIZED VENTILATION~~

Luc P Brion, UT Southwestern at Dallas

Martin Keszler, Brown University

Kristi Watterberg, University of New Mexico

Dennis Wallace, RTI

Carl d'Angio, University of Rochester

Rose Higgins, RTI

Protocol

Rev 02~~11~~/2787~~15~~/12~~1~~

Proposed secondary study to

"A RANDOMIZED CONTROLLED TRIAL OF THE EFFECT OF HYDROCORTISONE ON SURVIVAL WITHOUT BRONCHOPULMONARY DYSPLASIA AND ON NEURODEVELOPMENTAL OUTCOMES AT 18 – 22 MONTHS OF AGE IN INTUBATED INFANTS <30 WEEKS GESTATIONAL AGE".

Referred to as "Main Hydrocortisone Study" in this protocol

Kristi Watterberg, PI

Thanks to: Diana Vasil, RN, Coordinator at UT Southwestern at Dallas, and Glenn Metoyer, RT, Parkland Memorial Hospital

1. ABSTRACT (SYNOPSIS)

This observational study is primarily designed to evaluate whether a short endotracheal continuous positive airway pressure (ET CPAP) test ~~(also called spontaneous breathing test, (SBT)~~ may help predict the success of extubation of ~~very~~ premature infants ≤30 weeks estimated gestational age at birth who remain intubated at 14 - 28 days postnatal age. ~~–~~For this purpose, we will use the 3-minute ET CPAP test (also called "spontaneous breathing test" or SBT) described by Kamlin in a single center.[1] The primary aim of this study is to test the hypothesis that, among patients who are electively extubated based on criteria established in the main hydrocortisone study, ~~to~~ the SBT will be more useful than clinical information alone to predict successful extubation.~~compare the percentage of successful extubation among patients with positive SBT with that in those who failed the SBT and were extubated based on criteria established for extubation in the main hydrocortisone study.~~ The secondary aim is to evaluate the point estimates and confidence intervals of sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio of a positive test, and likelihood ratio of a negative test for the SBT. The large number of patients we plan to recruit will allow us to test the external validity of the SBT in different centers using different types of ventilators, ~~and~~ different modes of ventilation and different modes post-extubation therapy.

~~We will also assess if ventilation modes that support every breath, i.e., assist control (AC), pressure regulated volume control (PRVC), pressure support ventilation (PSV) or synchronized intermittent mandatory ventilation (SIMV) with PSV, are associated with shorter duration of mechanical ventilation than SIMV. Since there are many center and individual differences in approach to therapy we will use multivariate analysis ventilation to attempt to account for possible confounder. Shorter intubation will in part depend on approaches to fluids, volumes, sodium administration and nutritional management, caffeine, etc.~~

2. STATEMENT OF PROBLEM

Prediction of successful extubation in preterm infants remains a challenge. This question has not been addressed by the NRN, and specific data were not collected during the SUPPORT trial. Previous single-site studies suggested that successful extubation can be predicted by the SBT in preterm infants during the first days of life. However, validity of this test has not been established in a multicenter study, using different types of ventilators, ~~and~~ different modes of ventilation and different modes post-extubation therapy, in a population of infants of greater post-natal age than in the original study by Kamlin et al.[1].

~~There is limited information about the relative merits of SIMV vs. ventilation modes that support every breath as weaning modes of mechanical ventilation. There are important physiological considerations suggesting that SIMV, although widely used, may not provide optimal support in very premature infants during weaning.~~

3. HYPOTHESIS

~~Since this is an observational study there is no primary hypothesis.~~

~~The study is primarily designed to test the external validity of the SBT in a multicenter study, with multiple institutions, using different types of ventilators and different modes of ventilation, in a population of infants of greater post natal age than in the original study by Kamlin et al.~~[1]Previous studies suggest that the success of extubation may be higher in patients with a positive SBT.[1] Therefore, we hypothesize that SBT will be more useful than clinical information alone, as indicated by a greater proportion of babies who pass the SBT remaining extubated compared to those who fail the SBT~~the percentage of successful extubation among patients with positive~~who pass the SBT is greater than that in those who failed the SBT and were extubated based on criteria ~~established for extubation in the main hydrocortisone study~~.

The null hypothesis is that, among patients who are electively extubated based on criteria established in the main hydrocortisone study, ~~-~~the percentage of successful extubation among patients with positive SBT is not different from that in those who failed the SBT~~, and awere extubated based on criteria established for extubation in the main hydrocortisone study.~~.

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Secondary ~~n~~Secondary ~~a~~ull -hypotheses include :

1. The predictive value of the SBT is not affected by whether the baby is supported by a ventilator using a mode supporting all breaths or by SIMV,
2. The predictive value of the SBT is not affected by whether the baby is randomized to hydrocortisone or placebo. Hydrocortisone may affect lung compliance and laryngeal edema and thus improve success rate of extubation compared with placebo.
3. The predictive value of the SBT is not affected by the resistance of the endotracheal tube (ETT). While on CPAP small diameter and long length of the ETT may increase work of breathing and contribute to failing of the SBT while not affecting success of extubation.
4. The predictive value of the SBT is not affected by postnatal age (within the ranges expected in the hydrocortisone trial).
5. The predictive value of the SBT is not affected by the mode of respiratory support after extubation. We would expect that success of extubation will be greater on patients extubated to NIPPV than on CPAP or high-flow nasal cannula, and lowest on those extubated to low flow nasal cannula or room air.

~~5. Modes of ventilation supporting all breaths and SIMV are associated with a similar duration of mechanical ventilation.~~

4. SPECIFIC AIMS

Primary aim:

To compare, among patients who are electively extubated based on criteria established in the main hydrocortisone study, the percentage of successful extubation among patients with positive SBT with the percentage of successful extubation among those who fail the SBT ~~the percentage of successful extubation among patients with positive SBT with that in those extubated based on criteria established for extubation in the main hydrocortisone study.~~

~~To evaluate the point estimates and confidence intervals of sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio of a positive test, and likelihood ratio of a negative test for the SBT.~~

~~1.~~ *Secondary aims:*

1. To evaluate the point estimates and confidence intervals of sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio of a positive test, and likelihood ratio of a negative test for the SBT.
2. To evaluate point estimates and confidence intervals of sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio of a positive test, and likelihood ratio of a negative test for the SBT in various ~~two~~ subgroups: ~~infants ventilated with SIMV and infants ventilated using modes supporting all breaths.~~

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~~3. To determine if ventilation modes that support every breath are associated with shorter duration of mechanical ventilation than SIMV.~~

5. RATIONALE/JUSTIFICATION

Success of elective extubation is one of the quality measures in neonatal intensive care. This study is designed

1. To compare, among patients who are electively extubated based on criteria established in the main hydrocortisone study, the percentage of successful extubation among patients with positive SBT with the percentage of successful extubation among those who fail the SBT ~~, the percentage of successful extubation among patients with positive SBT with that in those extubated based on criteria established for extubation in the main hydrocortisone study~~

~~To~~

2. ~~1To~~ assess the external validity of the SBT to predict successful extubation in very premature infants. This proposal is the first multicenter study that will assess whether the predictive value of the SBT is better (or not) than other information available to the clinician (Fi02, PIP, PEEP, rate, presence of atelectasis, physiologic stability) to predict successful extubation.

~~1. and~~

~~2. To add to the limited body of knowledge regarding relative merits of various forms of synchronized ventilation during weaning.~~ Very little additional coordinator time will be needed to collect information that will be used in multivariate analysis that could build the basis for a future randomized trial.

6. BACKGROUND AND SIGNIFICANCE

Success of extubation is around 60-73% in extremely low birth weight infants.[2,3]; Higher success rates (80-86%) have been reported in series including all preterm infants.[4,5]; Infants who require re-intubation, with its attendant risks, may experience deterioration of their respiratory status due to atelectasis. Intermittent hypoxemia and/or hypercapnia prior to re-intubation may expose them to additional risks. On the other hand, a relatively large number of infants who self-extubate and remain extubated subsequently.[6,8] Those infants may be exposed to mechanical ventilation and potential ventilator-induced lung injury for longer than necessary or for elective reasons such as to facilitate growth or to prepare for surgery.

Thus, a test that improves the clinician's ability to predict readiness for extubation is highly desirable. Kamlin et al[1] compared three tests to predict success of extubation (no reintubation within 72 hours) in 50 infants with birth weight < 1250 grams using a 3-minute ET CPAP trial: (a) expired minute ventilation (VE) during ET CPAP; (b) ratio of minute ventilation during ET CPAP to minute ventilation during mechanical ventilation (VE ratio), (c) the spontaneous breathing test (SBT). The infant passed the SBT if there was no hypoxia or bradycardia during ET CPAP. The median age at the time of the study was 4 and 5 days, respectively, for successful extubations and for extubations followed by reintubation within 72 hours. Kamlin concluded that the SBT had the highest sensitivity (97%), specificity (73%), positive predictive value (93%), negative predictive value (89%), likelihood ratio of a positive test (3.6) and the smallest likelihood ratio of a negative test (0.04) among the three tests.[1] Success rate of extubation predicted by a positive SBT was ~~38403~~ 413 (93%), compared with a success rate of ~~139 950~~ (1178%) in those who failed the SBT. ~~the total cohort.~~ Limitations of this study included small sample size (n=50) and failure to

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separate infants ventilated by different synchronized modes. In that study infants were weaned by reducing the tidal volume to 3.5 ml/kg using AC or by reducing ventilator rates to 20–30 breaths/minute on SIMV.

A subsequent study (n=180) provided a degree of validation of the SBT, but compared this test to a historical cohort, which differed substantially from the practice at the time of the validation study. Once more, various modes of ventilation were used, and there was no subanalysis by mode.[76] Most babies in the validation cohort were on volume guarantee ventilation (94% vs 26% in the controls), and most of them were ventilated using AC at the time of extubation (81%, compared with 93% using SIMV in controls). The median age at extubation was 0 days (range 0-27) for babies undergoing the SBT and 0 days (range 0-11 days for controls). Compared with historical controls, infants were extubated at significantly higher ventilator rates and airway pressures using the SBT, but the success rate of extubation was not significantly different (78% with SBT versus 72% in historical controls). The sensitivity of the SBT was 83% (compared with 97% in the first study).

It is not known if the SBT is equally predictive in infants with evolving chronic lung disease and prolonged ventilator dependence. It is also not known if the SBT is equally predictive in infants on different modes of synchronized ventilation. It is possible that modes in which every breath is supported mask significant respiratory control center immaturity or afford less respiratory muscle training compared to SIMV. SIMV remains the most widely used mode of assisted ventilation in newborn infants,[7] despite its potential disadvantages related to high work of breathing resulting from the high resistance of small endotracheal tubes (ETT) in extremely low birth weight (ELBW) infants.[8-10] This is especially true as the SIMV rate is decreased during the weaning process. In contrast, AC and PSV (when used as a sole mode of ventilation) support each patient breath, thereby resulting in more even tidal volume, less tachypnea, lower work of breathing and lower tidal volume compared to SIMV.[11-13]

There is no information in the literature describing the success of extubation from various modes of ventilation. A practice survey of NRN investigators conducted in July 2011 yielded data from 10 centers. Ventilators include Draeger 8000 (n=6), Maquet Servol (n=5), Draeger Evita XL (n=2), Draeger VN500 (n=2), Avea (n=2), and Bird VIP (n=1). Pressure-controlled ventilation is predominantly used in 6 NRN centers, and volume-targeted ventilation in 3 centers, while both are used equally in 2 centers. Volume-targeted ventilation is used either often or most of the time in 7 centers, and is used both during the acute phase and during weaning; it is used during weaning by 5 of 10 centers. During weaning and for extubation SIMV is used predominantly by 5 centers and modes supporting all breaths are used predominantly by 5 centers. Extubation from high-frequency ventilation is either rarely or never used. Eight of 10 centers would be ready to perform a 3-min SBT in patients on high-frequency ventilation. In summary the survey showed substantial heterogeneity across centers, with approximate equal distribution of SIMV and modes supporting all breaths.

~~There are limited data regarding the relative efficacy of ventilation modes that support every breath vs. SIMV in weaning from mechanical ventilation and no large clinical trials to evaluate their effect on survival or the risk of bronchopulmonary dysplasia. Three small studies compared SIMV and AC during weaning. In two of these studies SIMV rate was reduced to10 breaths/min; these studies showed shorter duration of ventilation when using AC. In the third trial, SIMV rate was not reduced below 20 breaths/minute, and the authors showed no difference in duration of ventilation between the two modes.[14,15] These findings support the physiologic explanation that the narrow ETT of ELBW infants increases work of breathing and impairs weaning from mechanical ventilation. Reyes et al showed faster weaning from mechanical ventilation in ELBW infants using SIMV+ PSV, compared to SIMV alone, suggesting that PSV may obviate this problem to some extent.[16] However, this option is not available on all ventilators and may not be widely used. One larger randomized trial enrolled 212 VLBW infants (birth weight 500-1249 g) from initiation of mechanical ventilation through extubation on AC or SIMV.[17] The study showed no differences between the groups in survival, BPD, age at extubation, or length of ventilation in survivors. This study used pressure regulated volume control using the Siemens Servo 300 ventilator, in which the volume targeted mode uses tidal volume measurement at the ventilator end of the circuit, in contrast with ventilator adjusting volume closer~~

~~to the endotracheal tube. Cross-over for failure occurred in 33% of the infants receiving SIMV and 20% of those who received PRVC.~~

~~A practice survey of NRN investigators conducted in July 2011 yielded data from 10 centers. Ventilators include Draeger 8000 (n=6), Maquet Servo-i (n=5), Draeger Evita XL (n=2), Draeger VN500 (n=2), Avea (n=2), and Bird VIP (n=1). Pressure-controlled ventilation is predominantly used in 6 NRN centers, and volume-targeted ventilation in 3 centers, while both are used equally in 2 centers. Volume-targeted ventilation is used either often or most of the time in 7 centers, and is used both during the acute phase and during weaning; it is used during weaning by 5 of 10 centers. During weaning and for extubation SIMV is used predominantly by 5 centers and modes supporting all breaths are used predominantly by 5 centers. Extubation from high-frequency ventilation is either rarely or never used. Eight of 10 centers would be ready to perform a 3-min SBT in patients on high-frequency ventilation. In summary the survey showed substantial heterogeneity across centers, with approximate equal distribution of SIMV and modes supporting all breaths.~~

7. METHODS AND PROCEDURES

a) Study design

This is an observational study (prospective cohort) ~~with prospective data collection~~in a selected group of patients enrolled in a randomized trial (the main hydrocortisone study).
The study will involve analysis of (1) the frequency of successful elective extubation and (2) the operational characteristics of a diagnostic test (SBT) ~~and retrospective analysis of a cohort study (using two cohorts: babies ventilated using~~ SIMV and babies ventilated using modes supporting all breaths).
The spontaneous breathing test (SBT) will be performed by the study team just before elective extubation decided by the clinicians according to the protocol of the main hydrocortisone study~~trial~~. Clinicians will remain blinded to the
results.

b) Study population

We will use the same population as that for the ~~main study~~main hydrocortisone study. All patients enrolled in the ~~main study~~main hydrocortisone study will be approached for informed consent. It is up to each center to decide whether to use a separate consent for the sub-study, or ~~an optional consent, indicated by~~ a check on the consent form of ~~to the main study~~main hydrocortisone study.

c) Inclusion and exclusion criteria

Inclusion criteria:

These will be the same as for the ~~main study~~main hydrocortisone study, i.e.,:
Patients eligible for this study will be infants between 14 – 28 postnatal days who:
(a) are <30 weeks estimated gestational age, to be randomized in two strata: $\leq 26^{6/7}$ and $27^{0/7} - 29^{6/7}$ weeks);
(b) were inborn at an NRN site or were admitted to an NRN site before 72 hours postnatal age;
(c) have received ≥ 7days of mechanical ventilation;
(d) are receiving mechanical ventilation through an endotracheal tube .

We anticipate a starting time for this sub-study to be at the earliest 6/1/2012.

Exclusion criteria:

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Same as for the ~~main study~~main hydrocortisone study, i.e.:

(a) Major congenital anomalies
(b) Decision to limit support
(c) Indomethacin or ibuprofen treatment within 48 hours of study drug
(d) Previous corticosteroid treatment for BPD
(e) Hydrocortisone treatment for hypotension in the first week of life is common (35) and will not be an exclusion; however, infants will be excluded if they have received hydrocortisone:
  (i) for ≥ 14 cumulative days OR
  (ii) within 7 days of study entry.

In addition, we will exclude for this secondary study patients who have at the time of extubation an ETT size <2.5.

d) Enrollment centers and PIs

Case Western	Michele Walsh
Dallas	Luc P Brion
Wayne State	Seetha Shankaran
Emory	Barbara Stoll
Cincinnati	Kurt Schibler
Indiana	Brenda Poindexter
Brown	Martin Keszler
Stanford	Krisa Van Meurs
Alabama	Waldemar Carlo
Houston	Kathleen Kennedy
Duke	Ronald Goldberg
Iowa	Edward Bell
New Mexico	Kristi Watterberg
Pennsylvania	Barbara Schmidt
Rochester	Carl D'Angio
UCLA	Uday Devaskar
Ohio State	Leif Nelin
Missouri	William Truog

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e) Study intervention and procedures

We will perform a maximum of 2 SBTs per patient: one at the time of the first elective extubation and one at the time of the second elective extubation, if any. Spontaneous unplanned extubations will not be analyzed since SBT will not be performed.

Extubation criteria in the main hydrocortisone study are as follows: "Extubation must be attempted within 72 hours of starting study drug and within 24 hours after meeting the following criteria: the FiO2 is <0.40 to maintain a saturation of 88%, the mean airway pressure is < 8, and the infant is hemodynamically stable (as defined for the SUPPORT trial: "clinically acceptable blood pressure and perfusion in the opinion of the clinical team")."

We will request that the clinical team inform the NRN coordinator of any ~~of a~~ pending extubation after the baby has been enrolled to this sub-study.

The intervention (SBT) will be similar to that described by Kamlin et al.[1] Specifically, when the clinicians decide a baby is ready to be extubated, the investigator will perform the SBT within 4 hours of the planned extubation. This intervention will be masked in order to prevent bias that would occur if the clinical provider knew the result of the SBT. We propose that the SBT be conducted after rounds in centers that review the monitoring tracing during rounds.

The infant's ETT will be suctioned prior to the SBT if suctioning is clinically indicated. The SBT will be done no less than 10 minutes after suctioning to ensure adequate re-recruitment of lung volume.

The researcher will silence any alarms and will place screens around the bedside before initiating the test -to minimize the chance of unblinding. After ensuring that the clinical care team, including the patient's nurse, is away from be bedside (to maintain blinding) the investigator (respiratory therapist, fellow, nurse practitioner or attending), who must not be involved with the patient's clinical care, will switch the ventilator to CPAP for 3 minutes at the same pressure as the positive end-expiratory pressure setting. ~~The infant's ETT will be suctioned prior to the SBT if clinically indicated, T~~and the intervention will be done when the infant is in a quiet state, taking care to minimize stimulation and disturbance during the study.

The baby succeeds the SBT if he or she requires no more than a 15% increase in FiO_2~~FiO2~~ for isolated hypoxemia and does not develop bradycardia (HR <100) for more than 15 seconds. After 3 minutes on CPAP the study will be stopped, and ventilation will be restarted.

The baby fails the SBT if he or she develops a bradycardia (HR <100) for more than 15 seconds and/or a fall in SpO2 below 85% despite ~~a~~ 15% increase in FiO_2. If isolated hypoxemia develops, FiO_2 ~~FiO2~~ will be increased according to unit protocol. If hypoxemia does not respond to a 15% increase in FiO_2~~FiO2~~, or if bradycardia develops, manual breaths arewill be given through the ventilator and mechanical ventilation is will be restarted at the previous settings.

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~~because of bradycardia or desaturation, this will be considered a failed test. At this point the study will be stopped, and ventilation will be restarted. If manual breaths are given through the ventilator because of bradycardia or desaturation, this will be considered a failed test. Data on the mode of ventilation, success and time of extubation will be collected for subsequent analysis.~~

The baby will be placed back on previous ventilatory settings for~~to~~ 30 minutes, to limit the risk of derecruitment that could have resulted from performing the SBT. The investigator will document in the chart and communicate to the clinical team that the SBT was performed, the exact time of the procedure and the earliest time of extubation (30 min after the SBT). The results of the SBT will not be disclosed to the clinician or documented into the chart unless additional therapy is required as indicated below.

In rare circumstances, the baby may not respond well to the usual intervention described above. In that case, manual bagging will be is initiated and additional treatment will be provided according to NRP guidelines~~for 30 seconds~~, and the clinical team will be is informed. NRP guidelines will be followed if the infant requires more extensive intervention. Once stable, the infant will be placed back on mechanical ventilation.

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~~If the baby responds well, mechanical ventilation is restarted; otherwise appropriate treatment is initiated.~~

~~J)~~ *Required follow-up*

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None beyond 72 hours after the second elective extubation

e.f) Primary and secondary outcomes

Primary outcomes:

Comparison of the ~~Point estimates and confidence intervals of sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio of a positive test, and likelihood ratio of a negative test to predict successful (defined as no reintubation within 72 hours) extubation using SBT~~ percentage of successful extubation among patients with positive SBT with that in those with a negative SBT~~extubated based on criteria established for extubation in the main hydrocortisone study~~

Secondary outcomes:

1. Point estimates and confidence intervals of sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio of a positive test, and likelihood ratio of a negative test to predict successful (defined as no reintubation within 72 hours) extubation using SBT

   a) In the entire cohort undergoing SBT ~~Point estimates and confidence intervals of sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio of a positive test, and likelihood ratio of a negative test to predict successful (defined as no reintubation within 72 hours) extubation using SBT~~

   b) In two subgroups: infants with gestational age $\leq 26^{6/7}$ versus those with gestational age $27^{0/7} - 29^{6/7}$ weeks

   ~~I.~~c) ~~Point estimates and confidence intervals of sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio of a positive test, and likelihood ratio of a negative test to predict successful extubation using SBT~~ In two subgroups: infants ventilated with SIMV and infants ventilated using modes supporting all breaths at the time of the SBT

   d) ~~Point estimates and confidence intervals of sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio of a positive test, and likelihood ratio of a negative test to predict successful extubation using SBT~~ By primary study group (hydrocortisone versus placebo)

   ~~2.~~

   ~~3. Point estimates and confidence intervals of sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio of a positive test, and likelihood ratio of a negative test to predict successful extubation using SBT~~ According to ETT diameter, since resistance is proportionate to: $R \propto L / r4$, where L is the length of the tube and r is its radius~~ETT resistance calculated according to the formula:~~

   ~~$R \propto l. / r^4$;~~

   ~~where L is the length of the tube and r is its radius~~

   e)

   f) ~~Point estimates and confidence intervals of sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio of a positive test, and likelihood ratio of a negative test to predict successful extubation using SBT~~ According to postnatal age

   g) ~~Point estimates and confidence intervals of sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio of a positive test, and likelihood ratio of a negative test to predict successful extubation using SBT~~ According to the mode of respiratory support used after extubation: NIPPV;, CPAP or; high-flow nasal cannula;, low flow nasal cannula, or room airoxihood or ambient air;

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h) ~~Point estimates and confidence intervals of sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio of a positive test, and likelihood ratio of a negative test to predict successful extubation using SBT~~ Using different definitions of failed extubation (at 12, 24 and 48 hours instead of 72 hours after extubation)

2. Odds ratio of successful extubation taking into account the SBT and multiple possible confounders

~~4. Odds ratio of successful extubation taking into account the SBT and multiple possible confounders~~

~~5. Duration of mechanical ventilation in two subgroups: infants ventilated with SIMV and infants ventilated using modes supporting all breaths for the majority of the time on the ventilator starting at the time of randomization~~

~~1.~~ Data to collect for this study beyond those in the main trial (see Appendix B):

~~2.~~ Clinical information ~~about the situation~~ before the SBT: ~~At the time of randomization we will obtain the respiratory severity score, which will be calculated as mean airway pressure X FiO2.18~~

~~3.~~ Mode of ventilation, ventilatory settings, vital signs, m ~~between the time of randomization and the SBT~~,

1. Most recent blood gas, ~~ventilatory settings and~~ ETT size
2. Response to SBT
3. Respiratory support after the elective ~~second~~ extubation

~~4. just before SBT~~

g) *Sample size and power estimate*
~~h)~~

Criteria used for elective extubation in the main hydrocortisone trial were targeted toward the lower end of the criteria in the SUPPORT trial. ~~The percentage of successful elective extubation in the main hydrocortisone trial was estimated from data in the surfactant arm of the SUPPORT trial [Results pending from Dennis].~~ In Kamlin's original study[1] 86% of the infants had a positive SBT, and the success rate of extubation predicted by a positive SBT was 93%, compared with a success rate of 78% in the total cohort. ~~Therefore sample size was determined assuming 65% success rate using extubation criteria used for the main hydrocortisone trial and 75% for patients with a positive SBT. Using two-sided chi-square analysis, a p value of 0.05, and a power of 80% we would need 320 patients in each group; using a power of 90% we would need 430 patients in each group. Since not all patients will have a positive SBT, the denominator will not be identical in the 2 groups.~~

To the extent possible, we will use all available subjects from the total sample size of 800 available in the main trial. By the time the sub-study is expected to start, 100 of 800 patients will have been enrolled into the main trial. Patients who self extubate before the SBT and remain off mechanical ventilation will not be available for this analysis, leaving 630 patients to approach for consent. Those who are reintubated will have another SBT performed before attempting elective extubation. If we obtain 60% of consent, this will lead to 370 patients available for the~~We estimate that about 70% of the total sample size available in the main trial will be available for the analysis of this secondary study; thus sample size is estimated at 420~~ primary outcome.

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Estimates of the Ppower to detect a difference in probability of successful extubation between individuals with a positive ABT and those with a negative SBT for an assumed total of 370 subjects were calculated for a range of assumptions about rates positive SBT and of successful extubation werewas calculated usingbased on two-tailed chi-square ~~analysis and an alpha~~test of differences in proportions and a Type I error of 0.05. The percentage of successful extubations was assumed to be at least 60% (ranging from 60% to 80%), the percentage of individuals with positive SBT were also assumed to range between 60% and 80%, with the difference in successful extubation in those with positive SBT assumed to be in the range of 7% to 10% greater than the overall success rate. Under these assumptions, the power to detect a difference in extubation success in those individuals with a positive SBT and those with a negative SBT was 92% or greater if the difference in the overall success rate and the success rate in those with positive SBT was 7% and greater than 99% if the difference in success rate was 10%. ~~The following grid shows the estimated power using the estimated number of patients we will have available for the analysis (see next section). The table assuminge that 420370 patients will undergo elective extubation and an SBT, that 670-80% will have a positive SBT, that the success of extubation will be 60-75% in the whole group, and 10-105% higher among those with a positive SBT. We will have at least 79% power to detect a 10% difference success rate of extubation using clinical criteria and patients with a positive SBT.~~

~~% successful extubation if SBT is positive~~	~~Sample size with positive SBT (%)~~	~~% successful extubation if SBT is negative using criteria using in the main hydrocortisone study~~	~~Sample size undergoing elective extubation~~	~~Power~~
~~70%~~	~~259336 (780%)~~	~~3760%~~	~~111420 (30%)~~	~~10082%~~
~~705%~~	~~272336 (680%)~~	~~4560%~~	~~420148 (40%)~~	~~10099%~~
~~70%70%~~	~~296 (80%)294 (70%)~~	~~20%60%~~	~~74 (20%)420~~	~~100%79%~~
~~75%~~	~~294 (70%)~~	~~60%~~	~~420~~	~~99%~~
~~75%~~	~~336 (80%)~~	~~65%~~	~~420~~	~~85%~~
~~80%~~	~~336 (80%)~~	~~65%~~	~~420~~	~~100%~~
~~75%~~	~~294 (70%)~~	~~65%~~	~~420~~	~~82%~~
~~80%~~	~~294 (70%)~~	~~65%~~	~~420~~	~~99%~~
~~80%~~	~~336 (80%)~~	~~70%~~	~~420~~	~~89%~~
~~85%~~	~~336 (80%)~~	~~70%~~	~~420~~	~~100%~~
~~80%~~	~~294 (70%)~~	~~70%~~	~~420~~	~~86%~~
~~85%~~	~~294 (70%)~~	~~70%~~	~~420~~	~~100%~~
~~85%~~	~~336 (80%)~~	~~75%~~	~~420~~	~~97%~~
~~90%~~	~~336 (80%)~~	~~75%~~	~~420~~	~~100%~~
~~85%~~	~~294 (70%)~~	~~75%~~	~~420~~	~~91%~~
~~90%~~	~~294 (70%)~~	~~75%~~	~~420~~	~~100%~~

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The Kamlin study,[1] which compared -three tests, had a sample size of 50. This study was powered to detect a difference of one standard deviation in mean VE in the group failing extubation but not to detect differences in dichotomous outcomes between the three tests. This was a single-center study with a relatively uniform approach to ventilation. The high degree of variability of clinical practice within the NRN will impact the outcome measures in this proposed multicenter trial, thus clearly requiring a much larger sample size to detect a comparable effect size.

~~The Reyes study,[16] which was also a single center study, focused on a similar population demonstrated no significant difference in duration of mechanical ventilation (median [interquartile range] 22 [10-52] vs 34 d [19-59]). This study was powered to detect a 30% difference in the duration of oxygen dependency between groups at an alpha of 0.05 with a power of 90%; it did not reach statistical significance with n=107.~~

~~To the extent possible, we will use all available subjects from the total sample size of 800 available in the main trial. At the current date of this proposal, 40 of 800 patients have been enrolled into the main trial. Patients who self extubate before the SBT and remain off mechanical ventilation will not be available for this analysis. Those who are reintubated will have another SBT performed before attempting elective extubation. We estimate that about 670% of the total sample size available in the main trial will be available for the analysis of this secondary study; thus sample size is estimated at 272550.~~

The secondary ~~primary~~ aim ~~goal~~ of this study is to generate estimates of the operating characteristics (sensitivity [Se], specificity [Sp], positive predictive value [PPV] and negative predictive value [NPV]) of the 3-minute ET CPAP test ("spontaneous breathing test" or SBT) for predicting successful extubation in this population of infants. Each of the operating characteristics of interest is a conditional probability (where the calculation is conditioned on a either success or failure of the extubation or the positive or negative value for the SBT), and the primary sample size consideration for the study is the precision with which these probabilities can be estimated with the available sample sizes. Based on information provided earlier that suggests that 60% to 80% of the extubations are likely to be successful, we assume that between 20% and 80% of the 550 subjects will be used in the denominator of each of the calculations. Furthermore, operating characteristics in the range of 0.7 to 1 are of greatest interest. Given those assumptions the available sample sizes are sufficient to provide confidence intervals with half widths, where a 95% confidence interval is typically computed as the estimate of the sensitivity ± the half width, shown in the table below.

Estimates of Confidence Interval Half Width for Different Levels of True Measure Prevalence and Conditional Denominator

Se, Sp, PPV, NPV Value	Half Interval Width for Available Denominator						
	110	165	220	275	330	385	440
0.70	0.084	0.069	0.059	0.053	0.048	0.045	0.042
0.72	0.082	0.067	0.058	0.052	0.047	0.044	0.041
0.74	0.082	0.067	0.058	0.052	0.047	0.044	0.041
0.76	0.080	0.065	0.056	0.050	0.046	0.043	0.040
0.78	0.077	0.063	0.055	0.049	0.045	0.041	0.039
0.80	0.075	0.061	0.053	0.047	0.043	0.040	0.037
0.82	0.072	0.059	0.051	0.045	0.041	0.038	0.036
0.84	0.069	0.056	0.048	0.043	0.040	0.037	0.034
0.86	0.065	0.053	0.046	0.041	0.037	0.035	0.032
0.88	0.061	0.050	0.043	0.038	0.035	0.032	0.030
0.90	0.056	0.046	0.040	0.035	0.032	0.030	0.028
0.92	0.051	0.041	0.036	0.032	0.029	0.027	0.025
0.94	0.044	0.036	0.031	0.028	0.026	0.024	0.022
0.96	0.037	0.030	0.026	0.023	0.021	0.020	0.018
0.98	0.026	0.021	0.019	0.017	0.015	0.014	0.013

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i) *Available population/compatibility with other ongoing protocols*

Same as for the ~~main study~~main hydrocortisone study: Based on GDB data 06-07, and assuming 60% consent rate, 800 infants could be recruited to the ~~main study~~main hydrocortisone study over 3 years. Since the secondary study will start at the earliest 6/1/2012 we estimate 100 infants will have been recruited already in the main hydrocortisone study. Patients who self extubate before the SBT and remain off mechanical ventilation will not be available for this analysis.– leaving 630 patients to approach for consent. Those who are reintubated will have another SBT performed before attempting elective extubation. If we obtain 60% of consent, this will lead to 370 patients available for the primary outcome. ~~Those who are reintubated will have another SBT performed before attempting elective extubation. Since some centers may use a separate consent form for the current study while other centers may use an embedded consent w~~~~We estimate that about 70% of the total sample size available in the main trial will be available for the analysis of this secondary study; thus sample size is estimated at 420~~550.

~~Since the secondary study will start after the beginning of the main study, the total number of patients in this secondary study will be probably 10% smaller, i.e. 500 patients.~~

j) Projected recruitment time

The projected recruitment time for the ~~main study~~main hydrocortisone study was~~is~~ 30 months. However, as of November 2011, only 16 had been randomized per month (versus an original main trial estimate of 27 recruited per month). Initiation of the secondary study could be expected within 6 months (i.e., by 6/1/2012). ~~Therefore, projected recruitment time for the main study is estimated to be 24 months.~~ Since recruitment into the main hydrocortisone study is slower than expected, recruitment may last longer than initially expected.

k) Data Analysis Plan

We will use chi-square analysis to compare the success of extubation in patients who will successively pass the SBT with that among all patients who are electively extubated and undergoing the SBT.

~~1. We will determine the point estimates and 95% confidence intervals for the operating characteristics (sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio of a positive test, and likelihood ratio of a negative test) of successful extubation using the SBT.~~

We will ~~We will~~ determine the point estimates and 95% confidence intervals for the operating characteristics (sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio of a positive test, and likelihood ratio of a negative test) of successful extubation using the SBT in all patients undergoing SBT.

We will

~~use the same~~ determine the same point estimates and 95% confidence intervals for the operating characteristics tests in the following subgroups:

a) In the entire cohort undergoing SBT

b) In two subgroups: infants with gestational age $\leq 26^{6/7}$ versus those with gestational age $27^{0/7} - 29^{6/7}$ weeks

c) In two subgroups: infants ventilated with SIMV and infants ventilated using modes supporting all breaths at the time of the SBT

d) By primary study group (hydrocortisone versus placebo).

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e) According to ETT diameter, since resistance is proportionate to: $R \propto L / r^4$, where L is the length of the tube and r is its radius

f) According to postnatal age

g) According to the mode of respiratory support used after extubation: NIPPV; CPAP or high-flow nasal cannula; low flow nasal cannula, oxihood or ambient air

h) Using different definitions of failed extubation (at 12, 24 and 48 hours instead of 72 hours after extubation)

~~1.~~

~~2. infants ventilated with SIMV versus infants ventilated using modes supporting all breaths at the time of the SBT.~~

~~infants with gestational age $\leq 26^{6/7}$ versus those with gestational age $27^{0/7}$ - $29^{6/7}$ weeks~~

~~2. primary study group~~

~~3. infants ventilated with SIMV and infants ventilated using modes supporting all breaths at the time of the SBT~~

~~4. according to the mode of respiratory support used after extubation: NIPPV, CPAP, high flow nasal cannula, low flow nasal cannula or room air~~

~~3. 5. using different definitions of failed extubation (at 12, 24 and 48 hours instead of 72 hours after extubation)~~

We will use Receiving operator characteristic curve (ROC) to analyze whether the operating characteristics of the SBT vary according to ETT resistance and to postnatal age.

~~Duration of mechanical ventilation will be compared in the two subgroups using non-parametric tests (two-sided Mann-Whitney test, alpha < 0.05) because this variable has a non-normal distribution. We will use multiple regression analysis of the duration of ventilation using as factors the gestational age, the center, the respiratory severity score at the time of randomization, the randomization arm (hydrocortisone versus control), and the mode of ventilation. Additional factors that differ by $p < 0.10$ on univariate analysis will be tested for significance in the multiple regression analysis.~~

The likelihood of success of extubation may depend on multiple factors other than SBT, including patient characteristics, mode of ventilation, individual clinician and center. For this purpose we will use multivariate logistic regression analysis using as predictors:[1] gestational age, weight for age at birth, postnatal age, PEEP, mode of ventilation and ventilation settings at the time of SBT (SIMV vs. ventilation supporting every breath), SBT, hydrocortisone (vs. placebo), caffeine,- symptomatic patent ductus arteriosus, center, and mode of respiratory support after extubation (NIPPV, CPAP, high flow nasal cannula, low flow nasal cannula, room air). Additional factors that differ by $p \leq 0.10$ on univariate analysis will be tested for significance in the multiple regression analysis.

l) Data safety monitoring plan:

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Eight interim blocks are planned in the ~~main study~~main hydrocortisone study. The DSMC will review data from the main trial and from this secondary study at the same time. For this secondary study, the DSMC will review the frequency of required treatment (bagging, resuscitation) related to the SBT. Serious adverse events to be reported to NICHD within 24 hours include death that would occur after a code related to the SBT.

m) Stopping limits for protocol termination:

The DSMC may decide to stop the main trial or this secondary study.

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8. RISK, BENEFITS, LIMITATIONS

Ethical issues

Benefit: There is no direct benefit to participating in this secondary study.

Risks: Some babies may develop bradycardia or desaturation and may require increase in FiO_2 or manual breaths on the ventilator ~~bagging~~ at the time of SBT. It is possible that an occasional infant may require additional interventions. However, n~~N~~o case of resuscitation related to the SBT has been described in the two published studies. Any baby requiring resuscitation will be reported to the IRB as an adverse event.

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Blinding: SBT failure may be fairly predictive of failure of extubation. However, it is not part of standard practice in centers in the NRN. If the results of the SBT were provided to the clinical care team, it would result in bias in decision of extubation time. The SBT as described has been reported in two studies involving a total of 230 neonates, ~~more than~~ Since reported infants undergoing the SBT had an uneventful course even if failing the SBT, ~~therefore~~ blinding the clinical care team to the results of this test is defensible, except in the rare circumstance of ~~lack of response to ventilator breaths through the ventilator and re-initiation of mechanical ventilation,~~ a more serious deterioration that required more than a few ~~manual~~ breaths through the ventilator and resumption of mechanical ventilation (in which case the clinical team will be informed of the event).

~~A consent form will be obtained for participation in this study. There is a slight possibility that asking for permission for this secondary study would affect enrollment rate in the primary study. We think it is unlikely with the opt-in checkbox.~~

Consent form: A consent form will be obtained for participation in this study. There is a slight possibility that asking for permission for this secondary study would affect enrollment rate in the primary study. Each center PI will decide whether to use a separate ~~This~~ consent for this secondary study or to ~~could be~~ embedded it in the consent form for the ~~main study~~main hydrocortisone study.

Limitations and alternatives

Since this is an observational rather than a randomized study, success of extubation ~~the duration of mechanical ventilation~~ may be affected by multiple factors, biases and confounders, some of which we may not be able to quantify. Based on our survey, it appears that selection of the ventilation mode depends in large part on center and care provider/attending choice than on patient characteristics. For this purpose we will conduct multivariate analysis using patient characteristics (GA, prenatal steroids, disease severity), and information about individual patients. ~~NICU and providers' practices (fluid and salt administration, therapy for PDA, diuretics, caffeine, type of ventilator, choice of ventilator mode, blood gases at the time of extubation).~~

There may be inter-institutional and inter-individual variability in the decision about when to extubate. Variability will be limited by criteria set by Kristi Watterberg in the main trial protocol: "Extubation must be attempted within 72 hours of starting study drug and within 24 hours after meeting the following criteria: the FiO2 is <0.40 to maintain a saturation of 88%, the mean airway pressure is < 8, and the infant is hemodynamically stable (as defined for the SUPPORT trial: "clinically acceptable blood pressure and perfusion in the opinion of the clinical team"). The infant may be extubated from higher settings at the discretion of the attending physician. If the infant does not meet these criteria within 72 hours, he/she will be reassessed every 24 hours during the intervention period and extubation will be attempted within 24 hours of those criteria being met."

Success of extubation depends on absence of apnea. Apnea may not be detected during the 3 minutes during which the SBT will be performed. We expect that a majority but not all patients in the current trial may be on caffeine at the time of extubation, since a large multicenter randomized trial has shown it reduces the rate of bronchopulmonary dysplasia (oxygen requirement at 36 weeks postmenstrual age)[1420] and improves the rate of survival without neurodevelopmental disability at 18 to 21 months but not in early childhood in infants with very low birth weight infants.[21,15,1622]

Success of extubation will be limited in case of laryngeal edema, which may be more prevalent in the control arm. Hydrocortisone may limit this risk. We will record documentation of stridor and failure of successful extubation related to stridor.

We will not use VE as a predictor for extubation because the tidal volume cannot reliably be measured when the leak around the endotracheal tube is ≥ 30%. In spontaneously breathing infants, the tidal volume is not stable and the number of r breaths over which the VE is averaged varies among different types of ventilators.

SIMV with PS will be classified as a mode ~~modes~~ supporting all breaths; however this mode supports some breaths fully (SIMV) and other breaths to a lower extent (PS), in contrast with AC or PS.

~~Since subgroups for duration of mechanical ventilation will be based on the mode of respiratory support for the majority of the time on the ventilator from the time randomization, there will be possible overlap between the two groups, since some babies may be exposed to more than one mode. However, most changes in mode occur between the acute phase and beginning of weaning. Starting the count at the time of primary study entry (at least 14 d) will minimize this overlap.~~

We did consider alternatives to Kamlin's SBT.

1. During the SBT the baby will need to breathe against the resistance of the endotracheal tube. The resistance of the tube is proportional to L / r^4, where L is the length of the tube and r is its radius. We will record length and radius to assess whether the predictive value of the SBT decreases with increased resistance of the tube. An alternative to the SBT would be to design a modified SBT using PSV with minimal pressure instead of CPAP. Since no complications have been described with the SBT, this may not be necessary. Since this has not been tested in the past, we will not use this option.

2. Wilson et al[17,22] described a minute ventilation test (MVT) of 10 minutes duration instead of the 3-minute test described by Kamlin. In a single institution, a spontaneous minute ventilation ≥ 50% of the ventilator-generated minute ventilation correctly predicted successful extubation in 86% of preterm infants with birth weight < 2 kg and requiring mechanical ventilation for > 24 hours.[22] In a subsequent randomized trial[18,23] (mean GA 30 weeks), babies undergoing the MVT were extubated sooner than those in the control group. The positive predictive value of the MVT for extubation was 76% (95% CI, 55 to 89%) and the success of extubation was similar to the control group.[19,22] Kamlin's SBT is more appropriate for our study for several reasons: Hhis studies only included smaller babies; the SBT only uses 3 minutes and does not require

minute ventilation measurement and thus could be used in multicenter setting with various ventilators, and appears at least as good as the 10 minute MVT.

3. Dimitriou et al[5] have described composite indices such as the diaphragmatic pressure–time index and the noninvasive respiratory muscle pressure–time index to predict success of extubation in preterm with mean gestatational age of 30 weeks and mean birthweight of 1.36 kg. The test had ~86% positive predictive value of successful extubation in the validation group. Kamlin's SBT is more appropriate for our study for the same reasons as described for the 10 minute MVT.

~~There is a slight possibility that asking for permission for this secondary study would affect enrollment rate in the primary study. We think it is unlikely with the opt-in checkbox.~~

We also considered extracting data from the SUPPORT for sample size analysis. However, discussions with Marie Gantz and Abhik Das suggest that intubation and extubation data from SUPPORT were collected in a way that would not allow reliable estimation of the rate of successful extubation. Therefore, we used estimates from Kamlin and constructed appropriate confidence intervals.

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9.5 BUDGET

Direct Costs

Cost per patient: $ 190113

Respiratory therapist: 3015 minutes x $530 per hour = $ -508

Coordinator time: 43 hours x $35 per hour = $ 140105

Consent: ~~assuming consent for this secondary study is embedded in the consent for the main trial:~~ 3040 minutes

Screening for subjects who qualify for extubation: 6020 minutes

SBT: 6060 minutes

Data collection/entry/transmission: 90 minutes

Total Capitation ~~Direct~~ Cost for ~~4373~~6533 patients: $708259,8740963

~~*Training session at NRN steering committee* $ 2,000~~

Total direct costs $70284,8740

Indirect costs (52.6%): ~~$37844,278330626~~

Total costs: ~~$108112,148200466~~

Note: there is no CPT code for the SBT test

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Appendix A: Authorship Plan:

We will follow the Policies and Procedures of the NICHD Neonatal Research Network

For abstracts, Authors of the Secondary Study with be the authors followed by "for the NICHD Neonatal Research Network.

For publications, authors will include Authors of the Protocol Subcommittee, Remaining participating Center PIs (those not serving on the Protocol Subcommittee), listed in order by the Center's combined ranking of the number of infants enrolled and the percent of eligible infants enrolled in the study by the Center, Followed by the phrase "for the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network."

Appendix B1: Data sample sheet

Data obtained for the ~~main study~~main hydrocortisone study and location on GDB or main hydrocortisone study forms:

Center: HCO2

Gestational age~~,~~ HCO1

~~B~~birth weight~~,~~ GDB

Date of birth HCO1

~~date and time of birth, prenatal steroids,~~ Ddate of ~~and time of~~ randomization~~,~~ HCO2

Rrandomization ~~arm~~code ~~,~~ HCO2

Information about first extubation~~center~~ HCO5

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Appendix B2: Data sample sheet

~~1.~~ **Data obtained for the secondary study: first elective extubation:**

~~2. Exclusion criterion: ETT size < 2.5~~

~~3. At the time of randomization: FiO2 Mean airway pressure:~~

~~4. Ventilation mode and duration:~~

~~From~~	~~Until~~	~~SIMV~~	~~PS/SIMV +PS/AC/PRVC~~

~~SBT~~ Planned extubation date and time: ETT diameter (mm): ~~total length:~~

Symptomatic PDA: Yes No

Caffeine: yes No

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~~6.~~ SBT: ~~(when quiet, change to CPAP at same pressure as prior PEEP for 3 min):~~ date and time: _____

~~Planned extubation date and time:~~

Immediately before SBT	During SBT
~~PS/SIMV +PS/AC/PRVC SIMV~~ Ventilation mode: PS SIMV SIMV with PS AC Volume mode Pressure control	~~Date:~~ From ____ until ____
ETT diameter: ___ length at lips: ___	
Latest pH: ___ pCO2: ___ BE: ___	
PIP: ___ MAP: ___ Ventilator rate: ___ PEEP: ____ cm FiO2: _____ Sat: _____	CPAP: ____ cm
HR > 100: yes ____ no ____	Min HR < 100 for > 15 sec: Yes _____ No _____
FiO2: ___ Sat: ___	Fall < 85% despite 15% increase in FiO2: Yes _____ No _____
	Max FiO2 Manual breaths through ventilator: number: ___ Resuscitation needed: _bagging ___ minutes: ___ _chest compressions: ____ minutes: _epinephrine: _____

Exbutation to: NIPPV CPAP high-flow nasal cannula low flow nasal cannula oxihood _____ ambient air

Stridor: _____ Racemic epinephrine: ____

Reintubation: no ____ yes ___ date: _____ time _____

Appendix B3: Data sample sheet

Data obtained for the secondary study: second elective extubation:

Planned extubation date and time: _____ ETT diameter (mm): ____ ~~total length:~~ ____

Symptomatic PDA: Yes ____ No ____

Caffeine: yes ____ No ____

SBT: date and time: _____

Immediately before SBT	During SBT
Ventilation mode: PS ____ SIMV ____ SIMV with PS ____ AC ____ Volume mode ___ Pressure control ____	~~Date:~~ _____ From ____ until ____
ETT diameter: ___ length at lips: ___	
Latest pH: ___ pCO2: ___ BE: ___	
PIP: ____ MAP: ____ Ventilator rate: ____ PEEP: ____ cm FiO2: ____ Sat: ____	CPAP: ____ cm
HR > 100: yes ____ no ____	Min HR < 100 for > 15 sec: Yes ____ No ____
FiO2: ____ Sat: ____	Fall < 85% despite 15% increase in FiO2: Yes ____ No ____
	Max FiO2 Manual breaths through ventilator: number: ___ Resuscitation needed: _ bagging ___ minutes: ___ _ chest compressions: ____ minutes: _ epinephrine: ____

HCO5: same data form as for first extubation in the main trial

Extubation to: NIPPV __ CPAP ___ high-flow nasal cannula ___ low flow nasal cannula ___ oxihood ___ ambient air ___

Stridor: ____ Racemic epinephrine: ____

Reintubation: no ___ yes ___ date: ____ time ____

~~HCO5: same data form as for first extubation in the main trial~~

~~7. Reintubation within 72 hours after extubation: no ___ yes: ___~~

~~If yes: date and time: _____~~

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Neonatal Research Network — Estimated Start Date:

Predicting Success of Extubation during Hydrocortisone Therapy and the Effect of Different Modes of Sync

Detailed Budget — Consent rate: 60%

Cost Category	April 2011-March Projections	
	Unit	Rate
I. Capitation (includes night, weekend, & holiday coverage)		
Months of Recruitment	0 mos	
A. Secondary Study		
Coordinator time (recruitment, data collection)(4 hrs/subject)	0 patients	$140
Respiratory Therapist time (30 minutes)	0 patients	$50
Subtotal Secondary Study		
Total Capitation		
II. Material Costs		
A. Other Direct Costs (indirects applied)		
Subtotal Other Direct Costs (indirects applied)		
B. Training		
	0	
Subtotal Additional Training (indirects applied)		
C. Equipment and Supplies (no indirects applied)		
Subtotal Equipment and Supplies (no indirects applied)		
Total Material Costs		
TOTAL DIRECT COSTS (Items I-IV)		
III. Indirect Costs (Unit = Total Direct Costs - Equipment and Supplies)	$0	52.60%
Total Indirect Costs		
ESTIMATED TOTAL COST		

6/1/2012
chronized Ventilation

2012	April 2012-March 2013 Projections			April 2013-March 2014 Projections			April 2
Total	Unit	Rate	Total	Unit	Rate	Total	Unit
	10 mos			12 mos			4 mos
$0	160 patients	$140	$22,400	192 patients	$140	$26,880	21 patients
$0	160 patients	$50	$8,000	192 patients	$50	$9,600	21 patients
$0			**$30,400**			**$36,480**	
$0			**$30,400**			**$36,480**	
$0			**$0**			**$0**	
$0	0		$0	0		$0	0
$0			**$0**			**$0**	
$0			**$0**			**$0**	
$0			**$0**			**$0**	
$0			**$30,400**			**$36,480**	
$0	$30,400	52.60%	$15,990	$36,480	52.60%	$19,188	$3,990
$0			**$15,990**			**$19,188**	
$0			**$46,390**			**$55,668**	

014-March 2015 Projections		TOTAL Projections			Add notes in this column to describe each line
Rate	Total	Unit	Rate	Total	
$140	$2,940	373	$140	$52,220	
$50	$1,050	373	$50	$18,650	
	$3,990			**$70,870**	
	$3,990			**$70,870**	
					Listed items are intended as memory joggers; c
	$0			**$0**	
	$0	0	$0		
	$0			**$0**	
	$0			**$0**	
	$0			**$0**	
	$3,990			**$70,870**	
52.60%	$2,099	$70,870	52.60%	$37,278	
	$2,099			**$37,278**	
	$6,089			**$108,148**	

item.

hange or add items as needed.

PREDICTING SUCCESS OF EXTUBATION DURING HYDROCORTISONE THERAPY IN PRETERM INFANTS < 30 WEEKS OF GESTATIONAL AGE

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Protocol

Rev 02/27/12

Proposed secondary study to

"A RANDOMIZED CONTROLLED TRIAL OF THE EFFECT OF HYDROCORTISONE ON SURVIVAL WITHOUT BRONCHOPULMONARY DYSPLASIA AND ON NEURODEVELOPMENTAL OUTCOMES AT 18 – 22 MONTHS OF AGE IN INTUBATED INFANTS <30 WEEKS GESTATIONAL AGE",

Referred to as "Main Hydrocortisone Study" in this protocol

Kristi Watterberg, PI

Thanks to: Diana Vasil, RN, Coordinator at UT Southwestern at Dallas, and Glenn Metoyer, RT, Parkland Memorial Hospital

1. ABSTRACT (SYNOPSIS)

This observational study is primarily designed to evaluate whether a short endotracheal continuous positive airway pressure (ET CPAP) test may help predict the success of extubation of premature infants <30 weeks estimated gestational age at birth who remain intubated at 14 - 28 days postnatal age. For this purpose, we will use the 3-minute ET CPAP test (also called "spontaneous breathing test" or SBT) described by Kamlin in a single center.[1] The primary aim of this study is to test the hypothesis that, among patients who are electively extubated based on criteria established in the main hydrocortisone study, the SBT will be more useful than clinical information alone to predict successful extubation. The secondary aim is to evaluate the point estimates and confidence intervals of sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio of a positive test, and likelihood ratio of a negative test for the SBT. The large number of patients we plan to recruit will allow us to test the external validity of the SBT in different centers using different types of ventilators, different modes of ventilation and different modes post-extubation therapy.

2. STATEMENT OF PROBLEM

Prediction of successful extubation in preterm infants remains a challenge. This question has not been addressed by the NRN, and specific data were not collected during the SUPPORT trial. Previous single-site studies suggested that successful extubation can be predicted by the SBT in preterm infants during the first days of life. However, validity of this test has not been established in a multicenter study, using different types of ventilators, different modes of ventilation and different modes post-extubation therapy, in a population of infants of greater post-natal age than in the original study by Kamlin et al.[1]

3. HYPOTHESIS

Previous studies suggest that the success of extubation may be higher in patients with a positive SBT.[1] Therefore, we hypothesize that SBT will be more useful than clinical information alone, as indicated by a greater proportion of babies who pass the SBT remaining extubated compared to those who fail the SBT.

The null hypothesis is that, among patients who are electively extubated based on criteria established in the main hydrocortisone study, the percentage of successful extubation among patients with positive SBT is not different from that in those who fail the SBT.

Secondary null hypotheses include :

1. The predictive value of the SBT is not affected by whether the baby is supported by a ventilator using a mode supporting all breaths or by SIMV.

2. The predictive value of the SBT is not affected by whether the baby is randomized to hydrocortisone or placebo. Hydrocortisone may affect lung compliance and laryngeal edema and thus improve success rate of extubation compared with placebo.

3. The predictive value of the SBT is not affected by the resistance of the endotracheal tube (ETT). While on CPAP small diameter and long length of the ETT may increase work of breathing and contribute to failing of the SBT while not affecting success of extubation.

4. The predictive value of the SBT is not affected by postnatal age (within the ranges expected in the hydrocortisone trial).

5. The predictive value of the SBT is not affected by the mode of respiratory support after extubation. We would expect that success of extubation will be greater on patients extubated to NIPPV than on CPAP or high-flow nasal cannula, and lowest on those extubated to low flow nasal cannula or room air.

4. SPECIFIC AIMS

Primary aim:

To compare, among patients who are electively extubated based on criteria established in the main hydrocortisone study, the percentage of successful extubation among patients with positive SBT with the percentage of successful extubation among those who fail the SBT.

Secondary aims:

1. To evaluate the point estimates and confidence intervals of sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio of a positive test, and likelihood ratio of a negative test for the SBT.

2. To evaluate point estimates and confidence intervals of sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio of a positive test, and likelihood ratio of a negative test for the SBT in various subgroups.

5. RATIONALE/JUSTIFICATION

Success of elective extubation is one of the quality measures in neonatal intensive care. This study is designed

1. To compare, among patients who are electively extubated based on criteria established in the main hydrocortisone study, the percentage of successful extubation among patients with positive SBT with the percentage of successful extubation among those who fail the SBT

2. To assess the external validity of the SBT to predict successful extubation in very premature infants. This proposal is the first multicenter study that will assess whether the predictive value of the SBT is better (or not) than other information available to the clinician (Fi02, PIP, PEEP, rate, presence of atelectasis, physiologic stability) to predict successful extubation.

Very little additional coordinator time will be needed to collect information that will be used in multivariate analysis that could build the basis for a future randomized trial.

6. BACKGROUND AND SIGNIFICANCE

Success of extubation is around 60-73% in extremely low birth weight infants.[2,3] Higher success rates (80-86%) have been reported in series including all preterm infants.[4,5] Infants who require re-intubation, with its attendant risks, may experience deterioration of their respiratory status due to atelectasis. Intermittent hypoxemia and/or hypercapnia prior to re-intubation may expose them to additional risks. On the other hand, a relatively large number of infants who self-extubate and remain extubated subsequently.[6] Those infants may be exposed to mechanical ventilation and potential ventilator-induced lung injury for longer than necessary or for elective reasons such as to facilitate growth or to prepare for surgery.

Thus, a test that improves the clinician's ability to predict readiness for extubation is highly desirable. Kamlin et al[1] compared three tests to predict success of extubation (no reintubation within 72 hours) in 50 infants with birth weight < 1250 grams using a 3-minute ET CPAP trial: (a) expired minute ventilation (VE) during ET CPAP; (b) ratio of minute ventilation during ET CPAP to minute ventilation during mechanical ventilation (VE ratio); (c) the spontaneous breathing test (SBT). The infant passed the SBT if there was no hypoxia or bradycardia during ET CPAP. The median age at the time of the study was 4 and 5 days, respectively, for successful extubations and for extubations followed by reintubation within 72 hours. Kamlin concluded that the SBT had the highest sensitivity

(97%), specificity (73%), positive predictive value (93%), negative predictive value (89%), likelihood ratio of a positive test (3.6) and the smallest likelihood ratio of a negative test (0.04) among the three tests.[1] Success rate of extubation predicted by a positive SBT was 38/41 (93%), compared with a success rate of 1/9 (11%) in those who failed the SBT. Limitations of this study included small sample size (n=50) and failure to separate infants ventilated by different synchronized modes. In that study infants were weaned by reducing the tidal volume to 3.5 ml/kg using AC or by reducing ventilator rates to 20–30 breaths/minute on SIMV.

A subsequent study (n=180) provided a degree of validation of the SBT, but compared this test to a historical cohort, which differed substantially from the practice at the time of the validation study. Once more, various modes of ventilation were used, and there was no subanalysis by mode.[7] Most babies in the validation cohort were on volume guarantee ventilation (94% vs 26% in the controls), and most of them were ventilated using AC at the time of extubation (81%, compared with 93% using SIMV in controls). The median age at extubation was 0 days (range 0-27) for babies undergoing the SBT and 0 days (range 0-11 days for controls). Compared with historical controls, infants were extubated at significantly higher ventilator rates and airway pressures using the SBT, but the success rate of extubation was not significantly different (78% with SBT versus 72% in historical controls). The sensitivity of the SBT was 83% (compared with 97% in the first study).

It is not known if the SBT is equally predictive in infants with evolving chronic lung disease and prolonged ventilator dependence. It is also not known if the SBT is equally predictive in infants on different modes of synchronized ventilation. It is possible that modes in which every breath is supported mask significant respiratory control center immaturity or afford less respiratory muscle training compared to SIMV. SIMV remains the most widely used mode of assisted ventilation in newborn infants,[7] despite its potential disadvantages related to high work of breathing resulting from the high resistance of small endotracheal tubes (ETT) in extremely low birth weight (ELBW) infants.[8-10] This is especially true as the SIMV rate is decreased during the weaning process. In contrast, AC and PSV (when used as a sole mode of ventilation) support each patient breath, thereby resulting in more even tidal volume, less tachypnea, lower work of breathing and lower tidal volume compared to SIMV.[11-13]

There is no information in the literature describing the success of extubation from various modes of ventilation. A practice survey of NRN investigators conducted in July 2011 yielded data from 10 centers. Ventilators include Draeger 8000 (n=6), Maquet Servol (n=5), Draeger Evita XL (n=2), Draeger VN500 (n=2), Avea (n=2), and Bird VIP (n=1). Pressure-controlled ventilation is predominantly used in 6 NRN centers, and volume-targeted ventilation in 3 centers, while both are used equally in 2 centers. Volume-targeted ventilation is used either often or most of the time in 7 centers, and is used both during the acute phase and during weaning; it is used during weaning by 5 of 10 centers. During weaning and for extubation SIMV is used predominantly by 5 centers and modes supporting all breaths are used predominantly by 5 centers. Extubation from high-frequency ventilation is either rarely or never used. Eight of 10 centers would be ready to perform a 3-min SBT in patients on high-frequency ventilation. In summary the survey showed substantial heterogeneity across centers, with approximate equal distribution of SIMV and modes supporting all breaths.

7. METHODS AND PROCEDURES

a) Study design

This is an observational study (prospective cohort) in a selected group of patients enrolled in a randomized trial (the main hydrocortisone study).

The study will involve analysis of (1) the frequency of successful elective extubation and (2) the operational characteristics of a diagnostic test (SBT).

The spontaneous breathing test (SBT) will be performed by the study team just before elective extubation decided by the clinicians according to the protocol of the main hydrocortisone study. Clinicians will remain blinded to the results.

b) Study population

We will use the same population as that for the main hydrocortisone study. All patients enrolled in the main hydrocortisone study will be approached for informed consent. It is up to each center to decide whether to use a separate consent for the sub-study, or a check on the consent form of the main hydrocortisone study.

c) Inclusion and exclusion criteria

Inclusion criteria:

These will be the same as for the main hydrocortisone study, i.e.,:
Patients eligible for this study will be infants between 14 – 28 postnatal days who:
(a) are <30 weeks estimated gestational age, to be randomized in two strata: $\leq 26^{6/7}$ and $27^{0/7} - 29^{6/7}$ weeks);
(b) were inborn at an NRN site or were admitted to an NRN site before 72 hours postnatal age;
(c) have received ≥ 7days of mechanical ventilation;
(d) are receiving mechanical ventilation through an endotracheal tube .

We anticipate a starting time for this sub-study to be at the earliest 6/1/2012.

Exclusion criteria:

Same as for the main hydrocortisone study, i.e.:

(a) Major congenital anomalies
(b) Decision to limit support
(c) Indomethacin or ibuprofen treatment within 48 hours of study drug
(d) Previous corticosteroid treatment for BPD
(e) Hydrocortisone treatment for hypotension in the first week of life is common (35) and will not be an exclusion; however, infants will be excluded if they have received hydrocortisone:
    (i) for ≥ 14 cumulative days OR
    (ii) within 7 days of study entry.

In addition, we will exclude for this secondary study patients who have at the time of extubation an ETT size <2.5.

d) Enrollment centers and PIs

Case Western	Michele Walsh
Dallas	Luc P Brion
Wayne State	Seetha Shankaran
Emory	Barbara Stoll
Cincinnati	Kurt Schibler
Indiana	Brenda Poindexter
Brown	Martin Keszler
Stanford	Krisa Van Meurs
Alabama	Waldemar Carlo
Houston	Kathleen Kennedy
Duke	Ronald Goldberg
Iowa	Edward Bell
New Mexico	Kristi Watterberg
Pennsylvania	Barbara Schmidt

Rochester	Carl D'Angio
UCLA	Uday Devaskar
Ohio State	Leif Nelin
Missouri	William Truog

e) Study intervention and procedures

We will perform a maximum of 2 SBTs per patient: one at the time of the first elective extubation and one at the time of the second elective extubation, if any. Spontaneous unplanned extubations will not be analyzed since SBT will not be performed.

Extubation criteria in the main hydrocortisone study are as follows: "Extubation must be attempted within 72 hours of starting study drug and within 24 hours after meeting the following criteria: the FiO2 is <0.40 to maintain a saturation of 88%, the mean airway pressure is < 8, and the infant is hemodynamically stable (as defined for the SUPPORT trial: "clinically acceptable blood pressure and perfusion in the opinion of the clinical team")."

We will request that the clinical team inform the NRN coordinator of any pending extubation after the baby has been enrolled to this sub-study.

The intervention (SBT) will be similar to that described by Kamlin et al.[1] Specifically, when the clinicians decide a baby is ready to be extubated, the investigator will perform the SBT within 4 hours of the planned extubation. This intervention will be masked in order to prevent bias that would occur if the clinical provider knew the result of the SBT. We propose that the SBT be conducted after rounds in centers that review the monitoring tracing during rounds. The infant's ETT will be suctioned prior to the SBT if suctioning is clinically indicated. The SBT will be done no less than 10 minutes after suctioning to ensure adequate re-recruitment of lung volume.

The researcher will silence any alarms and will place screens around the bedside before initiating the test to minimize the chance of unblinding. After ensuring that the clinical care team, including the patient's nurse, is away from be bedside (to maintain blinding) the investigator (respiratory therapist, fellow, nurse practitioner or attending), who must not be involved with the patient's clinical care, will switch the ventilator to CPAP for 3 minutes at the same pressure as the positive end-expiratory pressure setting. The intervention will be done when the infant is in a quiet state, taking care to minimize stimulation and disturbance during the study.

The baby succeeds the SBT if he or she requires no more than a 15% increase in FiO_2 for isolated hypoxemia and does not develop bradycardia (HR <100) for more than 15 seconds. After 3 minutes on CPAP the study will be stopped, and ventilation will be restarted.

The baby fails the SBT if he or she develops a bradycardia (HR <100) for more than 15 seconds and/or a fall in SpO2 below 85% despite 15% increase in FiO_2. If isolated hypoxemia develops, FiO_2 will be increased according to unit protocol. If hypoxemia does not respond to a 15% increase in FiO_2, or if bradycardia develops, manual breaths will be given through the ventilator and mechanical ventilation will be restarted at the previous settings.

The baby will be placed back on previous ventilatory settings for 30 minutes, to limit the risk of derecruitment that could have resulted from performing the SBT. The investigator will document in the chart and communicate to the clinical team that the SBT was performed, the exact time of the procedure and the earliest time of extubation (30 min after the SBT). The results of the SBT will not be disclosed to the clinician or documented into the chart unless additional therapy is required as indicated below.

In rare circumstances, the baby may not respond well to the usual intervention described above. In that case, manual bagging will be initiated and additional treatment will be provided according to NRP guidelines, and the clinical

team will be informed. NRP guidelines will be followed if the infant requires more extensive intervention. Once stable, the infant will be placed back on mechanical ventilation.

Required follow-up

None beyond 72 hours after the second elective extubation

f) Primary and secondary outcomes

Primary outcome:

Comparison of the percentage of successful extubation among patients with positive SBT with that in those with a negative SBT

Secondary outcomes:

1. Point estimates and confidence intervals of sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio of a positive test, and likelihood ratio of a negative test to predict successful (defined as no reintubation within 72 hours) extubation using SBT

   a) In the entire cohort undergoing SBT

   b) In two subgroups: infants with gestational age $\leq 26^{6/7}$ versus those with gestational age $27^{0/7} - 29^{6/7}$ weeks

   c) In two subgroups: infants ventilated with SIMV and infants ventilated using modes supporting all breaths at the time of the SBT

   d) By primary study group (hydrocortisone versus placebo).

   e) According to ETT diameter, since resistance is proportionate to: $R \propto L / r4$, where L is the length of the tube and r is its radius

   f) According to postnatal age

   g) According to the mode of respiratory support used after extubation: NIPPV; CPAP or high-flow nasal cannula; low flow nasal cannula, oxihood or ambient air.

   h) Using different definitions of failed extubation (at 12, 24 and 48 hours instead of 72 hours after extubation)

2. Odds ratio of successful extubation taking into account the SBT and multiple possible confounders

Data to collect for this study beyond those in the main trial (see Appendix B):

1. Clinical information before the SBT: Mode of ventilation, ventilatory settings, vital signs, most recent blood gas, ETT size
2. Response to SBT
3. Respiratory support after the elective extubation

g) Sample size and power estimate

Criteria used for elective extubation in the main hydrocortisone trial were targeted toward the lower end of the criteria in the SUPPORT trial.. In Kamlin's original study[1] 86% of the infants had a positive SBT, and the success rate of extubation predicted by a positive SBT was 93%, compared with a success rate of 78% in the total cohort.

To the extent possible, we will use all available subjects from the total sample size of 800 available in the main trial. By the time the sub-study is expected to start, 100 of 800 patients will have been enrolled into the main trial. Patients who self extubate before the SBT and remain off mechanical ventilation will not be available for this analysis, leaving 630 patients to approach for consent. Those who are reintubated will have another SBT performed before attempting elective extubation. If we obtain 60% of consent, this will lead to 370 patients available for the primary outcome.

Estimates of the power to detect a difference in probability of successful extubation between individuals with a positive ABT and those with a negative SBT for an assumed total of 370 subjects were calculated for a range of assumptions about rates positive SBT and of successful extubation were calculated based on two-tailed chi-square test of differences in proportions and a Type I error of 0.05. The percentage of successful extubations was assumed to be at least 60% (ranging from 60% to 80%), the percentage of individuals with positive SBT were also assumed to range between 60% and 80%, with the difference in successful extubation in those with positive SBT assumed to be in the range of 7% to 10% greater than the overall success rate. Under these assumptions, the power to detect a difference in extubation success in those individuals with a positive SBT and those with a negative SBT was 92% or greater if the difference in the overall success rate and the success rate in those with positive SBT was 7% and greater than 99% if the difference in success rate was 10%.

The Kamlin study,[1] which compared three tests, had a sample size of 50. This study was powered to detect a difference of one standard deviation in mean VE in the group failing extubation but not to detect differences in dichotomous outcomes between the three tests. This was a single-center study with a relatively uniform approach to ventilation. The high degree of variability of clinical practice within the NRN will impact the outcome measures in this proposed multicenter trial, thus clearly requiring a much larger sample size to detect a comparable effect size.

The secondary aim of this study is to generate estimates of the operating characteristics (sensitivity [Se], specificity [Sp], positive predictive value [PPV] and negative predictive value [NPV]) of the 3-minute ET CPAP test ("spontaneous breathing test" or SBT) for predicting successful extubation in this population of infants. Each of the operating characteristics of interest is a conditional probability (where the calculation is conditioned on a either success or failure of the extubation or the positive or negative value for the SBT), and the primary sample size consideration for the study is the precision with which these probabilities can be estimated with the available sample sizes. Based on information provided earlier that suggests that 60% to 80% of the extubations are likely to be successful, we assume that between 20% and 80% of the 550 subjects will be used in the denominator of each of the calculations. Furthermore, operating characteristics in the range of 0.7 to 1 are of greatest interest. Given those assumptions the available sample sizes are sufficient to provide confidence intervals with half widths, where a 95% confidence interval is typically computed as the estimate of the sensitivity ± the half width, shown in the table below.

Estimates of Confidence Interval Half Width for Different Levels of True Measure Prevalence and Conditional Denominator

Se, Sp, PPV, NPV Value	Half Interval Width for Available Denominator						
	110	165	220	275	330	385	440
0.70	0.084	0.069	0.059	0.053	0.048	0.045	0.042
0.72	0.082	0.067	0.058	0.052	0.047	0.044	0.041
0.74	0.082	0.067	0.058	0.052	0.047	0.044	0.041
0.76	0.080	0.065	0.056	0.050	0.046	0.043	0.040
0.78	0.077	0.063	0.055	0.049	0.045	0.041	0.039
0.80	0.075	0.061	0.053	0.047	0.043	0.040	0.037
0.82	0.072	0.059	0.051	0.045	0.041	0.038	0.036
0.84	0.069	0.056	0.048	0.043	0.040	0.037	0.034
0.86	0.065	0.053	0.046	0.041	0.037	0.035	0.032
0.88	0.061	0.050	0.043	0.038	0.035	0.032	0.030
0.90	0.056	0.046	0.040	0.035	0.032	0.030	0.028
0.92	0.051	0.041	0.036	0.032	0.029	0.027	0.025
0.94	0.044	0.036	0.031	0.028	0.026	0.024	0.022
0.96	0.037	0.030	0.026	0.023	0.021	0.020	0.018
0.98	0.026	0.021	0.019	0.017	0.015	0.014	0.013

i) Available population/compatibility with other ongoing protocols

Same as for the main hydrocortisone study: Based on GDB data 06-07, and assuming 60% consent rate, 800 infants could be recruited to the main hydrocortisone study over 3 years. Since the secondary study will start at the earliest 6/1/2012 we estimate 100 infants will have been recruited already in the main hydrocortisone study. Patients who self extubate before the SBT and remain off mechanical ventilation will not be available for this analysis, leaving 630 patients to approach for consent. Those who are reintubated will have another SBT performed before attempting elective extubation. If we obtain 60% of consent, this will lead to 370 patients available for the primary outcome.

j) Projected recruitment time

The projected recruitment time for the main hydrocortisone study was 30 months. However, as of November 2011, only 16 had been randomized per month (versus an original main trial estimate of 27 recruited per month). Initiation of the secondary study could be expected within 6 months (i.e., by 6/1/2012). Since recruitment into the main hydrocortisone study is slower than expected, recruitment may last longer than initially expected.

k) Data Analysis Plan

We will use chi-square analysis to compare the success of extubation in patients who will successively pass the SBT with that among all patients who are electively extubated and undergoing the SBT.

We will determine the point estimates and 95% confidence intervals for the operating characteristics (sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio of a positive test, and likelihood ratio of a negative test) of successful extubation using the SBT in all patients undergoing SBT.

We will determine the same point estimates and 95% confidence intervals for the operating characteristics tests in the following subgroups:

a) In the entire cohort undergoing SBT

b) In two subgroups: infants with gestational age $\leq 26^{6/7}$ versus those with gestational age $27^{0/7} - 29^{6/7}$ weeks

c) In two subgroups: infants ventilated with SIMV and infants ventilated using modes supporting all breaths at the time of the SBT

d) By primary study group (hydrocortisone versus placebo).

e) According to ETT diameter, since resistance is proportionate to: $R \propto L / r^4$, where L is the length of the tube and r is its radius

f) According to postnatal age

g) According to the mode of respiratory support used after extubation: NIPPV; CPAP or high-flow nasal cannula; low flow nasal cannula, oxihood or ambient air

h) Using different definitions of failed extubation (at 12, 24 and 48 hours instead of 72 hours after extubation)

We will use Receiving operator characteristic curve (ROC) to analyze whether the operating characteristics of the SBT vary according to ETT resistance and to postnatal age.

The likelihood of success of extubation may depend on multiple factors other than SBT, including patient characteristics, mode of ventilation, individual clinician and center. For this purpose we will use multivariate logistic regression analysis using as predictors:[1] gestational age, weight for age at birth, postnatal age, PEEP, mode of ventilation and ventilation settings at the time of SBT (SIMV vs. ventilation supporting every breath), SBT, hydrocortisone (vs. placebo), caffeine, symptomatic patent ductus arteriosus, center, and mode of respiratory support after extubation (NIPPV, CPAP, high flow nasal cannula, low flow nasal cannula, room air). Additional factors that differ by $p < 0.10$ on univariate analysis will be tested for significance in the multiple regression analysis.

l) Data safety monitoring plan:

Eight interim blocks are planned in the main hydrocortisone study. The DSMC will review data from the main trial and from this secondary study at the same time. For this secondary study, the DSMC will review the frequency of required treatment (bagging, resuscitation) related to the SBT. Serious adverse events to be reported to NICHD within 24 hours include death that would occur after a code related to the SBT.

m) Stopping limits for protocol termination:

The DSMC may decide to stop the main trial or this secondary study.

8. RISK, BENEFITS, LIMITATIONS

Ethical issues

Benefit: There is no direct benefit to participating in this secondary study.

Risks: Some babies may develop bradycardia or desaturation and may require increase in FiO_2 or manual breaths on the ventilator at the time of SBT. It is possible that an occasional infant may require additional interventions.

However, no case of resuscitation related to the SBT has been described in the two published studies. Any baby requiring resuscitation will be reported to the IRB as an adverse event.

Blinding: SBT failure may be fairly predictive of failure of extubation. However, it is not part of standard practice in centers in the NRN. If the results of the SBT were provided to the clinical care team, it would result in bias in decision of extubation time. The SBT as described has been reported in two studies involving a total of 230 neonates. Since reported infants undergoing the SBT had an uneventful course even if failing the SBT, blinding the clinical care team to the results of this test is defensible, except in the rare circumstance of a more serious deterioration that required more than a few breaths through the ventilator and resumption of mechanical ventilation (in which case the clinical team will be informed of the event).

Consent form: A consent form will be obtained for participation in this study. There is a slight possibility that asking for permission for this secondary study would affect enrollment rate in the primary study. Each center PI will decide whether to use a separate consent for this secondary study or to embed it in the consent form for the main hydrocortisone study.

Limitations and alternatives

Since this is an observational rather than a randomized study, success of extubation may be affected by multiple factors, biases and confounders, some of which we may not be able to quantify. Based on our survey, it appears that selection of the ventilation mode depends in large part on center and care provider/attending choice than on patient characteristics. For this purpose we will conduct multivariate analysis using patient characteristics (GA, prenatal steroids, disease severity), and information about individual patients.

There may be inter-institutional and inter-individual variability in the decision about when to extubate. Variability will be limited by criteria set by Kristi Watterberg in the main trial protocol: "Extubation must be attempted within 72 hours of starting study drug and within 24 hours after meeting the following criteria: the FiO2 is <0.40 to maintain a saturation of 88%, the mean airway pressure is < 8, and the infant is hemodynamically stable (as defined for the SUPPORT trial: "clinically acceptable blood pressure and perfusion in the opinion of the clinical team"). The infant may be extubated from higher settings at the discretion of the attending physician. If the infant does not meet these criteria within 72 hours, he/she will be reassessed every 24 hours during the intervention period and extubation will be attempted within 24 hours of those criteria being met."

Success of extubation depends on absence of apnea. Apnea may not be detected during the 3 minutes during which the SBT will be performed. We expect that a majority but not all patients in the current trial may be on caffeine at the time of extubation, since a large multicenter randomized trial has shown it reduces the rate of bronchopulmonary dysplasia (oxygen requirement at 36 weeks postmenstrual age)[14] and improves the rate of survival without neurodevelopmental disability at 18 to 21 months but not in early childhood in infants with very low birth weight infants.[15,16]

Success of extubation will be limited in case of laryngeal edema, which may be more prevalent in the control arm. Hydrocortisone may limit this risk. We will record documentation of stridor and failure of successful extubation related to stridor.

We will not use VE as a predictor for extubation because the tidal volume cannot reliably be measured when the leak around the endotracheal tube is $\geq$ 30%, In spontaneously breathing infants, the tidal volume is not stable and the number of r breaths over which the VE is averaged varies among different types of ventilators.

SIMV with PS will be classified as a mode supporting all breaths; however this mode supports some breaths fully (SIMV) and other breaths to a lower extent (PS), in contrast with AC or PS.

We did consider alternatives to Kamlin's SBT.

1. During the SBT the baby will need to breathe against the resistance of the endotracheal tube. The resistance of the tube is proportional to L / r^4, where L is the length of the tube and r is its radius. We will record length and radius to assess whether the predictive value of the SBT decreases with increased resistance of the tube. An alternative to the SBT would be to design a modified SBT using PSV with minimal pressure instead of CPAP. Since no complications have been described with the SBT, this may not be necessary. Since this has not been tested in the past, we will not use this option.

2. Wilson et al[17] described a minute ventilation test (MVT) of 10 minutes duration instead of the 3-minute test described by Kamlin. In a single institution, a spontaneous minute ventilation $\geq$ 50% of the ventilator-generated minute ventilation correctly predicted successful extubation in 86% of preterm infants with birth weight < 2 kg and requiring mechanical ventilation for > 24 hours. In a subsequent randomized trial[18] (mean GA 30 weeks), babies undergoing the MVT were extubated sooner than those in the control group. The positive predictive value of the MVT for extubation was 76% (95% CI, 55 to 89%) and the success of extubation was similar to the control group.[19] Kamlin's SBT is more appropriate for our study for several reasons: His studies only included smaller babies; the SBT only uses 3 minutes and does not require minute ventilation measurement and thus could be used in multicenter setting with various ventilators, and appears at least as good as the 10 minute MVT.

3. Dimitriou et al[5] have described composite indices such as the diaphragmatic pressure–time index and the noninvasive respiratory muscle pressure–time index to predict success of extubation in preterm with mean gestatational age of 30 weeks and mean birthweight of 1.36 kg. The test had 86% positive predictive value of successful extubation in the validation group. Kamlin's SBT is more appropriate for our study for the same reasons as described for the 10 minute MVT.

We also considered extracting data from the SUPPORT for sample size analysis. However, discussions with Marie Gantz and Abhik Das suggest that intubation and extubation data from SUPPORT were collected in a way that would not allow reliable estimation of the rate of successful extubation. Therefore, we used estimates from Kamlin and constructed appropriate confidence intervals.

9. BUDGET

Direct Costs

Cost per patient:		$ 190
Respiratory therapist: 30 minutes x $50 per hour =		$ 50
Coordinator time: 4 hours x $35 per hour =		$ 140
Consent:	30 minutes	
Screening for subjects who qualify for extubation:	60 minutes	
SBT:	60 minutes	
Data collection/entry/transmission:	90 minutes	
Total Capitation Cost for 373 patients:		$70,870
Total direct costs		$70,870
Indirect costs (52.6%):		$37,278
Total costs:		$108,148

Note: there is no CPT code for the SBT test

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Appendix A: Authorship Plan:

We will follow the Policies and Procedures of the NICHD Neonatal Research Network

For abstracts, Authors of the Secondary Study with be the authors followed by "for the NICHD Neonatal Research Network.

For publications, authors will include Authors of the Protocol Subcommittee, Remaining participating Center PIs (those not serving on the Protocol Subcommittee), listed in order by the Center's combined ranking of the number of infants enrolled and the percent of eligible infants enrolled in the study by the Center, Followed by the phrase "for the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network."

Appendix B1: Data sample sheet

Data obtained for the main hydrocortisone study and location on GDB or main hydrocortisone study forms:

Center:	HCO2
Gestational age	HCO1
Birth weight	GDB
Date of birth	HCO1
Date of randomization	HCO2
Randomization code	HCO2
Information about first extubation	HCO5

Appendix B2: Data sample sheet

Data obtained for the secondary study: first elective extubation:

Planned extubation date and time: _____ ETT diameter (mm): ____

Symptomatic PDA: Yes ____ No _____ Caffeine: yes ____ No _____

SBT: date and time:_____Immediately before SBT	During SBT
Ventilation mode: _ PS _____ SIMV _____ SIMV with PS _____AC _____ Volume mode ___ Pressure control _____	From ____ until _____
ETT diameter: ___ length at lips: ___	
Latest pH:___ pCO2: ___ BE: ____	
PIP:_____ MAP: _____Ventilator rate:_____ PEEP: ____ cm FiO2: _____ Sat: _____	CPAP: ____ cm
HR > 100: yes ____ no ____	Min HR < 100 for > 15 sec: Yes _____ No _____
FiO2: ___ Sat: ____	Fall < 85% despite 15% increase in FiO2: Yes _____ No _____
	Max FiO2 Manual breaths through ventilator: number: ___ Resuscitation needed: bagging ___ minutes: ___ chest compressions: ____ minutes: epinephrine: _____

Exbutation to: NIPPV __ CPAP ___ high-flow nasal cannula ___low flow nasal cannula ___ oxihood ___ ambient air ___

Stridor: _____ Racemic epinephrine: ____

Reintubation: no ____ yes ___ date: _____ time_____

Appendix B3: Data sample sheet

Data obtained for the secondary study: second elective extubation:

Planned extubation date and time: _____ ETT diameter (mm): ____

Symptomatic PDA: Yes ____ No _____ Caffeine: yes ____ No _____

SBT: date and time: _____

Immediately before SBT	During SBT
Ventilation mode: _ PS _____ SIMV _____ SIMV with PS _____AC _____ Volume mode ___ Pressure control _____	From ____ until _____
ETT diameter: ___ length at lips: ___	
Latest pH:___ pCO2: ___ BE: ____	
PIP:_____ MAP: _____Ventilator rate:_____ PEEP: ____ cm FiO2: _____ Sat: _____	CPAP: ____ cm
HR > 100: yes ____ no ____	Min HR < 100 for > 15 sec: Yes _____ No _____
FiO2: ___ Sat: ____	Fall < 85% despite 15% increase in FiO2: Yes _____ No _____
	Max FiO2 Manual breaths through ventilator: number: ___ Resuscitation needed: bagging ___ minutes: ___ chest compressions: ____ minutes: epinephrine: _____

HCO5: same data form as for first extubation in the main trial

Extubation to: NIPPV __ CPAP ___ high-flow nasal cannula ___low flow nasal cannula ___ oxihood ___ ambient air ___

Stridor:_____Racemic epinephrine: ____

Reintubation: no ____ yes ___ date: _____ time_____

DATE: *February 10, 2012*

TO: *Brenda Poindexter*
Chair, Protocol Review Subcommittee

FROM: *Luc Brion*

RE: *Itemized response to the Protocol Review Subcommittee re: "Predicting Success of Extubation During Hydrocortisone Therapy and the Effect of Different Modes of Synchronized Ventilation"*

Cc: *Dennis Wallace, Carl d'Angio, Martin Keszler, Kristi Watterberg, Rose Higgins*

We thank the protocol review subcommittee for a careful review of our proposal. We added itemized responses to each comment that required either a response or a change in the protocol. We modified the protocol considerably along the guidelines provided by the committee. Our responses are in italics.

The Protocol Review Subcommittee reviewed this protocol during its conference call on January 3, 2012. Written comments were provided by Kurt Schibler, Brenda Poindexter, and Stephanie Archer and are included below.

The Subcommittee discussed differences between the population of infants studied in the Melbourne trial of spontaneous breathing versus those that will be in the hydrocortisone trial. It was noted that the investigators in Melbourne who described this test were using it every day on rounds, the purpose being to extubate VLBW infants as soon as possible (median age 4-5 days). On the other hand, infants in the hydrocortisone trial are a unique subgroup of babies who are stuck on the ventilator. The investigators need to explain how the results of the spontaneous breathing test (SBT) in the hydrocortisone cohort will be generalizable in the typical NICU setting.

We agree that the postnatal age of patients in the hydrocortisone study is different from those in the Melbourne study. We also agree data in the proposed study will not be generalizable to all patients in the NICU. The proposed study is specifically designed to address the current knowledge gap in the literature, i.e., vailidity of the SBT at later postnatal age. We have clarified the protocol to indicate this and expanded the rationale for the study.

The specific aim related to modes of ventilation was discussed at length by the Subcommittee. Given center differences in the use of assisted modes of ventilation, the consensus of the Subcommittee is that this aim is not feasible. In addition, only a limited amount of data is currently being collected for the Hydrocortisone trial (see HCO4 respiratory data collection form); in order to address the aim related to assisted ventilation, a significant increase in data collection would need to be incorporated into the study design.

We have removed the specific aim related to duration of ventilation based on different modes of ventilation.

Finally, the Subcommittee discussed the potential confounding of post-extubation management. In the current protocol, it is not clear how differences in clinical management following extubation will be handled (many which could significantly impact the success of extubation).

This may actually be a strength of the proposed study, which is aimed at finding out if the SBT is a better predictor of readiness for extubation than clinician choice across multiple centers using multiple approaches to post-extubation therapy (CPAP, high-flow nasal cannula, NIPPV). We will collect this information and analyze it by secondary subgroup analysis and by multivariate analysis.

As currently written, the Subcommittee had low enthusiasm for the proposed secondary. However, the Subcommittee would be willing to review a revised version of the protocol which addresses the concerns outlined below.

Comments submitted by Kurt Schibler:

This observational study is primarily designed to evaluate whether a short endotracheal continuous positive airway pressure (ET CPAP) test may help predict the success of extubation of very premature infants.

1) The primary aim of this study is evaluate the point estimates and confidence intervals of sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio of a positive test, and likelihood ratio of a negative test for the spontaneous breathing test (SBT).

2) Secondary aims are 1) To evaluate point estimates and confidence intervals of sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio of a positive test, and likelihood ratio of a negative test for the SBT in two subgroups: infants ventilated with SIMV and infants ventilated using modes supporting all breaths and 2) To determine if ventilation modes that support every breath are associated with shorter duration of mechanical ventilation than SIMV.

Methods

Study design - This is an observational study with prospective data collection.

The study will involve analysis of the operational characteristics of a diagnostic test (SBT) and retrospective analysis of a cohort study (using two cohorts: babies ventilated using SIMV and babies ventilated using modes supporting all breaths).

The spontaneous breathing test (SBT) will be performed by the study team just before extubation decided by the clinicians. Clinicians will remain blinded to the results.

Study population - We will use the same population as that for the main study. All patients enrolled in the main study will be approached for an optional consent, indicated by a check on the consent to the main study

Study intervention - when the clinicians decide a baby is ready to be extubated, the investigator will perform the SBT within 4 hours of the planned extubation.

The researcher will silence any alarms and will place screens around the bedside before initiating the test to minimize the chance of unblinding. After ensuring that the clinical care team, including the patient's nurse, is away from be bedside (to maintain blinding) the investigator (respiratory therapist, fellow, nurse practitioner or attending), who must not be involved with the patient's clinical care, will switch the ventilator to CPAP for 3 minutes at the same pressure as the positive end-expiratory pressure setting. The infant's ETT will be suctioned prior to the SBT if clinically indicated, and the intervention will be done when the infant is in a quiet state, taking care to minimize stimulation and disturbance during the study. The baby fails the SBT if he or she develops a bradycardia (HR <100) for more than 15 seconds and/or a fall in SpO2 below 85% despite a 15% increase in FIO2. At this point the study will be stopped, and ventilation will be restarted. If manual breaths are given through the ventilator because of bradycardia or desaturation, this will be considered a failed test. Data on the mode of ventilation, success and time of extubation will be collected for subsequent analysis.

The baby will be placed back on previous ventilatory settings to 30 minutes, to limit the risk of derecruitment that could have resulted from performing the SBT.

Sample size

The investigators estimate that about 70% of the total sample size available in the main trial will be available for the analysis of this secondary study; thus sample size is estimated at 550. Since the secondary study will start after the beginning of the main study, the total number of patients in this secondary study will be probably 10% smaller, i.e. 500 patients.

Analysis plan

The investigators will determine the point estimates and 95% confidence intervals for the operating characteristics (sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio of a positive test, and likelihood ratio of a negative test) of successful extubation using the SBT.

Investigators will use the same tests in subgroups:

1. infants ventilated with SIMV versus infants ventilated using modes supporting all breaths at the time of the SBT.
2. infants with gestational age $\leq 26^{6/7}$ versus those with gestational age $27^{0/7} - 29^{6/7}$ weeks

Receiving operator characteristic curve (ROC) will be used to analyze whether the operating characteristics of the SBT vary according to ETT resistance and to postnatal age.

Comments

1. Allowing time after suctioning and after the SBT for potential re-recruitment of alveoli is important particularly in the lower gestational age strata. – *We added a minimum of 10 minutes between suctioning and the SBT.*

2. The reasons for failure to remain extubated for 72 hours are multifactorial including individual infant associate factors and factors related to providers or center. – *This fact is acknowledged in the protocol and in the limitations. We will use multivariate analysis for this purpose; however we will not control for individual providers. We may actually consider this heterogeneity of approach to patient care as one strength of this study: this will enhance external validation of the SBT test, which so far has only been tested in single-center studies.*

3. It may not be possible to have SBT performed by someone not involved in clinical care of the study infant. *We believe it is important to maintain blinding of SBT. The study cannot be done without masking the clinical team. If the caregivers know whether the baby has passed or failed the SBT, they will be biased by the study, and therefore it will be impossible to determine the outcomes described for the study. It would be up to each center to decide whether the study PI, coordinator, respiratory therapist, fellow, attending, or NNP not currently providing clinical care of the infant would be involved in the SBT. Centers who are not able to perform blinding SBT should not participate.*

4. The effects of the study medication in the main trial may influence the utility of the SBT to predict extubation success. *The study is designed to determine this as one of the secondary outcomes and this will be included in the multivariate analysis. We realize that steroids may improve lung compliance and reduce the risk of laryngeal edema.*

5. The study forms and additional data to be collected should be included with the protocol in order to determine how time intensive the secondary study will be. *Appendix B includes all the additional information required for the study, and was edited to include all the comments and suggestions from the reviewer. Further development of the forms will be done in the manual.*

6. The respiratory support variable collected around the time of the test may have little bearing on modes of support and their influence on extubation success or failure. *We agree with the reviewer that this variable may not affect the validity of the SBT. This will be one among many variables we will test.*

7. Whether consent should be imbedded or not should be at the discretion of the centers. *We changed the protocol accordingly.*

Comments submitted by Brenda Poindexter:

SUMMARY: The proposed study is a secondary study to the hydrocortisone trial to assess the sensitivity, specificity, positive and negative predictive value of the spontaneous breathing test (SBT) in predicting successful extubation in ELBW infants.

1. The authors state that because this is an observational study, there is no primary hypothesis. This needs to be revised to reflect the analyses that will be done (hypothesis could be that the SBT will be more useful than clinical information alone). *Thank you for this suggestion. The null hypothesis is that the percentage of successful extubation among patients with positive SBT is not different from that in those extubated based on criteria established for extubation in the main hydrocortisone study. This will be analyzed by comparing patients with positive SBT with those with negative SBT. The study has enough power to do this analysis in the whole group..*In the methods and procedures section of the protocol the authors state that the study will involve analysis of the operational characteristics of the SBT and retrospective analysis of a cohort study. The retrospective analysis is not mentioned anywhere else in the protocol. As currently written, it seems that all infants enrolled as part of the hydrocortisone for extubation main trial will all receive the SBT, so it is is not clear where the retrospective cohort will come from. *Thank you for this comment; this was a mistake and we have removed this sentence from the study design.* If the primary question is whether the SBT has better predictive ability than typical clinical information (such as FiO2, PIP, PEEP, etc.) as stated in the rationale/justification, then wouldn't there need to be a control group of infants who are subjected to the SBT? *We changed the primary aim of the study: "To compare the percentage of successful extubation among patients with positive SBT with that in those extubated based on criteria established for extubation in the main hydrocortisone study.",*

2. Secondary aim – the second secondary aim is to determine if ventilation modes that support every breath are associated with shorter duration of mechanical ventilation than SIMV. Although data will be collected related to mode of ventilation at time of extubation, it would seem that detailed data related to respiratory support prior to the time of extubation would be required. The HC04 respiratory form collects only very limited information related to type of ventilator support on study days 1, 3, 5, 7, 10, and 14 and collects no information related to assist control or pressure support. If modes of assisted ventilation shorten the duration of mechanical ventilation, wouldn't the duration of being on an assisted mode also contribute to the outcome? In other words, I would think there would be a difference between infants whose entire course on the ventilator is in SIMV versus those who are only changed to SIMV during the final stages of weaning (for 12-24 hrs) prior to extubation. In the data analysis plan, the subgroups are only divided by mode of ventilation at the time of the SBT. How will duration of time in assisted ventilation mode be dealt with in the analyses? The investigators state that "very little additional coordinator time will be needed to collect information that will be used in multivariate analysis that could build the basis for a future randomized trial" but have not provided a draft of the proposed data collection forms to be utilized in the secondary study. The wide range of practice variation in modes of ventilator management at NRN centers provided by the survery results in the protocol highlight the likelihood that center

differences will bias the ability to evaluate this secondary aim (this concern was also raised in the concept comments). *We agree with the reviewer's concerns and eliminated this part of the study.*

3. Unplanned extubations – the investigators have not taken into account unplanned extubations (some of which are likely to be successful). How will these infants be handled in the analyses? *These events will be excluded from the analysis, since SBT is not performed.*

4. Post-extubation management – the role of post-extubation management is not addressed in the protocol as a potential confounder to prediction of extubation success. What type of data will be collected during the immediate post-extubation period and what variables (such as extubation to CPAP versus HFNC or SiPAP, use of racemic epinephrine, etc.) will be considered in the analytic plan. *This information was added to the protocol and to appendix B.*

5. Treatment group – one of the secondary null hypotheses is that the predictive value of the SBT is not affected by whether the baby is randomized to hydrocortisone or placebo. This hypothesis needs to be justified as hydrocortisone, if efficacious as defined by the primary outcome measure of the main trial, could significantly confound the primary outcome of likelihood of extubation success (in addition to the other potential confounders mentioned in the protocol including fluid management, caffeine, etc.). *We agree with the reviewer's comments. In this protocol we describe null hypotheses. "2. The predictive value of the SBT is not affected by whether the baby is randomized to hydrocortisone or placebo. Hydrocortisone may affect lung compliance and laryngeal edema and thus improve success rate of extubation compared with placebo." We will analyze potential confounders by using multivariate analysis, which is now listed as secondary outcome.*

6. Masking – the protocol states that the individual performing the SBT should not be involved in the clinical care of the infant. Clarification is needed regarding the duration of time that this individual cannot be involved in the clinical care (before and after performance of the SBT). Regardless of who performs the test, it may be impossible to avoid having this person involved in the clinical care of the infant. It would be helpful to specify the period of time that the person administering the SBT should not be involved in the clinical care of the infant. The issue of clinical documentation and masking also needs to be addressed in the protocol. If an infant has significant hypoxia and/or bradycardia during the SBT, how will the documentation in the medical record be addressed? Given that data from our monitors in the NICU is recorded and reviewed on rounds on a daily basis, significant episodes of desaturation and/or bradycardia will be difficult to not relay to the clinical team; in addition, if the infant does require PPV or other intervention following a failed SBT, the clinical team will need to be informed. I would think that the IRB would question the plan to not inform the clinical team of a significant desaturation or bradycardia event knowing that an extubation attempt is being planned by the clinical team in the immediate future. In this regard, I disagree with the investigators that blinding the clinical team of a failed SBT (at least in the case of significant bradycardia or need for resuscitation) is "defensible". *Thank you for your comments. The study cannot be done without masking the clinical team. If the caregivers know whether the baby has passed or failed the SBT, they will be biased by the study, and therefore it will be impossible to*

determine the outcomes described for the study. The large majority of the babies undergoing an SBT tolerate the procedure well and those who fail the SBT respond rapidly to manual breaths on the ventilator. The results of the SBT will not be disclosed to the clinician or documented into the chart unless additional therapy is required as indicated below. In rare circumstances, the baby may not respond well to the usual intervention described above. In that case, manual bagging will be initiated and additional treatment will be provided according to NRP guidelines, and the clinical team will be informed. NRP guidelines will be followed if the infant requires more extensive intervention. Once stable, the infant will be placed back on mechanical ventilation.. We have modified the protocol accordingly. We propose that the SBT be conducted after rounds in centers that review the monitoring tracing during rounds.

7. Budget – Two areas of the proposed budget warrant further consideration – first, there is a budget for a respiratory therapist for 15 minutes – does this mean that the SBT must be performed by a study respiratory therapist? I would assume that the majority of centers do not have respiratory therapists on their paid research team. For other NRN studies requiring support from respiratory therapists (such as SUPPORT, Benchmarking, and the iNO studies), we have always relied on respiratory therapists at the centers providing their time without reimbursement. - *The protocol leaves to each center the choice of who will be involved in performing the SBT; in some centers only respiratory therapists are allowed to change ventilator settings.* The second point that requires clarification is the 20 minutes of coordinator time for screening for subject who qualify for extubation. This would not be a one-time event, but rather would require daily screening until the infant met criteria for consideration of extubation. In addition, the decision to extubate is often made during morning rounds – therefore, this protocol will require that the clinical team inform the research coordinator of the intent to extubate in a timely manner (within the required 4 hours) or the opportunity to perform the SBT may be missed. In addition, for infants who require reintubation, the protocol states that a second SBT will be performed prior to the next extubation attempt; this effort for continuing to follow the infant after the first reintubation is not accounted for in the budget (nor is it required for the main RCT); the protocol is also inconsistent in this regard as the required follow-up is listed as being none beyond 72 hours after extubation (First extubation? Second if first one fails?). Finally, the budget needs to be adjusted to reflect the additional data collection for type of respiratory support (as mentioned above, HC04 does not record whether infant is on assist control, SIMV, or pressure support). Thus, the time estimate for coordinator effort for this secondary study is markedly underestimated in the current budget. - *We now indicate in the protocol that we will use only the first 2 elective extubations after randomization. Sample size analysis s is based on the first elective extubation only. The coordinator time was increased to 4 hours based on your recommendations. We increased the time by only one hour because we have eliminated the collection of ventilator mode and support between randomization and the day of the SBT. We further revised the budget to follow Stephanie Archer's recommendations. We propose to leave the respiratory therapist in the budget. At Parkland, the plan is that one of the 2 respiratory therapists on call (the one is not assigned to take care of the baby as a provider) assigned to the NICU will perform the SBT. Each center will decide who could do the SBT; some centers may use the*

coordinator, the PI, the alternate PI, another attending, fellow or NNP for this purpose. Alternatively, we may further revise the budget if we decide that respiratory therapists will not be involved in the study.

8. Consent – the authors state that they do not feel that the imbedded consent will affect enrollment in the main trial because of the opt-out ability, but I do think that this issue will need to be prospectively monitored to ensure that enrollment in the main trial is not compromised. I am not in favor of imbedding consent for this secondary into the main trial; I would suggest that the decision of whether or not to imbed consent be left to the individual centers. *We changed the protocol accordingly and will let each center choose whether to use a separate consent from or to imbed it into the consent for the main trial.*

9. Data collection forms – drafts of the proposed data collection forms need to be included in the protocol; without these, it is impossible to ascertain whether the time estimates in the budget are appropriate or not. *The data collection form is included in Appendix B and was updated based on all the comments from the review subcommittee.*

Comments submitted by Stephanie Archer:

Questions:

- Estimated Start Date. I'm assuming no earlier than 6/1/12. Obviously, the later this is, the smaller the sample size, and the cheaper the cost. *We modified the protocol accordingly.*
- Consent rate. Not sure how you can say you will capture 70% of the original study population with only a 60% consent rate. I've used 70% in this estimate. *We changed to 60% as is usual for NRN studies.* Sample size. This will depend on the start date, consent rate, and the rate of recruitment for the Main trial. As of November 2011, only 16 randomized (versus an original main trial estimate of 27 recruited per month). *We changed the protocol accordingly.*
- Respiratory therapist. This rate is too low. For IPGE, we used $100/hour, which is probably still too low. *We changed the budget accordingly.*
- Training costs. Assuming no need for extensive training for this secondary – with any training done at a Steering Committee meeting or via teleconference. *We changed the budget accordingly.*

Comments submitted during Concept Presentation (17 yes, 3 no votes):

Comments with yes votes

- This study can add critical information to the steroid tria.
- AC vs SIMV length of ventilation comparison is unlikely to yield useful results.
- Simple, inexpensive, important study.
- We'd enthusiastically test this hypothesis.
- Validation of SBT particularly among subgroups would be very valuable. Comparison of ventilator modes will b e hopelessly biased by center difference. It might be worth looking at multiple definitions of failure at 12, 24 and even 48 hours. *Comparison of duration of ventilation*

support by ventilator modes was eliminated from the protocol. We added various definitions of failure, as suggested, to secondary outcomes.

- Will PDA influence SBT? *This will be one of the variables assessed in the multivariate analysis.*
- Where is ref 4 cited? *All references are cited.*
- Good use of the HC extubation main trial to gain additional information.
- Consent should not be embedded as it may decrease consent into main trial. *This was changed; each center PI will decide whether to embed the consent into that of the main trial or to use a separate consent form.*
- Coordinator and RTI seemed to be an under-estimate. *The budget was revised accordingly.*
- SBT validation more worthwhile than trying to get at length of ventilation. Focus on SBT component. *The length of ventilation was removed from the protocol.*

Comments with no votes

- Not easy to predict by ~ 3 minute of CPAP. *Previous studies have shown that the SBT is superior to clinical parameters to predict successful extubation in preterm infants.* Issues with upper airway obstruction and apnea despite caffeine. *This information is being collected in this study.*
- Post extubation variation HFNC/CPAP. *This information will be collected and analyzed.*

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: Fw: New England Journal of Medicine - 12-01618
Date: Thursday, February 09, 2012 6:34:03 PM

Submitted!

----- Original Message -----
From: editorial@nejm.org [mailto:editorial@nejm.org]
Sent: Thursday, February 09, 2012 06:23 PM
To: mperalta@peds.uab.edu <mperalta@peds.uab.edu>; yvaucher@ucsd.edu <yvaucher@ucsd.edu>; wcarlo@peds.uab.edu <wcarlo@peds.uab.edu>; nfiner@ucsd.edu <nfiner@ucsd.edu>; mgantz@rti.org <mgantz@rti.org>; mcw3@po.CWRU.edu <mcw3@po.CWRU.edu>; alaptook@wihri.org <alaptook@wihri.org>; Bradley.yoder@hsc.utah.edu <Bradley.yoder@hsc.utah.edu>; roger.faix@hsc.utah.edu <roger.faix@hsc.utah.edu>; adas@rti.org <adas@rti.org>; kurt.schibler@cchmc.org <kurt.schibler@cchmc.org>; wrich@ucsd.edu <wrich@ucsd.edu>; Nancy.Newman@UHhospitals.org <Nancy.Newman@UHhospitals.org>; BVohr@wihri.org <BVohr@wihri.org>; kimberly.yolton@cchmc.org <kimberly.yolton@cchmc.org>; roy.heyne@utsouthwestern.edu <roy.heyne@utsouthwestern.edu>; (b)(6) @aol.com <(b)(6) @aol.com>; Patricia.W.Evans@uth.tmc.edu <Patricia.W.Evans@uth.tmc.edu>; golds005@mc.duke.edu <golds005@mc.duke.edu>; michael.acarregui@providence.org <michael.acarregui@providence.org>; iadamsc@emory.edu <iadamsc@emory.edu>; apappas@med.wayne.edu <apappas@med.wayne.edu>; srhintz@stanford.edu <srhintz@stanford.edu>; bpoindex@iupui.edu <bpoindex@iupui.edu>; emcgowan@tuftsmedicalcenter.org <emcgowan@tuftsmedicalcenter.org>; richard.ehrenkranz@yale.edu <richard.ehrenkranz@yale.edu>; (b)(6) @gmail.com <(b)(6) @gmail.com>; cbauer@peds.med.miami.edu <cbauer@peds.med.miami.edu>; jafuller@salud.unm.edu <jafuller@salud.unm.edu>; moshea@wfubmc.edu <moshea@wfubmc.edu>; gary_myers@urmc.rochester.edu <gary_myers@urmc.rochester.edu>; Higgins, Rosemary (NIH/NICHD) [E]; (b)(6) @aol.com (b)(6) @aol.com>
Subject: New England Journal of Medicine - 12-01618

Dear Dr. Peralta Carcelen and co-authors,

Thank you for submitting your manuscript, "Neurodevelopmental Outcome of Extremely Preterm Infants in a Trial of Two Different Oxygen Saturation Targets" to the New England Journal of Medicine.

Your manuscript has been forwarded to members of our editorial staff, who will make an initial evaluation and decide whether it merits further consideration. You will be notified of the decision as soon as possible.

Your manuscript ID is 12-01618.

Please mention the above manuscript ID in all future correspondence or when calling the office for questions. If there are any changes in your street address or e-mail address, please log in to ScholarOne Manuscripts at http://mc05.manuscriptcentral.com/nejm and edit your user information as appropriate. You may also view the status of your manuscript at any time by checking For Authors section of the site.

We are undertaking evaluation of your manuscript with the understanding that neither the substance of the article nor the figures or tables have been published or will be submitted for publication elsewhere during the period of review.

Please provide the editors with copies of other manuscripts by you or your coauthors addressing similar or related research questions that are in preparation or under consideration at other journals. This does not apply to abstracts published in connection with scientific meetings or to news reports based on presentations at such meetings.

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Please call us at 617-734-9800 if you have any questions.

Sincerely,

Jeffrey M. Drazen, M.D.
Editor-in-Chief
New England Journal of Medicine
Distinguished Parker B. Francis Professor of Medicine
Harvard Medical School

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10 Shattuck Street
Boston, MA 02115
(617) 734-9800
Fax: (617) 739-9864
http://www.nejm.org

From: Vaucher, Yvonne
To: Archer, Stephanie (NIH/NICHD) [E]; Abbot Laptook (alaptook@wihri.org); Abhik Das (adas@rti.org); "Brad Yoder (Bradley.yoder@hsc.utah.edu)"; Kristin Zaterka-Baxter (kzaterka@rti.org); Kurt Schibler (kurt.schibler@cchmc.org); Marie Gantz (mgantz@rti.org); "Michele Walsh (mcw3@cwru.edu)"; "Nancy Newman (nxs5@cwru.edu)"; Finer, Neil; Roger Faix (roger.faix@hsc.utah.edu); Vaucher, Yvonne; Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade; "Wally Carlo (wacarlo@uab.edu)"
Cc: Tim Stevens (Timothy_Stevens@URMC.Rochester.edu); Myriam Peralta-Carcelen (MPeralta@peds.uab.edu)
Subject: RE: PAS Late-Breaker Abstract | SUPPORT Breathing Outcomes
Date: Thursday, February 09, 2012 5:34:57 PM

Looks good.

In Results: Myriam's and my paper state a different total number of enrolled patients "1316 extremely preterm infants (24 weeks 0 days to 27 weeks 6 days) born between February 2005 and February 2009 at 20 centers..... The abstract states that " 1323 patients enrolled in SUPPORT...."

Also- the sentence reading "..However, at 6 mo.....pts treated with low vs. high sat....might be a bit clearer as "...pts treated with low sat....were less likely to report less wheezing, etc.....compared to those treated with high sat.

Yvonne

From: Archer, Stephanie (NIH/NICHD) [E] [archerst@mail.nih.gov]
Sent: Thursday, February 09, 2012 7:11 AM
To: Abbot Laptook (alaptook@wihri.org); Abhik Das (adas@rti.org); 'Brad Yoder (Bradley.yoder@hsc.utah.edu)'; Kristin Zaterka-Baxter (kzaterka@rti.org); Kurt Schibler (kurt.schibler@cchmc.org); Marie Gantz (mgantz@rti.org); 'Michele Walsh (mcw3@cwru.edu)'; 'Nancy Newman (nxs5@cwru.edu)'; Nancy Newman (nxs5@cwru.edu); Finer, Neil; Roger Faix (roger.faix@hsc.utah.edu); Higgins, Rosemary (NIH/NICHD) [E]; Archer, Stephanie (NIH/NICHD) [E]; Rich, Wade; 'Wally Carlo (wacarlo@uab.edu)'
Cc: Tim Stevens (Timothy_Stevens@URMC.Rochester.edu); Myriam Peralta-Carcelen (MPeralta@peds.uab.edu); Vaucher, Yvonne
Subject: PAS Late-Breaker Abstract | SUPPORT Breathing Outcomes

Attached is Tim Stevens Pulmonary Outcomes abstract that he would like to submit as a late-breaker to PAS.

Please send any comments back to Tim, Myriam, and Yvonne by February 15, 2012.

Thank you,

Stephanie

Stephanie Wilson Archer
The Eunice Kennedy Shriver
National Institute of Child Health and Human Development
Pregnancy & Perinatology Branch
6100 Executive Boulevard, Room 4B03
Rockville, MD 20852

Tel. 301-496-0430
Fax 301-496-3790
archerst@mail.nih.gov<mailto:archerst@mail.nih.gov>

From: Stevens, Timothy [mailto:Timothy_Stevens@URMC.Rochester.edu]
Sent: Wednesday, February 08, 2012 08:40 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Breathing Outcomes

Hi Rose

Here is a first draft of a late breaker abstract for the Breathing Outcomes Study. The abstract is at 99.38% of the allowed length.

Can you please forward to the SUPPORT subcommittee?

Thank you

Tim

Results: Of 1,323 patients enrolled in SUPPORT, 944 gave consent to participate in the Breathing Outcomes Study (BOS). Survey response rates exceeded 94.5% at each of the 6, 12 and 18-22 m. time points. As seen in SUPPORT, there were no differences between either Surf v. CPAP or Low v. High Sat in the incidence of either traditional BPD (oxygen at 36 wks) or physiologic BPD among pts in BOS. However, at 6 m corrected age, patients treated with Low v. High Sat were less likely to have parental report of wheezy breathing (27.8% v. 36.4%, p< 0.04), documented wheezing (36.3% v. 43.4%, p<0.05) or use a home nebulizer (1.2% v. 3.9%, p<0.02). Differences in these outcomes or in incidence of chronic cough were not seen in the Surf v. CPAP groups at 6 m. or between either the Surf v. CPAP or Low v. High Sat groups at 12 or 18-22 m. CA. Hospitalization, physician visit and emergency department visit rates, overall and for respiratory related conditions, were similar between the Surf v. CPAP and Low v. High Sat groups at each time point.

Conclusions: Among extremely preterm infants managed with Surf v. CPAP or Low v. High Sat, no significant difference in respiratory outcomes were observed at 18 to 22 months. Based upon the finding of greater mortality with Low vs. High Sat targets seen in SUPPORT, the benefit of reduced wheezing and nebulizer use at 6 months corrected age does not justify low oxygen saturation targets in patients 24 - 27 6/7 wks gestation.

Other Previews:

Abstract Disclosure Info: **Disclosures**

Print

From: Luc Brion
To: D"Angio, Carl; Keszler, Martin; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Kristi Watterberg; Pablo Sanchez; dwallace@rti.org
Subject: FW: revised protocol
Date: Thursday, February 09, 2012 12:39:20 AM
Attachments: Secondary - predicting ext success - Revised (2) 02-07-2012.docx
Watterberg, Hydrocortisone, 02-07-2012 rev.xlsx
SBT response 7Feb12 LPB revised.doc

Carl, Martin:

I would like to submit this protocol Friday morning to the protocol committee. Please let me know if you have any comments or suggestions.

Thanks,

Luc

Luc P. Brion, MD
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luc.brion@utsouthwestern.edu

From: Luc Brion
Sent: Tuesday, February 07, 2012 3:14 PM
To: Carl_Dangio@URMC.Rochester.edu; Martin Keszler
Cc: Pablo Sanchez; Kristi Watterberg; Dennis Wallace
Subject: FW: revised protocol

Carl and Martin:

Please let me know if this is ready.

Thanks

Luc

Luc P. Brion, MD

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From: Luc Brion
Sent: Tuesday, February 07, 2012 2:06 PM
To: 'Kristi Watterberg'; Dennis Wallace
Cc: Carl_Dangio@URMC.Rochester.edu; Martin Keszler
Subject: RE: revised protocol

Kristi et al:

Thanks a lot for your comments.

I eliminated the 2,000 $ cost for training as suggested.

I responded to all your comments and corrected one mistake (60%, not 70% consent rate in the text).

I will email Brenda next.

Best regards,

Luc

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luc.brion@utsouthwestern.edu

From: Kristi Watterberg [mailto:KWatterberg@salud.unm.edu]
Sent: Tuesday, February 07, 2012 10:39 AM
To: Dennis Wallace; Luc Brion
Cc: Carl_Dangio@URMC.Rochester.edu; Martin Keszler

Subject: RE: revised protocol

I have attached the protocol and committee comments with a few new comments and suggested changes. I think it's ready to go back to protocol review. You've done a LOT of work on this!

Kristi

>>> Luc Brion <Luc.Brion@UTSouthwestern.edu> 2/7/2012 8:52 AM >>>
Dennis,
Thanks a lot for your help.
Thanks for discussing with Marie Gantz and Abhik.
Did you have the chance to look whether we have enough power to look into the subgroup analyses?

Kristi, Martin, Carl, Dennis:
I attached the proposed documents for the protocol review committee.
I removed all the comments.
I added a brief discussion at end of limitations and alternatives section stating we cannot use SUPPORT data for sample size of this project.
Please let me know whether this is ready for submitting. If it is, I will send this version and a clean copy.
Thanks for your help and collaboration.

Best regards,

Luc

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Fax: (214) 648-2481
luc.brion@utsouthwestern.edu

From: Wallace, Dennis [mailto:dwallace@rti.org]
Sent: Tuesday, February 07, 2012 9:02 AM
To: Luc Brion
Cc: Kristi Watterberg; Keszler, Martin; Carl_Dangio@URMC.Rochester.edu
Subject: RE: revised protocol

Luc,

Sorry that I didn't get back with you yesterday. I spent several hours in the SUPPORT database over the weekend trying to determine how I could get extubation success rates from the data without much success. Yesterday, I talked with Marie Gantz and Abhik, who both know the data better than I do, and their consensus was that manner in which the extubation data were collected on the SUPPORT forms was not conducive to getting the estimates that you wanted without a substantial amount of programming; furthermore, based on some preliminary work that Marie has tried to do with the intubation and extubation data from SUPPORT, she's a bit skeptical about the data quality. Given those constraints, I think that the only reasonable approach is to use the information from the literature to evaluate power over a range of assumptions, and I've done that in the attached version of the revised protocol. Let me know what you think.

Dennis

From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
Sent: Tuesday, February 07, 2012 12:17 AM
To: Wallace, Dennis
Cc: Kristi Watterberg; Keszler, Martin; Carl_Dangio@URMC.Rochester.edu
Subject: RE: revised protocol

Dennis:
Any chance to submit to the protocol review?
Luc

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luc.brion@utsouthwestern.edu

From: Wallace, Dennis [mailto:dwallace@rti.org]
Sent: Friday, February 03, 2012 10:21 AM
To: Luc Brion
Subject: RE: revised protocol

Luc,

I just got back in town from a week of meetings. I'll get to it over the weekend.

Dennis

From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
Sent: Thursday, February 02, 2012 10:29 PM
To: Wallace, Dennis
Cc: Kristi Watterberg; Keszler, Martin; Carl_Dangio@URMC.Rochester.edu
Subject: FW: revised protocol

Dennis:

I know you are very busy.
Will have a chance to look at this soon?
I would like to submit this to the protocol committee on time for the next review standing committee call on Feb. 7

Thanks

Luc

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luc.brion@utsouthwestern.edu

From: Luc Brion
Sent: Saturday, January 28, 2012 12:56 PM
To: 'Wallace, Dennis'; Keszler, Martin; Kristi Watterberg
Cc: Carl_Dangio@URMC.Rochester.edu; higginsr@mail.nih.gov; Pablo Sanchez
Subject: RE: revised protocol

Dennis, Carl, Martin, Kristi:

Thanks for all the comments.

As discussed, I think we need to comply to the requests of the protocol review committee if we want this proposal to go through.
I have updated the proposal, taking into account all the comments, and corrected the chi-square to its correct calculations.
I would not be too worry about having too much power in the whole group, and take advantage of this: since power to detect a difference in the whole group, we may have power to detect in subgroups as well; this would be very important to assess the validity of SBT in multiple subgroups.
Luc

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luc.brion@utsouthwestern.edu

From: Wallace, Dennis [mailto:dwallace@rti.org]
Sent: Friday, January 27, 2012 9:56 AM
To: Luc Brion; Keszler, Martin; Kristi Watterberg
Cc: Carl_Dangio@URMC.Rochester.edu; higginsr@mail.nih.gov; Pablo Sanchez
Subject: RE: revised protocol

Luc,

Sorry that I've taken a while to respond, but I believe that the hypothesis test problem is a bit more complicated than suggested by the current version of the protocol (which is why we decided not to move in that direction originally), and I'm trying to determine how one could actually do the tests that you are wanting and then do the power calculations that are needed for that hypothesis test.

As the proposal is currently written, you've described an analysis and a set of power calculations for a study set up as follows. You have two independent cohorts of individuals, one of which has extubated participants based on the results of a positive clinical test and one of which has extubated participants based on the result of a positive SBT. However, that study is not the one that we're doing. In our study, we have a single cohort of individuals, specifically a cohort of individuals that is "positive" on some set of clinical criteria. Within that cohort, we are dividing the cohort into

two sub-cohorts, those that are positive for SBT and those that are negative for SBT. As such, the only hypotheses that I know how to test are those associated with the different sub-cohorts, not those comparing a sub-cohort to the total cohort being tested. I think that's why we didn't try to do a hypothesis test initially, as we thought that the operating characteristics of the SBT were a more interesting question than testing hypotheses about individuals who were positive on the SBT and those who were negative on the SBT.

Given the concerns outlined in the paragraph above, my preference would be to maintain the original focus on the characterization of the operating characteristics of the SBT. However, if you think that we are going to have to do hypothesis testing to move this forward, we'll need to frame the hypothesis tests in terms of the two sub-cohorts (at least that's the only way that I see to do it easily without having all sorts of complications). In doing so, testing whether the probability of successful extubation is higher in individuals with a positive SBT than in individuals with a "positive" clinical test, with the data that we have is equivalent to testing whether the probability of a successful extubation is higher in individuals with a positive SBT than in individuals with a negative SBT. I did some quick calculations based on the information that I saw in the latest version of the proposal. If I understand that proposal correctly, you think we will have approximately 370 subjects available for this cohort study. Under the assumption that 70% or 80% of those individuals will have a positive SBT, the sample sizes for the two sub-cohorts (positive, negative) would be (259, 111) and (296, 74). Under these assumptions and taking the numbers in the table in the latest proposal if you assume that the success among those with positive SBT is 10% greater than success in the total cohort (with total cohort success in the range of 60% to 75 %) then success in those with a negative SBT will only be in the range of 20% to 50%. Thus the difference in success between those with positive SBT and those with negative SBT is generally in the range of 30% to 50%. With the sample sizes shown, you have a very large power (always greater than 95%) to show that difference. Again, I don't find that these hypothesis tests are nearly as interesting as the operating characteristics of the screening tool, but if the group thinks that the primary aim should be to test successful extubation in those who have a positive test to those who have a negative test, then you have an excess of power to do that.

I need to spend this afternoon getting ready for another Steering Committee meeting that starts at 8 tomorrow morning, but if you want me to write this up formally, I'm happy to do some other analyses this weekend and try to get that to you next week, but I don't think that the power calculations in the current version reflect that study that you are actually doing.

Dennis

From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
Sent: Thursday, January 26, 2012 4:24 PM
To: Keszler, Martin; Kristi Watterberg; Wallace, Dennis
Cc: Carl_Dangio@URMC.Rochester.edu; Rose (higginsr@mail.nih.gov); Pablo Sanchez
Subject: RE: revised protocol

Thanks, I am waiting for Dennis.

Dennis:
Will you have the time to look at the protocol by tomorrow?
Luc

Luc P. Brion, MD
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luc.brion@utsouthwestern.edu

From: Keszler, Martin [mailto:MKeszler@Wihri.org]
Sent: Thursday, January 26, 2012 3:22 PM
To: Luc Brion; Kristi Watterberg
Cc: Carl_Dangio@URMC.Rochester.edu; dwallace@rti.org; Rose (higginsr@mail.nih.gov); Pablo Sanchez
Subject: RE: revised protocol

Looks good, as best as I can sort it out ☺.
Go for it!
Cheers,
M

Martin Keszler MD
Mkeszler@WIHRI.org
(401) 274-1122, x7490

From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
Sent: Monday, January 23, 2012 7:25 PM
To: Keszler, Martin; Kristi Watterberg
Cc: Carl_Dangio@URMC.Rochester.edu; dwallace@rti.org; Rose (higginsr@mail.nih.gov); Pablo Sanchez
Subject: RE: revised protocol

Thanks, Martin.

All:
I attach the revised version, in which I eliminated several manuscripts, which are not needed anymore. I also eliminated Martin's comments except the one for Dennis
Please let me know if you have any additional suggestions by January 27th so I can I send the protocol to the review committee at least one week before the next protocol review standing committee call (February 7th).

Dennis:

Please could you extract the data from SUPPORT as indicated in my previous email sent Fri 1/20/2012 8:58 AM. This information is for the bottom of page 7 of the version without the Word tracking [Results pending from Dennis].
Please let us know if we are planning too many secondary analyses.

Thanks for your help,

Luc

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luc.brion@utsouthwestern.edu

From: Keszler, Martin [mailto:MKeszler@Wihri.org]
Sent: Monday, January 23, 2012 5:37 PM
To: Luc Brion; Kristi Watterberg
Cc: Carl_Dangio@URMC.Rochester.edu; dwallace@rti.org; Rose (higginsr@mail.nih.gov); Pablo Sanchez
Subject: RE: revised protocol

Luc, here are my edits and comments. Sorry I could not get this back to you sooner.
Keep up the good work. We're almost there!
Cheers,
M.

Martin Keszler MD
Mkeszler@WIHRI.org
(401) 274-1122, x7490

From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
Sent: Monday, January 23, 2012 5:14 PM
To: Kristi Watterberg
Cc: Carl_Dangio@URMC.Rochester.edu; Keszler, Martin; dwallace@rti.org; Rose (higginsr@mail.nih.gov); Pablo Sanchez
Subject: RE: revised protocol

Kristi:

Oops! I missed a few more mistakes! Thanks a lot for taking the time to read the documents and thanks your comments.

Kristi: Carl, Martin, Dennis, Rose:

I looked carefully at the printout and edited the text further; corrections should come in blue this time; this will allow you to detect changes I made today.

Best regards,

Luc

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luc.brion@utsouthwestern.edu

From: Kristi Watterberg [mailto:KWatterberg@salud.unm.edu]
Sent: Monday, January 23, 2012 2:42 PM
To: Luc Brion
Cc: Carl_Dangio@URMC.Rochester.edu; MKeszler@Wihri.org
Subject: Re: revised protocol

A lot of work in a short time, Luc! A couple of minor points:

Background: this must be a typo: "extubation predicted by a positive SBT was 3/43 (93%), compared with a success rate of 39/50 (78%) in the"

The two statements below seem to conflict - in each, you are looking at the SBT vs. clinical factors to predict successful extubation, even though they're stated a little differently.

The null hypothesis is that the percentage of successful extubation among patients with positive SBT is not different from that in those extubated based on criteria established for extubation in the main hydrocortisone study.

The primary question is not to determine whether SBT is better predictive than clinical information;

this would be best studied by a randomized trial.

There seems to be a missing clause in the following sentence: "If an occasional infant requires more than this, e.g., bag and mask ventilation or additional resuscitation."

Kristi

>>> Luc Brion <Luc.Brion@UTSouthwestern.edu> 1/21/2012 4:59 PM >>>
Martin, Carl, Kristi, Dennis, Rose:

Thanks a lot for all the feedback at the meeting.

Here is the updated protocol, taking into account all the suggestions from the protocol review committee and a first draft of the revised sample size analysis (not seen by Dennis yet).
Please let me know your suggestions (if possible by January 27th) so I can I send the protocol to the review committee at least one week before the next protocol review standing committee call (February 7th).
Thanks and best regards,
Luc

Luc P. Brion, MD
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luc.brion@utsouthwestern.edu

DATE: *February 7, ~~January 19,~~ 2012*

Formatted: Font: Italic

TO: *Brenda Poindexter*
Chair, Protocol Review Subcommittee

FROM: *Luc Brion*

RE: *Itemized response to the Protocol Review Subcommittee re: "Predicting Success of Extubation During Hydrocortisone Therapy and the Effect of Different Modes of Synchronized Ventilation"*

Cc: *Dennis Wallace, Carl d'Angio, Martin Keszler, Kristi Watterberg, Rose Higgins*

We thank the protocol review subcommittee for a careful review of our proposal. We added itemized responses to each comment that required either a response or a change in the protocol. We modified the protocol considerably along the guidelines provided by the committee.

The Protocol Review Subcommittee reviewed this protocol during its conference call on January 3, 2012. Written comments were provided by Kurt Schibler, Brenda Poindexter, and Stephanie Archer and are included below.

The Subcommittee discussed differences between the population of infants studied in the Melbourne trial of spontaneous breathing versus those that will be in the hydrocortisone trial. It was noted that the investigators in Melbourne who described this test were using it every day on rounds, the purpose being to extubate VLBW infants as soon as possible (median age 4-5 days). On the other hand, infants in the hydrocortisone trial are a unique subgroup of babies who are stuck on the ventilator. The investigators need to explain how the results of the spontaneous breathing test (SBT) in the hydrocortisone cohort will be generalizable in the typical NICU setting.

We agree that the postnatal age of patients in the hydrocortisone study is different from those in the Melbourne study. We also agree data in the proposed study will not be generalizable to all patients in the NICU. The proposed study is specifically designed to address the current knowledge gap in the literature, i.e., validity of the SBT at later postnatal age. We have clarified the protocol to indicate this and expanded the rationale for the study.

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The specific aim related to modes of ventilation was discussed at length by the Subcommittee. Given center differences in the use of assisted modes of ventilation, the consensus of the Subcommittee is that this aim is not feasible. In addition, only a limited amount of data is currently being collected for the Hydrocortisone trial (see HCO4 respiratory data collection form); in order to address the aim related to assisted ventilation, a significant increase in data collection would need to be incorporated into the study design.

We have removed the specific aim related to duration of ventilation based on different modes of ventilation.

Finally, the Subcommittee discussed the potential confounding of post-extubation management. In the current protocol, it is not clear how differences in clinical management following extubation will be handled (many which could significantly impact the success of extubation).

This may actually be a strength of the proposed study, which is aimed at finding out if the SBT is a better predictor ~~or not to clinical decision about~~ of readiness ~~to~~for extubation than clinician choice across multiple centers using ~~and~~ multiple approaches to post-extubation therapy (CPAP, high-flow nasal cannula, NIPPV). We will collect this information and analyze it by secondary subgroup analysis and by multivariate analysis.

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As currently written, the Subcommittee had low enthusiasm for the proposed secondary. However, the Subcommittee would be willing to review a revised version of the protocol which addresses the concerns outlined below.

Comments submitted by Kurt Schibler:

This observational study is primarily designed to evaluate whether a short endotracheal continuous positive airway pressure (ET CPAP) test may help predict the success of extubation of very premature infants.

1) The primary aim of this study is evaluate the point estimates and confidence intervals of sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio of a positive test, and likelihood ratio of a negative test for the spontaneous breathing test (SBT).

2) Secondary aims are 1) To evaluate point estimates and confidence intervals of sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio of a positive test, and likelihood ratio of a negative test for the SBT in two subgroups: infants ventilated with SIMV and infants ventilated using modes supporting all breaths and 2) To determine if ventilation modes that support every breath are associated with shorter duration of mechanical ventilation than SIMV.

Methods

Study design - This is an observational study with prospective data collection.

The study will involve analysis of the operational characteristics of a diagnostic test (SBT) and retrospective analysis of a cohort study (using two cohorts: babies ventilated using SIMV and babies ventilated using modes supporting all breaths).

The spontaneous breathing test (SBT) will be performed by the study team just before extubation decided by the clinicians. Clinicians will remain blinded to the results.

Study population - We will use the same population as that for the main study. All patients enrolled in the main study will be approached for an optional consent, indicated by a check on the consent to the main study

Study intervention - when the clinicians decide a baby is ready to be extubated, the investigator will perform the SBT within 4 hours of the planned extubation.

The researcher will silence any alarms and will place screens around the bedside before initiating the test to minimize the chance of unblinding. After ensuring that the clinical care team, including the patient's nurse, is away from be bedside (to maintain blinding) the investigator (respiratory therapist, fellow, nurse practitioner or attending), who must not be involved with the patient's clinical care, will switch the ventilator to CPAP for 3 minutes at the same pressure as the positive end-expiratory pressure setting. The infant's ETT will be suctioned prior to the SBT if clinically indicated, and the intervention will be done when the infant is in a quiet state, taking care to minimize stimulation and disturbance during the study. The baby fails the SBT if he or she develops a bradycardia (HR <100) for more than 15 seconds and/or a fall in SpO2 below 85% despite a 15% increase in FIO2. At this point the study will be stopped, and ventilation will be restarted. If manual breaths are given through the ventilator because of bradycardia or desaturation, this will be considered a failed test. Data on the mode of ventilation, success and time of extubation will be collected for subsequent analysis.

The baby will be placed back on previous ventilatory settings to 30 minutes, to limit the risk of derecruitment that could have resulted from performing the SBT.

Sample size

The investigators estimate that about 70% of the total sample size available in the main trial will be available for the analysis of this secondary study; thus sample size is estimated at 550. Since the secondary study will start after the beginning of the main study, the total number of patients in this secondary study will be probably 10% smaller, i.e. 500 patients.

Analysis plan

The investigators will determine the point estimates and 95% confidence intervals for the operating characteristics (sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio of a positive test, and likelihood ratio of a negative test) of successful extubation using the SBT.

Investigators will use the same tests in subgroups:

1. infants ventilated with SIMV versus infants ventilated using modes supporting all breaths at the time of the SBT.
2. infants with gestational age ≤ $26^{6/7}$ versus those with gestational age $27^{0/7} - 29^{6/7}$ weeks

Receiving operator characteristic curve (ROC) will be used to analyze whether the operating characteristics of the SBT vary according to ETT resistance and to postnatal age.

Comments

1. Allowing time after suctioning and after the SBT for potential re-recruitment of alveoli is important particularly in the lower gestational age strata. *– We added a minimum of 10 minutes between suctioning and the SBT.*

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2. The reasons for failure to remain extubated for 72 hours are multifactorial including individual infant associate factors and factors related to providers or center. *– This fact is acknowledged in the protocol and in the limitations. We will use multivariate analysis for this purpose; however we will not control for individual providers. We may actually consider this heterogeneity of approach to patient care as ~~one of the~~ strength of this study: this will enhance external validation of the SBT test, which so far has only been tested in single-center studies.*

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3. It may not be possible to have SBT performed by someone not involved in clinical care of the study infant. *We believe it is important to maintain blinding of SBT. The study cannot be done without masking the clinical team. If the caregivers know whether the baby has passed or failed the SBT, they will be biased by the study, and therefore it will be impossible to determine the outcomes described for the study. It would be up to each center to decide whether the study PI, coordinator, respiratory therapist, fellow, attending, or NNP not currently providing clinical care of the infant would be involved in the SBT. Centers who are not able to perform blinding SBT should not participate.*

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4. The effects of the study medication in the main trial may influence the utility of the SBT to predict extubation success. *The study is designed to determine this as one of the secondary outcomes and this will be included in the~~by using~~ multivariate analysis. We realize that steroids may improve lung compliance and reduce the risk of laryngeal edema.*

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5. The study forms and additional data to be collected should be included with the protocol in order to determine how time intensive the secondary study will be. *Appendix B includes all the additional information required for the study, and was edited to include all the comments and suggestions from the reviewer. Further development of the forms will be done in the manual.*

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6. The respiratory support variable collected around the time of the test may have little bearing on modes of support and their influence on extubation success or failure. *We agree with the reviewer that this variable may not affect the validity of the SBT. This will be one among many variables we will test.*

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7. Whether consent should be imbedded or not should be at the discretion of the centers. *We changed the protocol accordingly.*

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Comments submitted by Brenda Poindexter:

SUMMARY: The proposed study is a secondary study to the hydrocortisone trial to assess the sensitivity, specificity, positive and negative predictive value of the spontaneous breathing test (SBT) in predicting successful extubation in ELBW infants.

~~1.~~ The authors state that because this is an observational study, there is no primary hypothesis. This needs to be revised to reflect the analyses that will be done (hypothesis could be that the SBT will be more useful than clinical information alone). *Thank you for this suggestion. The null hypothesis is that the percentage of successful extubation among patients with positive SBT is not different from that in those extubated based on criteria established for extubation in the main hydrocortisone study. This will be analyzed by comparing patients with positive SBT with those with negative SBT. The study has enough power to do this analysis in the whole group. ~~and in subgroup analyses~~.*

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~~2.~~ 1. In the methods and procedures section of the protocol the authors state that the study will involve analysis of the operational characteristics of the SBT and retrospective analysis of a cohort study. The retrospective analysis is not mentioned anywhere else in the protocol. As currently written, it seems that all infants enrolled as part of the hydrocortisone for extubation main trial will all receive the SBT, so it is is not clear where the retrospective cohort will come from. *Thank you for this comment; ~~we agree with you~~this was a mistake and ~~W~~we have removed this sentence from the study design. ~~This was a mistake we have overlooked; there is no retrospective data in this study.~~* If the primary question is whether the SBT has better predictive ability than typical clinical information (such as FiO2, PIP, PEEP, etc.) as stated in the rationale/justification, then wouldn't there need to be a control group of infants who are subjected to the SBT? *We changed the primary aim of the study: "To compare the percentage of successful extubation among patients with positive SBT with that in those extubated based on criteria established for extubation in the main hydrocortisone study." ~~The primary question is not to determine whether SBT is better predictive than clinical information; this would be best studied by a randomized trial.~~*

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~~3.~~ 2. Secondary aim – the second secondary aim is to determine if ventilation modes that support every breath are associated with shorter duration of mechanical ventilation than SIMV. Although data will be collected related to mode of ventilation at time of extubation, it would seem that detailed data related to respiratory support prior to the time of extubation would be required. The HC04 respiratory form collects only very limited information related to type of ventilator support on study days 1, 3, 5, 7, 10, and 14 and collects no information related to assist control or pressure support. If modes of assisted ventilation shorten the duration of mechanical ventilation, wouldn't the duration of being on an assisted mode also contribute to the outcome? In other words, I would think there would be a difference between infants whose entire course on the ventilator is in SIMV versus those who are only changed to SIMV during the final stages of weaning (for 12-24 hrs) prior to extubation. In the data analysis plan, the subgroups are only divided by mode of ventilation at the time of the SBT. How will duration of time in assisted ventilation mode be dealt with in the analyses? The investigators state that "very little additional coordinator time will be needed to

collect information that will be used in multivariate analysis that could build the basis for a future randomized trial" but have not provided a draft of the proposed data collection forms to be utilized in the secondary study. The wide range of practice variation in modes of ventilator management at NRN centers provided by the survery results in the protocol highlight the likelihood that center differences will bias the ability to evaluate this secondary aim (this concern was also raised in the concept comments). *We agree with the reviewer's concerns and eliminated this part of the study.*

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4.3. Unplanned extubations – the investigators have not taken into account unplanned extubations (some of which are likely to be successful). How will these infants be handled in the analyses? *These events will be excluded from the analysis, since SBT is not performed.*

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5.4. Post-extubation management – the role of post-extubation management is not addressed in the protocol as a potential confounder to prediction of extubation success. What type of data will be collected during the immediate post-extubation period and what variables (such as extubation to CPAP versus HFNC or SiPAP, use of racemic epinephrine, etc.) will be considered in the analytic plan. *This information was added to the protocol and to appendix B.*

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6.5. Treatment group – one of the secondary null hypotheses is that the predictive value of the SBT is not affected by whether the baby is randomized to hydrocortisone or placebo. This hypothesis needs to be justified as hydrocortisone, if efficacious as defined by the primary outcome measure of the main trial, could significantly confound the primary outcome of likelihood of extubation success (in addition to the other potential confounders mentioned in the protocol including fluid management, caffeine, etc.). *We agree with the reviewer's comments. In this protocol we describe null hypotheses. "2. The predictive value of the SBT is not affected by whether the baby is randomized to hydrocortisone or placebo. Hydrocortisone may affect lung compliance and laryngeal edema and thus improve success rate of extubation compared with placebo."~~We hypothesize that hydrocortisone might improve lung compliance and reduce laryngeal edema, thereby improving the success rate of extubation in comparison to the control group.~~ We will analyze potential confounders by using multivariate analysis, which is now listed as~~in the~~ secondary outcome.*

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7.6. Masking – the protocol states that the individual performing the SBT should not be involved in the clinical care of the infant. Clarification is needed regarding the duration of time that this individual cannot be involved in the clinical care (before and after performance of the SBT). Regardless of who performs the test, it may be impossible to avoid having this person involved in the clinical care of the infant. It would be helpful to specify the period of time that the person administering the SBT should not be involved in the clinical care of the infant. The issue of clinical documentation and masking also needs to be addressed in the protocol. If an infant has significant hypoxia and/or bradycardia during the SBT, how will the documentation in the medical record be addressed? Given that data from our monitors in the NICU is recorded and reviewed on rounds on a daily basis, significant episodes of desaturation and/or bradycardia will be difficult to not relay to the clinical team; in addition, if the infant does require PPV or other intervention following a failed SBT, the clinical team will need to be informed. I would think that the IRB would question the plan to not

inform the clinical team of a significant desaturation or bradycardia event knowing that an extubation attempt is being planned by the clinical team in the immediate future. In this regard, I disagree with the investigators that blinding the clinical team of a failed SBT (at least in the case of significant bradycardia or need for resuscitation) is "defensible". *Thank you for your comments. The study cannot be done without masking the clinical team. If the caregivers know whether the baby has passed or failed the SBT, they will be biased by the study, and therefore it will be impossible to determine the outcomes described for the study. The large majority of the babies undergoing an SBT tolerate the procedure well and those who fail the SBT respond rapidly to manual breaths on the ventilator. The results of the SBT will not be disclosed to the clinician or documented into the chart unless additional therapy is required as indicated below. In rare circumstances, the baby may not respond well to the usual intervention described above. In that case, manual bagging will be initiated and additional treatment will be provided according to NRP guidelines, and the clinical team will be informed. NRP guidelines will be followed if the infant requires more extensive intervention. Once stable, the infant will be placed back on mechanical ventilation. ~~If an occasional infant requires more than this, e.g., bag and mask ventilation or additional resuscitation~~. We have modified the protocol accordingly. We propose that the SBT be conducted after rounds in centers that review the monitoring tracing during rounds.*

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8.7 Budget – Two areas of the proposed budget warrant further consideration – first, there is a budget for a respiratory therapist for 15 minutes – does this mean that the SBT must be performed by a study respiratory therapist? I would assume that the majority of centers do not have respiratory therapists on their paid research team. For other NRN studies requiring support from respiratory therapists (such as SUPPORT, Benchmarking, and the iNO studies), we have always relied on respiratory therapists at the centers providing their time without reimbursement. *- The protocol leaves to each center the choice of who will be involved in performing the SBT; in some centers only respiratory therapists are allowed to change ventilator settings.* The second point that requires clarification is the 20 minutes of coordinator time for screening for subject who qualify for extubation. This would not be a one-time event, but rather would require daily screening until the infant met criteria for consideration of extubation. In addition, the decision to extubate is often made during morning rounds – therefore, this protocol will require that the clinical team inform the research coordinator of the intent to extubate in a timely manner (within the required 4 hours) or the opportunity to perform the SBT may be missed. In addition, for infants who require reintubation, the protocol states that a second SBT will be performed prior to the next extubation attempt; this effort for continuing to follow the infant after the first reintubation is not accounted for in the budget (nor is it required for the main RCT); the protocol is also inconsistent in this regard as the required follow-up is listed as being none beyond 72 hours after extubation (First extubation? Second if first one fails?). -Finally, the budget needs to be adjusted to reflect the additional data collection for type of respiratory support (as mentioned above, HC04 does not record whether infant is on assist control, SIMV, or pressure support). Thus, the time estimate for coordinator effort for this secondary study is markedly underestimated in the current budget. *- We now indicate in the protocol that we will use only the first 2 elective extubations after randomization. Sample size*

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analysis s is based on the first elective extubation only. The coordinator time was increased to 4 hours based on your recommendations. We increased the time by only one hour because we have eliminated the collection of ventilator mode and support between randomization and the day of the SBT. We further revised the budget to follow Stephanie Archer's recommendations. We propose to leave the respiratory therapist in the budget. At Parkland, the plan is that one of the 2 respiratory therapists on call (the one is not assigned to take care of the baby as a provider) assigned to the NICU will perform the SBT. Each center will decide who could do the SBT; some centers may use the coordinator, the PI, the alternate PI, another attending, fellow or NNP for this purpose. Alternatively, we may further revise the budget if we decide that respiratory therapists will not be involved in the study.

9.8. Consent – the authors state that they do not feel that the imbedded consent will affect enrollment in the main trial because of the opt-out ability, but I do think that this issue will need to be prospectively monitored to ensure that enrollment in the main trial is not compromised. I am not in favor of imbedding consent for this secondary into the main trial; I would suggest that the decision of whether or not to imbed consent be left to the individual centers. *We changed the protocol accordingly and will let each center choose whether to use a separate consent from or to imbed it into the consent for the main trial.*

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10.9. Data collection forms – drafts of the proposed data collection forms need to be included in the protocol; without these, it is impossible to ascertain whether the time estimates in the budget are appropriate or not. *The data collection form is included in Appendix B and was updated based on all the comments from the review subcommittee.*

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Comments submitted by Stephanie Archer:

Questions:

- Estimated Start Date. I'm assuming no earlier than 6/1/12. Obviously, the later this is, the smaller the sample size, and the cheaper the cost. *We modified the protocol accordingly.*
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- Consent rate. Not sure how you can say you will capture 70% of the original study population with only a 60% consent rate. I've used 70% in this estimate. *We changed to 60% as is usual for NRN studies, ~~selected 70% because some centers may select centers may select a separate consent form for the secondary study while other centers may select an embedded consent.~~*
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- Sample size. This will depend on the start date, consent rate, and the rate of recruitment for the Main trial. As of November 2011, only 16 randomized (versus an original main trial estimate of 27 recruited per month). *We changed the protocol accordingly.*
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- Respiratory therapist. This rate is too low. For IPGE, we used $100/hour, which is probably still too low. *We changed the budget accordingly.*
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- Training costs. Assuming no need for extensive training for this secondary – with any training done at a Steering Committee meeting or via teleconference. *We changed the budget accordingly.*
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Comments submitted during Concept Presentation (17 yes, 3 no votes):

Comments with yes votes

- This study can add critical information to the steroid tria.
- AC vs SIMV length of ventilation comparison is unlikely to yield useful results.
- Simple, inexpensive, important study.
- We'd enthusiastically test this hypothesis.
- Validation of SBT particularly among subgroups would be very valuable. Comparison of ventilator modes will b e hopelessly biased by center difference. It might be worth looking at multiple definitions of failure at 12, 24 and even 48 hours. *Comparison of duration of ventilation support by ventilator modes was eliminated from the protocol. We ~~will~~ added various definitions of failure, as suggested, to secondary outcomes.* Formatted: Font: Italic
- Will PDA influence SBT? *This will be one of the variables assessed in the multivariate analysis.* Formatted: Font: Italic
- Where is ref 4 cited? *All references are cited.* Formatted: Font: Italic
- Good use of the HC extubation main trial to gain additional information.
- Consent should not be embedded as it may decrease consent into main trial. *This was changed; each center PI will decide whether to embed the consent into that of the main trial or to use a separate consent form.* Formatted: Font: Italic
- Coordinator and RTI seemed to be an under-estimate. *The budget was revised accordingly.* Formatted: Font: Italic
- SBT validation more worthwhile than trying to get at length of ventilation. Focus on SBT component. *The length of ventilation was removed from the protocol.* Formatted: Font: Italic

Comments with no votes

- Not easy to predict by ~ 3 minute of CPAP. *Previous studies have shown that the SBT is superior to clinical parameters to predict successful extubation in preterm infants.* Issues with upper airway obstruction and apnea despite caffeine. *This information is being collected in this study.* Formatted: Font: Italic
- Post extubation variation HFNC/CPAP. *T~~-~~this information will be collected and analyzed.* Formatted: Font: Italic

From: Finer, Neil
To: Myriam Peralta, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; Vaucher, Yvonne; Wally Carlo, M.D.; Das, Abhik; Gantz, Marie
Subject: RE: Final version of manuscript for authors to review
Date: Wednesday, February 08, 2012 6:08:41 PM

This looks very nice
Thanks Myriam
Neil

From: Myriam Peralta, M.D. [mailto:MPeralta@peds.uab.edu]
Sent: Wednesday, February 08, 2012 1:14 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Vaucher, Yvonne; Finer, Neil; Wally Carlo, M.D.; Das, Abhik; Gantz, Marie
Subject: FW: Final version of manuscript for authors to review

Attached please find the final version of the Oxygen Support paper to be submitted to the New England Journal of Medicine. We will submit this afternoon please let me know if you are Ok with this. thanks.

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Finer, Neil"
Subject: FW: New England Journal of Medicine - 12-01547
Date: Wednesday, February 08, 2012 3:15:00 PM

This went through - thanks for your help!!
Rose

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Subject: New England Journal of Medicine - 12-01547

Dear Dr. Finer and co-authors,

Thank you for submitting your manuscript, "Early CPAP versus Surfactant in Extremely Preterm Infants: Neurodevelopmental Outcomes in Early Childhood" to the New England Journal of Medicine.

Your manuscript has been forwarded to members of our editorial staff, who will make an initial evaluation and decide whether it merits further consideration. You will be notified of the decision as soon as possible.

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Sincerely,

Jeffrey M. Drazen, M.D.
Editor-in-Chief
New England Journal of Medicine
Distinguished Parker B. Francis Professor of Medicine
Harvard Medical School

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: New England Journal of Medicine - 12-01547
Date: Wednesday, February 08, 2012 3:15:00 PM

CPAP FU paper is in!!

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Subject: New England Journal of Medicine - 12-01547

Dear Dr. Finer and co-authors,

Thank you for submitting your manuscript, "Early CPAP versus Surfactant in Extremely Preterm Infants: Neurodevelopmental Outcomes in Early Childhood" to the New England Journal of Medicine.

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New England Journal of Medicine
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Harvard Medical School

New England Journal of Medicine
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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Finer, Neil"
Subject: RE: Two papers
Date: Wednesday, February 08, 2012 2:20:00 PM

The site grant numbers are in the acknowledgements – do you want us to send separate boilerplate for the paper??
A simple letter of submission with the title and that we appreciate their serious consideration, etc is fine

Thanks
Rose

Rosemary D. Higgins, MD
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From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Wednesday, February 08, 2012 2:16 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Two papers

Hi Rose
I am working at uploading the Follow-up Paper
Do you want me to indicate all the site grants as in the manuscript for funding – do you have a preferred wording for this
Also do you use a standard letter for submission. Or can I just write a sentence about this being an original prospective trial conducted by the NRN etc
Thanks
Neil

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, February 08, 2012 6:57 AM
To: 'Myriam Peralta, M.D.'; Vaucher, Yvonne; Finer, Neil; wcarlo@peds.uab.edu; 'Das, Abhik'; Gantz, Marie
Subject: FW: Two papers

I have communicated with Dr. Solomon at NEJM – see below – let's upload the papers!!
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From: Solomon, Caren, M.D. [mailto:csolomon@nejm.org]
Sent: Wednesday, February 08, 2012 9:56 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Two papers

Thanks for letting me know. We look forward to reading them.

Caren

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, February 08, 2012 9:03 AM
To: Solomon, Caren, M.D.
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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Miriam Adhikari"
Subject: RE: FW: Support 1_23_2012
Date: Wednesday, February 08, 2012 1:46:00 PM

Thank you
Rose

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From: Miriam Adhikari [mailto:ADHIKARI@ukzn.ac.za]
Sent: Wednesday, February 08, 2012 1:46 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: FW: Support 1_23_2012

Received this email
Deleted the other. Will maintain confidentiality
Miriam Adhikari

Professor M Adhikari
Assistant Dean Postgraduate & Research (MMed)
Nelson R Mandela School of Medicine, University of KwaZulu Natal. Dean's Suite, 1st Floor Medical School, 719 Umbilo Road, Durban 4001. Private Bag 7 Congella, 4013
Tel 27 31 2604147
Fax 27 31 2604659>>> "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> 08/02/2012 20:39 >>>

Please confirm receipt of the current email

Rose

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From: Miriam Adhikari [mailto:ADHIKARI@ukzn.ac.za]
Sent: Wednesday, February 08, 2012 1:37 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: FW: Support 1_23_2012

Dear Rosemary
I am not clear on my role in this
Can you clarify
Miriam

Professor M Adhikari
Assistant Dean Postgraduate & Research (MMed)
Nelson R Mandela School of Medicine, University of KwaZulu Natal. Dean's Suite, 1st Floor Medical School, 719 Umbilo Road, Durban 4001. Private Bag 7 Congella, 4013
Tel 27 31 2604147
Fax 27 31 2604659>>> "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> 08/02/2012 17:49 >>>
Here you go
Rose

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From: Myriam Peralta, M.D. [mailto:MPeralta@peds.uab.edu]
Sent: Friday, January 27, 2012 5:46 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Wally Carlo, M.D.
Subject: Support 1_23_2012

Rose I included the review with responses, and make a few changes in the manuscript, please let me know what do you think, I will review this more this weekend and try to get it ready for the final review to send to authors next week and send out let me know thanks

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Vaucher, Yvonne"; "Myriam Peralta, M.D."; "Finer, Neil"; "wcarlo@peds.uab.edu"; "Das, Abhik"; "Gantz, Marie"
Cc: (b)(6)
Subject: RE: Two papers
Date: Wednesday, February 08, 2012 11:30:00 AM

Fabulous

Thanks
Rose

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-----Original Message-----
From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]
Sent: Wednesday, February 08, 2012 11:11 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; 'Myriam Peralta, M.D.'; Finer, Neil; wcarlo@peds.uab.edu; 'Das, Abhik'; Gantz, Marie
Cc: Vaucher, Yvonne; (b)(6)
Subject: RE: Two papers

Rose,

Since I will be away (b)(6) for 6 weeks with intermittent email access, Neil Finer will be the corresponding author for the NEJM to assure rapid response.

Turns out I have 2 gmail accounts so some confusion as to which one to use. Please use the one above (b)(6) in addition to the UCSD address yvaucher@ucsd.edu<mailto:yvaucher@ucsd.edu> for any communication.

Thanks

yvonne

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]
Sent: Wednesday, February 08, 2012 6:56 AM
To: 'Myriam Peralta, M.D.'; Vaucher, Yvonne; Finer, Neil; wcarlo@peds.uab.edu; 'Das, Abhik'; Gantz, Marie
Subject: FW: Two papers

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To: Higgins, Rosemary (NIH/NICHD) [E]; "Myriam Peralta, M.D."; Vaucher, Yvonne; wcarlo@peds.uab.edu; "Das, Abhik"; Gantz, Marie
Subject: RE: Two papers
Date: Wednesday, February 08, 2012 10:51:52 AM

Absolutely
Good luck to all
Neil

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, February 08, 2012 6:57 AM
To: 'Myriam Peralta, M.D.'; Vaucher, Yvonne; Finer, Neil; wcarlo@peds.uab.edu; 'Das, Abhik'; Gantz, Marie
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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Gantz, Marie"
Cc: "Myriam Peralta, M.D."; "Miriam Adhikari"
Subject: FW: Support 1_23_2012
Date: Wednesday, February 08, 2012 10:49:00 AM
Attachments: Peralta SUPPORT FU Oximetry 2011 with responses.docx
Support 1_23_2012.doc

Here you go
Rose

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Cc: Wally Carlo, M.D.
Subject: Support 1_23_2012

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Neurodevelopmental Outcome of Extremely Preterm Infants in a Trial of Different Oxygen Saturation Targets

Myriam Peralta-Carcelen, MD, MPD et al

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Formatted: Spanish (International Sort)

Reviewer 1

Major Comments

This manuscript describes the 20-month corrected age detailed neurodevelopmental evaluations for survivors of the SUPPORT study randomizing infants to be maintained at pulse Doppler saturation ranges of either 85% to 89%, or of 91% to 95%.

No mention is made in the manuscript of the fact that this was actually a two-by-two study in which these infants were also randomized to either early CPAP or early intubation with surfactant administration. Although other papers from the SUPPORT study have acknowledged that these were non-interacting studies, mention needs to be made at this more complex design in this manuscript. This is included in the methods already, not sure if I need to expand on this.

The most important criticism of this manuscript is that the authors continue to emphasize that there was no significant difference in primary outcome, and that severe retinopathy of prematurity (ROP) was decreased in the low S_PO_2 infants, as assessed during the acute hospitalization. Yet, at twenty months corrected age, there was no difference in unilateral or bilateral blindness (~1%) and no difference among survivors in the incidence of neurodevelopmental impairment. Therefore, one conclusion might be that there is nothing but hazard associated with using lower range of S_PO_2. If the hoped for outcome of improvement in severity of ROP was not demonstrated at two years, and if there is no difference among survivors for risk of NDI, but a statistically and clinically significant increased risk of death at some point from birth to discharge, then the conclusion is obvious, and the goal of comparing NDI rates in the survivors of two groups become less significant. I do not believe I need to change anything on this manuscript, any comments on this.

Could the authors take other data that might have been collected during the course of this study, albeit blinded at the time, and seek correlations of NDI among survivors by combining both groups and assessing duration of S_PO_2 below 80% for example? I do not believe we can do this with this manuscript Given the findings of other concurrent or subsequent studies addressing the same issue (as are referenced in Reference #6), the findings as presented are less significant because nobody is going to be using the lower saturation range and therefore the results of the infants randomized to that group alone will be of less interest. Indeed the authors understate the impact of the letter to the NEJM (Reference #6), in which it is not just that other studies showed reduced survival, but that the studies were stopped early. I added a sentence regarding that trials included were stopped. It seems unlikely that any study would continue enrolling infants

purposefully to a lower oxygen saturation range, given what has now been published in letter form or complete form.

It is odd that the authors would continue to state on Page 15 in the first sentence of the first full paragraph, that safe limits of oxygen saturation targets are not clearly established. I think that are still not clearly established any suggestions on how to phrase this?. It seems that there are now established lower oxygen saturation targets.

Also missing from the Discussion is any mention about the other two components of oxygen delivery: hemoglobin, and blood pressure as a proxy for cerebral blood flow. I added a sentence on this in the discussion. The authors might acknowledge these limitations in the original study design. It may also be useful to include in this manuscript the postnatal age at which the limitations were lifted on maintaining the randomly assigned saturation range (eg – 36 weeks, 34 weeks PMA). I added this to the methods.

Minor Points

- Dr. Das is listed twice as an author in the Author List. corrected
- Background – first paragraph, last sentence, should the reference be 6, or 5 and 6? References are both
- Second paragraph, sentence beginning "*Recent preliminary pool results analysis*.... Included three trials that were completed. I believe in at least some of those cases of those trials, the trials were stopped early based upon the findings already available. To say they were completed may not be quite accurate. I added a sentence stating that studies were stopped
- Animal research *indicate* not *indicates*... changed in manuscript
- Page 9, top the authors need to specify about bronchopulmonary dysplasia as to whether the current or old classification was being used added a sentence on this
- Page 11 under Results – in the data regarding patients lost to follow-up versus those that were evaluated at 20 months, the comparison is made about mothers marital status. I don't think these need to be extended to two decimal points, and similarly regarding issues of insurance status. I put one decimal point now.

Reviewer 2

Thank you for the opportunity to do an internal review of this well written and important paper which explains the outcome of two different oxygen saturation targets. The science and presentation of the research is quite strong and the paper reads well. The study design is appropriate. I will list a few suggestions below but first wanted to talk about the use of composite outcome this study.

Using the composite outcome of death or NDI does not sufficiently highlight the findings of this study. It is clear that the differences between the 2 interventions did not reach significance for NDI (p=0.21) but did for death (p=0.046) and it is stated that there is no significant difference in the composite outcome. My concern is that this can be

misleading to the less careful reader who does not go on to look more closely at the findings. The paper is accurate in the use of labeling "composite" but a better understanding of the outcome could be reached by un-bundling death and NDI. The rationale for using it that is stated in the paper should be edited to better explain the use. We separated the outcomes I think it is clear.

Other comments:

Page 1 Consider using "trial of two different oxygen saturation targets" in title not sure but we can try

Page 4 Methods- Bayley III cognitive >2sd below mean. Added this to methods instead of less than 70

(this is very optional as most readers are familiar with the scoring but this just explains the cut off)

Results- if p=.046 is considered significant, then add the words "significantly different" to third sentence. I added this

Page 9 There are three rationales for the use of composite score stated in the paper. I changed a little bit these paragraphs to be more detailed.

I think this section could use more clarity. If the first reason is to maintain the highest statistical power for analysis, then that should be stated in a clearer manner. If the first reason was to use the intention to treat principle and analysis, then that should be stated in a clearer manner.

For the second reason. Some children who died after discharge but before an 18 months evaluation, might have been classified as having a NDI. For those children with deaths after 6 months of age, it might be know if they had cp, blindness, hearing impairment or significant developmental delay. I suggest that you state that infants who died before 18 months could not be classified using the same standardized criteria. But having an understanding of the ND status of these children even though it will not be in a standardized manner could be a help in this and other studies.

The third reason might be clearer if it was stated that it is important to give death and significant neurodevelopmental disability equal weighting in making a comparison of an intervention.

Page 11 When explaining the status of the lost to follow-up group, it is not clear how you know that some children were alive. Were death records searched? Of those who were not known to be alive, is there simply no knowledge?

I changed a little bit to use the located alive and evaluated.

I suggest using same terms throughout this section– for example, Located, alive and evaluated. Located, alive but not evaluated. Not located, health status unknown, not evaluated.

The sentence "Neurodevelopmental assessment was performed in 990/1058 infants who were thought to be alive (93.6%)." This sentence struck me as funny. As a psychologist I am always quite sure that the child I am assessing is alive. I think what you meant is that "ND

assessment was performed on 990 of the 1058 toddlers who were located and alive at the time of the 18 month visit"
At the outcome points I suggest the use of the word child or toddler rather than infant.

Page 12 Last sentence of primary outcome section. Replace "prevalence of death or neurodevelopmental impairment" with "in the composite primary outcome of death or neurodevelopmental impairment" Added the composite

Page 13 Although this is the table, I suggest that you add a sentence about no significant differences in severe cerebral palsy and hearing loss. Added a sentence

Discussion Replace "pre-specified outcome of death or neurodevelopmental impairment" with pre-specified composite outcome of death or neurodevelopmental impairment"done

Page 15 Since the focus of this paper is on the comparison of two interventions of the same birth cohort. I do not think that the BSID II v III difference is needed to be listed as a limitation. I kept the comment as many people will wander about this but took out word limitation.

Page 16 Add word "composite" in first sentence. "no significant differences in composite outcome of ....." done

Reviewer 3

In this manuscript, Peralta and colleagues report 18-22 month neurodevelopmental follow-up of infants enrolled in the SUPPORT trial. The manuscript is succinct, clear and well-written. The major outcomes are analyzed carefully and presented in an easily-understood fashion. I have only minor comments that I hope will improve the clarity even further.

1. Death as an outcome. The importance of the persisting difference in death between the groups is perhaps overstated. While one could hypothesize that death after discharge would be worsened by one or the other arm of therapy, post-discharge deaths were equal between the two groups. As a result, this manuscript really only restates the finding of the primary trial. This could be clarified by separating pre- and post-discharge deaths in Figure 1 and by stating that the difference in death between the two groups "persisted" at follow-up. (In most cases, death didn't "occur" between discharge and follow-up, so words like "occur" confuse the issue a bit.) Change the wording to persist

2. Undetermined neurodevelopmental status (pg. 11). I was left wondering about the 14 children who had neurodevelopmental evaluation, but for whom neurodevelopmental status could not be determined. The authors could spend a sentence explaining their fate. Were they untestable? If so, why?
I added a sentence on these children. I will add some to the figure as well.
3. Subgroup analysis. The authors state that there were no significant differences in death or NDI in gestational age substrata and reference Table 2. No data are

available in Table 2 about the substrata. The authors should consider reporting adjusted RR and 95% CI for the primary outcome for each substratum, rather than just reporting no differences.

We had decided before to take out the subtrata so it was taking out, I took out the reference of table 2 which was forgotten to be taken out. If you think I should put the substrata back I can do this.

Formatted: Indent: Left: 0.25"

Overall, this manuscript is excellent. I wish the authors well.

Neurodevelopmental Outcome of Extremely Preterm Infants in a Trial of Two Different Oxygen Saturation Targets

Myriam Peralta-Carcelen, M.D., M.P.H.[1], Yvonne E. Vaucher, M.D., M.P.H.[2], Waldemar A. Carlo, M.D.[1], Neil N. Finer, M.D.[2], Marie G. Gantz, Ph.D.[3], Michele C. Walsh, M.D., M.S.[4], Abbott R. Laptook, M.D.[5], Bradley A. Yoder, M.D.[6], Roger G. Faix, M.D.[6], Abhik Das, Ph.D.[7], Kurt Schibler, M.D.[8], Wade Rich, R.R.T.[2], Nancy S. Newman, R.N.[4], Betty R. Vohr, M.D.[5], Kimberly Yolton, Ph.D.[8], Roy J. Heyne, M.D.[9], Deanne E. Wilson-Costello, M.D.[4], Patricia W. Evans, M.D.[10], Ricki F. Goldstein, M.D.[11], Michael J. Acarregui, M.D.[12], Ira Adams-Chapman, M.D. [13], Athina Pappas, M.D.[14], Susan R. Hintz, M.D., M.S., Epi[15], Brenda B. Poindexter, M.D., M.S.[16], Elisabeth C. McGowan, M.D.[17], Richard A. Ehrenkranz, M.D.[18], Anna Bodnar, M.D.[6], Charles R. Bauer, M.D.[19], Janell Fuller, M.D.[20], T. Michael O'Shea, M.D., M.P.H.[21], Gary J. Myers, M.D.[22], Rosemary D. Higgins, M.D.[23] for the SUPPPORT Study Group of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network.

[1] Department of Pediatrics, University of Alabama at Birmingham, Birmingham, AL; [2] University of California at San Diego, San Diego, CA; [3] Statistics and Epidemiology Unit, RTI International, Research Triangle Park, NC; [4] Department of Pediatrics, Rainbow Babies & Children's Hospital, Case Western Reserve University, Cleveland, OH; [5] Department of Pediatrics, Women & Infants Hospital, Brown University, Providence, RI; [6] Department of Pediatrics, Division of Neonatology, University of Utah School of Medicine, Salt Lake City, UT;

[7] Statistics and Epidemiology Unit, RTI International, Rockville, MD; [8] Department of Pediatrics, Cincinnati Children's Hospital Medical Center and University of Cincinnati, Cincinnati, OH; [9] Department of Pediatrics, University of Texas Southwestern Medical Center, Dallas, TX; [10] Department of Pediatrics, University of Texas Medical School at Houston, Houston, TX; [11] Department of Pediatrics, Duke University, Durham, NC; [12] Department of Pediatrics, University of Iowa, Iowa City, IA; [13] Emory University School of Medicine, Department of Pediatrics, and Children's Healthcare of Atlanta, Atlanta, GA; [14] Department of Pediatrics, Wayne State University, Detroit, MI; [15] Department of Pediatrics, Division of Neonatal and Developmental Medicine, Stanford University School of Medicine and Lucile Packard Children's Hospital, Palo Alto, CA; [16] Department of Pediatrics, Indiana University School of Medicine, Indianapolis, IN; [17] Department of Pediatrics, Division of Newborn Medicine, Floating Hospital for Children, Tufts Medical Center, Boston, MA; [18] Department of Pediatrics, Yale University School of Medicine, New Haven, CT; [19] University of Miami Miller School of Medicine, Miami, FL; [20] University of New Mexico Health Sciences Center, Albuquerque, NM; [21] Wake Forest University School of Medicine, Winston-Salem, NC; [22] Department of Pediatrics, University of Rochester Medical Center, Rochester, NY

Corresponding author and reprints:

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1600 7th Avenue South, Suite CPPI 4110
Birmingham, AL 35233

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Word Count

Abstract: 248

Text: 1,148

ABSTRACT

BACKGROUND

Targeting lower (vs. higher) oxygen saturations in the SUPPORT Trial decreased severe retinopathy of prematurity but increased mortality before discharge. Our pre-specified hypothesis was that compared to higher oxygen saturation targets, lower oxygen saturation targeting would decrease the risk of the composite outcome of death or long term neurodevelopmental impairment.

METHODS

Children born at 24 to 27 week gestation were randomized to higher (91-95%) or lower oxygen saturation targets (85-89%) from birth to 36 weeks corrected age. The primary outcome of the follow up study was a composite of death or neurodevelopment impairment at 18 to 22 months corrected age. Neurodevelopmental impairment (NDI) was defined as a Bayley III cognitive composite score > 2 SD below the mean, modified Gross Motor Function Classification System ≥2, moderate to severe cerebral palsy, permanent hearing loss, and/or bilateral blindness. Analyses of all outcomes were adjusted for gestational age stratum, center and familial clustering.

RESULTS

Primary outcome was available for 1234/1316 (93.8%) of children enrolled in SUPPORT; 93.6% (990/1058) of survivors were evaluated at 18 to 22 months corrected age. Death or NDI occurred in 30.2% (185/612) children in the lower oxygen saturation group and 27.5% (171/622) children in the higher oxygen saturation group (relative risk 1.12; 95% confidence interval 0.94, 1.32;

p=0.21). Death persisted significantly higher (140 or 22.1%) in the children in the lower oxygen saturation group than (118 or 18.2%) the higher oxygen saturation group (relative risk 1.25; 95% confidence interval 1, 1.55, p=0.046). NDI among survivors was present in 9.5% (45/472) of the lower oxygen saturation group and 10.5 % (53/504) of the higher oxygen saturation group survivors (relative risk 0.87, 95% confidence interval 0.6, 1.28; p=0.49).

CONCLUSIONS

Among extremely preterm children targeted at different levels of oxygen saturation, no significant difference in the composite outcome of death or neurodevelopmental impairment was observed at 18 to 22 months. Mortality at 18 to 22 months persisted increased in the lower oxygen saturation target group.

BACKGROUND

For many preterm infants with respiratory disorders, oxygen supplementation is vital for survival. However, oxygen supplementation may increase the risk of retinopathy of prematurity, {Tin, 2001, Pulse oximetry`, severe retinopathy`, and outcome at one year in babies of less than 28 weeks gestation.} bronchopulmonary dysplasia{Saugstad, 2011}{Saugstad, 2003}, periventricular leukomalacia, {Haynes, 2003} and cerebral palsy {Collins, 2001} Restrictive oxygen therapy decreases retinopathy but has resulted in increased deaths in recent randomized controlled trials. {Carlo, 2010, Target ranges of oxygen saturation in extremely preterm infants.} {Stenson, 2011}

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development SUPPORT Trial demonstrated no significant difference in a composite outcome of severe retinopathy of prematurity or death before discharge between a lower oxygen saturation target group (85-89%) and a higher oxygen saturation target group (91-95%). However, severe retinopathy of prematurity among survivors was decreased (8.6% vs. 17.9%; relative risk 0.52; 95% CI 0.37 to 0.73; $p<0.001$) and death before discharge was increased (19.9% vs. 16.2%; relative risk 1.27; 95% CI 1.01 to 1.60; $p=0.04$) in the lower oxygen saturation target group compared to the higher saturation target group. {Carlo, 2010, Target ranges of oxygen saturation in extremely preterm infants.} Similarly, a recent preliminary pooled results analysis that included the SUPPORT trial data and three other subsequently completed multi-center randomized controlled trials (two trials were stopped due to data available) with a total of 3631 infants showed that infants randomized to an oxygen saturation target of 91-95% had a lower mortality rate than infants randomized to oxygen saturation targets of 85-89% (14.4% versus 17.3% respectively, $P=0.015$). {Stenson, 2011}

The effects of oxygen on the immature brain are not clearly understood. {Saugstad, 2005, Oxidative stress in the newborn--a 30-year perspective.} Oxidative stress injury in the premature infant may have many underlying pathophysiological processes. {Escobar, 2011} Animal research data indicate that hyperoxia may cause periventricular white matter injury {Schmitz, 2011}. There has been a keen interest in determining whether higher or lower oxygen supplementation can reduce neurodevelopmental impairment. {Stenson, 2011} {Askie, 2009} However, in a non-randomized study of oxygen saturation targeting, {Tin, 2001, Pulse oximetry`, severe retinopathy`, and outcome at one year in babies of less than 28 weeks gestation.}, neurodevelopmental outcome did not differ by oxygen targets.

This study evaluated the composite outcome of death or neurodevelopmental impairment at 18 to 22 months corrected age in the subjects enrolled in the SUPPORT trial and randomized to lower (85-89%) or higher oxygen saturation targets (91-95%) from birth until 36 weeks postmenstrual age. The pre-specified hypothesis in the SUPPORT trial was that compared to a higher oxygen saturation target, a lower saturation target decreases the risk of the composite outcome of death or neurodevelopmental impairment.

METHODS

Study Design

Extremely preterm infants (24 weeks 0 days to 27 weeks 6 days) born between February 2005 and February 2009 at 20 centers in the United States participating in the Neonatal Research Network of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development were enrolled at delivery in the randomized controlled SUPPORT trial. Permuted block randomization was used, with stratification according to center and gestational age (24

weeks 0 days to 25 weeks 6 days or 26 weeks 0 days to 27 weeks 6 days) and multiple births were assigned to the same treatment group. The infants were randomly assigned in the first 2 hours of life to a target range of oxygen saturation of 85% to 89% (the lower oxygen saturation group) or 91 to 95% (the higher oxygenation group). The target ranges were kept unchanged from birth until 36 weeks of postmenstrual age. Using a 2-by-2 factorial design, participants were also randomly assigned to receive either CPAP immediately following delivery and a limited ventilation strategy if subsequent intubation was required or intubation with surfactant administration within an hour after birth. Procedures for enrollment, intervention and data collection have been previously reported. {Carlo, 2010, Target ranges of oxygen saturation in extremely preterm infants.}. The study was approved by the institutional review board at each participating center and at RTI International which is the independent data coordinating center for the Neonatal Research Network. Written informed consent was obtained from at least one parent or guardians of each child before delivery. Consent was also obtained for follow up at 18-22 months corrected age.

Assessments

A comprehensive neurodevelopmental assessment was performed on survivors at 18-22 months corrected age by neurologic examiners and neurodevelopmental testers who were unaware of the treatment assignments. Developmental status was assessed using the Bayley Scales of Infant and Toddler Development 3rd edition (BSID III) {Bayley, 2006, Bayley scales of infant development - (Bayley III)}. Cognitive Composite Scores are reported as a standardized score with a mean of 100 and a standard deviation of 15. Examiners also recorded the presence of cerebral palsy defined as a non-progressive disorder of the central nervous system characterized by abnormal muscle tone in at least one arm or leg associated with abnormal control of movement or posture

with delayed attainment of motor milestones.{Vohr, 2003, Longitudinal multicenter follow-up of high-risk infants: why`, who`, when`, and what to assess.} The modified Gross Motor Function Classification System (GMFCS) {Palisano, 1997, Development and reliability of a system to classify gross motor function in children with cerebral palsy.} was used to classify gross motor performance using a range from 0 (normal) to 5 (severely impaired). Cerebral palsy was classified depending on severity as mild (GMFCS $\leq$1), moderate (GMFCS 2 or 3) or severe (GMFCS $\geq$ 4). Hearing and visual impairment were determined based on parent report and examination. A 2-day workshop was held annually to train examiners and ensure reliability of assessments.

Certified research nurses collected demographic and neonatal data using NRN definitions. Data collected included gestational age, birth weight, sex, multiple gestation, race/ethnicity, retinopathy of prematurity status, bronchopulmonary dysplasia (persistent oxygen use by 36 weeks gestation), history of medical or surgical necrotizing enterocolitis (modified Bell's stage $\geq$ 2), grades 3-4 intraventricular hemorrhage or periventricular leukomalacia, history of late onset sepsis, use of postnatal steroids. Socioeconomic variables included insurance status, maternal marital status, maternal education, household income, language spoken at home, and whether living with biological parents. Socioeconomic data from the neonatal period were used and when not available, data updated at the 18-22 month visit were used.

Outcome

The pre-specified primary follow-up outcome of the SUPPORT trial was the composite of death or neurodevelopmental impairment at 18 to 22 months corrected age. This composite outcome was selected because (a) the data would be analyzed as an intention to treat principle and is

available on the entire randomized trial cohort, (b) children who died before 18 months could not be classified using our standard criteria as having neurodevelopmental impairment and (c) death and significant neurodevelopmental impairment among survivors are considered to be of equally weighting when making a comparison of an intervention. Neurodevelopmental impairment was defined as having any of the following: BSID III cognitive composite score less than 70, GMFCS ≥ 2, presence of moderate or severe cerebral palsy, permanent hearing loss that does not permit the child to understand directions of the examiner and communicate despite amplification with hearing aids, or bilateral visual impairment (vision < 20/200).

Analysis

Data were entered in standard forms and were transmitted to the Neonatal Research Network Data Coordinating Center at RTI International which stored, managed and analyzed the data for this study. Details regarding sample size calculations for the SUPPORT trial have been previously reported {Carlo, 2010, Target ranges of oxygen saturation in extremely preterm infants.}. The sample size calculations were based on infants born in the year 2000 which included the rate of death or neurodevelopmental impairment at 18-22 months corrected age. All analyses were performed according to the intention to treat principle. Unadjusted comparisons of birth and demographic characteristics between treatment groups were conducted using chi-square tests for categorical variables and t tests for continuous variables. The primary analysis focused on the percentage of infants in each group for whom the primary outcome of death or NDI at 18 to 22 months corrected age could be assigned. Analysis of this and all other categorical outcomes was performed using robust Poisson regression in a generalized-estimating-equation model to

obtain adjusted relative risks with 95% confidence intervals. The denominator used to calculate the rate of each outcome was the number of infants for whom the outcome was known. Continuous outcomes were analyzed using mixed-effects linear models to obtain adjusted means and standard errors. Pre-specified subgroup analyses were also conducted within each gestational age strata.

Analysis of all neonatal and follow-up outcomes results were adjusted, as pre-specified, for gestational-age strata, center, and familial clustering (because multiple births from the same mother were randomized to the same treatment group). Two-sided p values of less than 0.05 were considered statistically significant. For the 79 secondary outcomes analyzed according to treatment, we would expect no more than 4 tests to have p values of less than 0.05 on the basis of chance alone. Subgroup analyses were conducted within pre-specified gestational age strata for the same outcomes. Although these tests have not been adjusted for multiple comparisons, we would expect no more than 4 tests per stratum to have p values of less than 0.05 on the basis of chance alone.

RESULTS

Characteristics of the Study Sample

The SUPPORT trial enrolled 1316 infants (Figure 1). The baseline characteristics and hospital outcomes of the entire group have been reported.{Carlo, 2010, Target ranges of oxygen saturation in extremely preterm infants.} Five hundred twenty four infants in the lower oxygen saturation group and 555 in the higher oxygen saturation group survived to discharge or transfer from the hospital. Ten children in the lower oxygen saturation group and 11 children in the higher oxygen saturation group died after discharge from the nursery and prior to the 18 to 22

month corrected age follow up visit. Thirty five children in the lower saturation group and 33 children in the higher saturation group were not evaluated in the follow up visit. However, 14/35 in the lower saturation group and 19/33 in the higher saturation group were located and known to be alive but not evaluated at the 18 to 22 months corrected age visit. Neurodevelopmental assessment was performed in 990/1058 children who were located and alive at the time of the 18-22 month visit (93.6%). Of those who were evaluated at the 18 to 22 months corrected age, neurodevelopmental status was determined for 976 children. Fourteen children attended the follow up visit but were not able to complete the cognitive portion of test therefore neurodevelopmental status could not be determined. The pre-specified outcome of death or neurodevelopmental impairment could be determined for 93.8% (1234/1316) of enrolled children. Compared to mothers of children who were followed, mothers of children who were lost to follow up were less likely to be married (47.0% vs. 30.9% p=0.01) and more likely to have only public health insurance (52.4% vs. 69.1% p=0.008). There were no other statistically significant differences in other baseline characteristics of the cohort that was followed up compared to those lost to follow up. The mean corrected age for neurodevelopmental evaluation was similar for both groups (lower oxygen saturation, 19.9 $\pm$ 2.4 months vs. higher oxygen saturation 20.2 $\pm$ 2.7 months, p=0.08).

Baseline characteristics of the follow up cohort and the entire trial cohort are presented in Table 1. Among children who were followed, the percentage of children who were small for gestational age was greater in the higher oxygen saturation target group compared to the lower saturation target group. In addition, as reported previously,{Carlo, 2010, Target ranges of oxygen saturation in extremely preterm infants.} the incidence of severe retinopathy of prematurity was higher in the higher oxygen saturation group compared to the lower saturation group but no other

significant differences were found in the baseline characteristics or major hospital outcomes of the children with follow up data including presence of retinopathy of prematurity.

Primary Outcome

The composite primary outcome of death or neurodevelopmental impairment was not significantly different between the lower (185/612, 30.2%) and higher (171/662, 27.5%) oxygen saturation target groups (relative risk 1.12, 95% confidence interval 0.94, 1.32; p=0.21). (Table 2) In the 24 to 25 weeks gestational age stratum, primary outcome data were available for 261 of 276 children in the lower saturation group and 276 of 289 in the higher saturation group. For the stratum of 26 to 27 weeks' gestation, outcome data were available for 351 of 378 of the lower oxygen saturation group and 346 of 373 of the higher oxygen saturation group. Similar to the entire cohort, there were no significant differences in the prevalence of death or neurodevelopmental impairment within both gestational age strata.

Components of the Primary Outcome

Death prior to the 18 to 22 month adjusted age visit persisted significantly higher among infants in the lower oxygen saturation target group compared to those in the higher saturation target group (lower oxygen saturation, 140/633, 22.1% vs. higher oxygen saturation, 118/648, 18.2%; relative risk 1.25; 95% CI 1.0038, 1.55, p=0.046).

Neurodevelopmental impairment among survivors examined at the 18 to 22 month corrected age visit was similar between the lower and the higher oxygen saturation target groups (45/472, 9.5% vs. 53/504, 10.5%; relative risk 0.87 95%CI 0.6, 1.28, p=0.49)

Other outcomes among survivors at follow up

The percentage of children with BSID III cognitive scores below 70 was not significantly different between the lower and higher oxygen saturation group, nor was the percentage of children with cognitive scores below 85. Adjusted means of cognitive composite scores were not significantly different between the two groups and are presented in table 3.

The rates of severe retinopathy of prematurity and eye surgery among survivors to follow up were increased in the higher oxygen target group compared to the lower oxygen target group; however the rate of bilateral blindness (lower oxygen saturation, 1.04% vs. higher oxygen saturation, 1.17%, relative risk 0.9, 95% CI 0.28, 2.9; p=0.86) or blindness of at least one eye (lower oxygen saturation, 1.04% vs. higher oxygen saturation, 1.57%, relative risk 0.67, CI 0.22, 2.02; p=0.48) were not significantly different at the 18 to 22 month corrected age visit. Other visual outcomes are presented in Table 3.

There were no significant differences in severe cerebral palsy or hearing loss.

DISCUSSION

In this multicenter follow up study of infants randomized to a lower target range of oxygen saturation (85 to 89%) or higher target oxygen saturation range (91 to 95%), no significant difference was found between treatment groups in the pre-specified composite outcome of death or neurodevelopmental impairment at 18-22 months corrected age. To our knowledge this is the first large comprehensive study published to date that has included neurodevelopmental impairment as an outcome for evaluating effects of different oxygen target saturation levels started at birth in extremely premature neonates within a randomized multicenter trial, although the outcomes of other similarly designed trials will be reported {Askie, 2011} {Stenson, 2011} The results of recent trials have raised concerns about using lower oxygen saturation targets

because of potentially increased mortality in extremely premature infants {Saugstad, 2011} A recent pooled analysis included studies that were completed with different oximeter calibration algorithms which was revised {Johnston, 2011, Oxygen targeting in preterm infants using the Masimo SET Radical pulse oximeter.}. The SUPPORT study was included in the old algorithm arm and the investigators of this analysis did not adjust for clustering for multiple births. In addition, there are still other randomized trials with pending results evaluating this question. Studies included in these preliminary analyses also have a prespecified outcome at 2 years follow up which will not be available until 2014. {Stenson, 2011}{Askie, 2011} In the SUPPORT trial it was found that death prior to discharge, was increased among neonates randomized to lower target saturation levels, and this difference persisted at 18 to 22 months corrected age in the current follow up study. The distribution of major causes of death has been published previously and there were no significant differences between both groups {Carlo, 2010}. Major causes of death after discharge were not available for this study.

We had previously reported that the lower saturation oxygen target was associated with a large reduction in the incidence of severe retinopathy of prematurity among survivors. {Carlo, 2010, Target ranges of oxygen saturation in extremely preterm infants.} It has been previously reported that severe ROP may be associated with poor visual outcomes even with treatment. {Chen, 2011, Current update on retinopathy of prematurity: screening and treatment.;Palmer, 2005, 15-year outcomes following threshold retinopathy of prematurity: final results from the multicenter trial of cryotherapy for retinopathy of prematurity.} Although our study was not designed to collect detailed data on eye disorders or visual function at 18 to 22 months of age, we found that there were no significant differences in the report of unilateral and bilateral blindness between the two groups. Eye surgery was higher in the group with a higher oxygen saturation target and was

likely related to a higher incidence of severe retinopathy of prematurity in this group and to the criteria used to define severe retinopathy of prematurity {Carlo, 2010, Target ranges of oxygen saturation in extremely preterm infants.}. Specific visual outcomes of eye function after the presence of retinopathy of prematurity were not included in the outcome data collected in this trial. However, there were no differences in other reported visual outcomes, including nystagmus, strabismus or use of corrective lenses.

Safe limits of Oxygen saturation targets for preterm infants are not clearly established and concerns have been raised that lower oxygen saturation targets might increase the risk of long term neurodevelopmental impairment {Askie, 2009, Restricted versus liberal oxygen exposure for preventing morbidity and mortality in preterm or low birth weight infants.}. Two other components of oxygen deliver that will also affect cerebral blood flow were not reported in this study, however, pulse oxymetry is non invasive and is widely accepted as a standard technique for oxygen monitoring.{Johnston, 2011} Neurodevelopmental Impairment as defined in this study was not found to be significantly different between survivors in the lower and higher oxygen saturation groups. In addition the incidence of cerebral palsy did not differ between the treatment groups, though it is noteworthy that the incidence of cerebral palsy was lower than previously reported in other outcome studies.{Marlow, 2005, Neurologic and developmental disability at six years of age after extremely preterm birth.}

The present study reports results of a single follow up visit only at 18 to 22 months corrected age, which may not be long enough time to detect the presence of minor but important disabilities. There is an ongoing follow up of a sub-cohort of the SUPPORT study that will be followed to school age which will be important to help better evaluate neurodevelopmental status in these children. In this study we used the Bayley Scales of Infant development 3rd edition

(BSID-III) which may result in higher cognitive scores than an earlier vision of the Bayley Scales of Infant development (BSID-II); and a lower sensitivity if a cognitive composite score of less than 70 is used as the criterion for impairment{Anderson, 2010, Underestimation of developmental delay by the new Bayley-III Scale.} {Moore, 2011, Relationship between Test Scores Using the Second and Third Editions of the Bayley Scales in Extremely Preterm Children.}. Use of a cutoff of less than 85 for the Bayley III cognitive composite scores did not reveal significant differences between groups. Patients were enrolled in 20 tertiary care centers across the US, which might limit the generalizibility of our conclusions.

In summary, we found no significant differences in the composite outcome of death or neurodevelopmental impairment at 18 to 22 months corrected age in extremely premature infants who were randomized to a lower target oxygen saturation or higher target oxygen saturation. The increased death rate at discharge previously reported in the lower target oxygen saturation group was still present at 18 to 22 months corrected age. Although higher rates of retinopathy of prematurity were associated with higher oxygen saturation target levels, blindness was not significantly different among survivors at 18 to 22 months.

Acknowledgements

The National Institutes of Health, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), and the National Heart, Lung, and Blood Institute (NHLBI) provided grant support for the Neonatal Research Network's SUPPORT Trial.

Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Drs. Abhik Das (DCC Principal Investigator) and Marie Gantz (DCC Statistician) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study. The following investigators, in addition to those listed as authors, participated in this study:

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Case Western Reserve University, Rainbow Babies & Children's Hospital (U10 HD21364, M01 RR80) – Avroy A. Fanaroff, MD; Bonnie S. Siner, RN; Arlene Zadell RN; Julie DiFiore, BS; Monika Bhola, MD; Harriet G. Friedman, MA; Gulgun Yalcinkaya, MD.

Cincinnati Children's Hospital Medical Center, University of Cincinnati Hospital, and Good Samaritan Hospital (U10 HD27853, M01 RR8084) – Edward F. Donovan, MD; Vivek Narendran, MD MRCP; Kate Bridges, MD; Barbara Alexander, RN; Cathy Grisby, BSN CCRC; Marcia Worley Mersmann, RN CCRC; Holly L. Mincey, RN BSN; Jody Hessling, RN; Teresa L. Gratton, PA.

Duke University School of Medicine, University Hospital, Alamance Regional Medical Center, and Durham Regional Hospital (U10 HD40492, M01 RR30) – Ronald N. Goldberg, MD; C. Michael Cotten, MD MHS; Patricia Ashley, MD; Kathy J. Auten, MSHS; Kimberley A. Fisher, PhD FNP-BC IBCLC; Katherine A. Foy, RN; Sharon F. Freedman, MD; Kathryn E. Gustafson, PhD; Melody B. Lohmeyer, RN MSN; William F. Malcolm, MD; David K. Wallace, MD MPH.

Emory University, Children's Healthcare of Atlanta, Grady Memorial Hospital, and Emory Crawford Long Hospital (U10 HD27851, RR25008, M01 RR39) – Barbara J. Stoll, MD; Susie Buchter, MD; Anthony J. Piazza, MD; David P. Carlton, MD; Linda Black, MD; Ann M. Blackwelder, RNC BS MS; Sheena Carter, PhD; Elisabeth Dinkins, PNP; Sobha Fritz, PhD; Ellen C. Hale, RN BS CCRC; Amy K. Hutchinson, MD; Maureen Mulligan LaRossa, RN; Gloria V. Smikle, PNP MSN.

Eunice Kennedy Shriver National Institute of Child Health and Human Development – Stephanie Wilson Archer, MA.

Indiana University, University Hospital, Methodist Hospital, Riley Hospital for Children, and Wishard Health Services (U10 HD27856, M01 RR750) – Brenda B. Poindexter, MD MS; James A.

Lemons, MD; Leslie D. Wilson, BSN CCRC; Faithe Hamer, BS; Ann B. Cook, MS; Dianne E. Herron, RN; Carolyn Lytle, MD MPH; Heike M. Minnich, PsyD HSPP.

National Heart, Lung, and Blood Institute – Mary Anne Berberich, PhD; Carol J. Blaisdell, MD; Dorothy B. Gail, PhD; James P. Kiley, PhD.

RTI International (U10 HD36790) – W. Kenneth Poole, PhD; Jamie E. Newman, PhD MPH; Betty K. Hastings; Jeanette O'Donnell Auman, BS; Carolyn Petrie Huitema, MS; James W. Pickett II, BS; Dennis Wallace, PhD; Kristin M. Zaterka-Baxter, RN BSN.

Stanford University and Lucile Packard Children's Hospital (U10 HD27880, UL1 RR25744, M01 RR70) – Krisa P. Van Meurs, MD; David K. Stevenson, MD; M. Bethany Ball, BS CCRC; Barbara Bentley, PsychD MSEd; Elizabeth F. Bruno, PhD; Alexis S. Davis, MD MS; Maria Elena DeAnda, PhD; Anne M. DeBattista, RN, PNP; Jean G. Kohn, MD MPH; Melinda S. Proud, RCP; Renee P. Pyle, PhD; Nicholas H. St. John, PhD; Hali E. Weiss, MD.

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University of California – San Diego Medical Center and Sharp Mary Birch Hospital for Women (U10 HD40461) – Maynard R. Rasmussen, MD; Paul R. Wozniak, MD; Kathy Arnell, RNC; Rene Renee Bridge, RN; Clarence Demetrio, RN; Martha G. Fuller, RN MSN;

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University of New Mexico Health Sciences Center (U10 HD53089, M01 RR997) – Kristi L. Watterberg, MD; Robin K. Ohls, MD; Julie Rohr, MSN RNC CNS; Conra Backstrom Lacy, RN; Jean Lowe, PhD; Rebecca Montman, BSN.

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University of Texas Southwestern Medical Center at Dallas, Parkland Health & Hospital System, and Children's Medical Center Dallas (U10 HD40689, M01 RR633) – Pablo J. Sánchez, MD; Charles R. Rosenfeld, MD; Walid A. Salhab, MD; Sally S. Adams, MS RN CPNP; James Allen, RRT; Laura Grau, RN; Alicia Guzman; Gaynelle Hensley, RN; Elizabeth T. Heyne, PsyD PA-C; Melissa H. Lepps, RN; Linda A. Madden, RN CPNP; Melissa Martin, RN; Nancy A. Miller, RN; Janet S. Morgan, RN; Araceli Solis, RRT; Lizette E. Torres, RN; Catherine Twell Boatman, MS CIMI; Diana M Vasil, RNC-NIC; Kerry Wilder, RN.

University of Texas Health Science Center at Houston Medical School and Children's Memorial Hermann Hospital (U10 HD21373) – Kathleen A. Kennedy, MD MPH; Jon E. Tyson, MD MPH; Nora I. Alaniz, BS; Patricia Evans, MD; Beverly Foley Harris, RN BSN; Charles Green, PhD; Margarita Jiminez, MD MPH; Anna E. Lis, RN BSN; Sarah Martin, RN BSN; Georgia E. McDavid, RN; Brenda H. Morris, MD; Margaret L. Poundstone, RN BSN; Stacy Reddoch, BA; Saba Siddiki, MD; Patti L. Pierce Tate, RCP; Laura L. Whitely, MD; Sharon L. Wright, MT (ASCP).

University of Utah Medical Center, Intermountain Medical Center, LDS Hospital, and Primary Children's Medical Center (U10 HD53124, M01 RR64) – Shawna Baker, RN; Karie Bird, RN; Jill Burnett, RN; Laura Cole, RN; Karen A. Osborne, RN BSN CCRC; Cynthia Spencer, RNC; Mike Steffens, PhD; Kimberlee Weaver-Lewis, RN BSN; Karen Zanetti, RN.

Wake Forest University, Baptist Medical Center, Brenner Children's Hospital, and Forsyth Medical Center (U10 HD40498, M01 RR7122) – Robert G. Dillard, MD; Lisa K. Washburn, MD; Nancy J. Peters, RN CCRP; Barbara G. Jackson, RN BSN; Korinne Chiu, MA; Deborah Evans Allred, MA LPA; Donald J. Goldstein, PhD; Raquel Halfond, MA; Carroll Peterson, MA; Ellen L. Waldrep, MS; Cherrie D. Welch, MD MPH; Melissa Whalen Morris, MA; Gail Wiley Hounshell, PhD.

Wayne State University, Hutzel Women's Hospital, and Children's Hospital of Michigan (U10 HD21385) – Seetha Shankaran, MD; Beena G. Sood, MD MS; Rebecca Bara, RN BSN; Elizabeth Billian, RN MBA; Laura A. Goldston, MA; Mary Johnson, RN BSN.

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Data and Safety Monitoring Committee – Gordon Avery, MD, chair, Children's National Medical Center; Christine A. Gleason, MD, chair, University of Washington; Marilee C. Allen, MD, Johns Hopkins University School of Medicine; Shrikant I. Bangdiwala, PhD, University of North Carolina; Carol J. Blaisdell, MD, National Heart, Lung, and Blood Institute; Robert J. Boyle, MD, University of Virginia Health System; Traci Clemons, PhD, The EMMES Corporation; Mary E. D'Alton, MD, Columbia University; Abhik Das (ex officio), PhD, RTI International; Dorothy B. Gail, PhD, National Heart, Lung, and Blood Institute; Carl Hunt, MD, National Heart, Lung, and Blood Institute; Martin Keszler, MD, Georgetown University Hospital; W. Kenneth Poole (ex officio), PhD, RTI International; Carol K. Redmond, ScD, University of Pittsburg; Michael G. Ross, MD, MPH; UCLA School of Medicine and Public Health; Merran A. Thomson, MD, Hammersmith Hospital, UK; Steven J. Weiner, MS, The George Washington University; Marian Willinger (ex officio), PhD, Eunice Kennedy Shriver National Institute of Child Health and Human Development.

Retinopathy of Prematurity Adjudication Committee - Gary David Markowitz, MD, University of Rochester; Amy K. Hutchinson, MD, Emory University; David K. Wallace, MD, MPH, Duke University; Sharon F. Freedman, MD, Duke University.

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Table 1. Baseline characteristics of the SUPPORT group

Characteristic	Trial Cohort		Cohort with Follow-up Visit	
	Lower Oxygen Saturation	Higher Oxygen Saturation	Lower Oxygen Saturation	Higher Oxygen Saturation
	N=654	N=662	N=479	N=511
Birth weight – g	835.5 ± 193.4	824.8± 193	857.8 ± 186.3	843.7± 191.5
Gestational age – wk	26.2 ± 1.1	26.1 ± 1.1	26.3 ± 1.1	26.2 ± 1
Small for gestational age – no./total no. (%)	41/654 (6.3)	55/662 (8.3)	17/479 (3.5)*	38/511 (7.4)*
Male sex – no./total no. (%)	341/654 (52.1)	371/662 (56.0)	240/479 (50.1)	282/511 (55.2)
Race or ethnic group – no./total no. (%)				
Non Hispanic Black	257/654 (39.3)	232/662 (35.0)	201/479 (42.0)	176/511 (34.4)
Non Hispanic White	242/654 (37.0)	279/662 (42.1)	178/479 (37.2)	218/511 (42.6)

Hispanic	132/654 (20.2)	127/662 (19.2)	86/479 (18.0)	97/511 (19.0)
Other or unknown	23/654 (3.5)	24/662 (3.6)	14/479 (2.9)	20/511 (3.9)
Multiple births – no./total no. (%)	161/654 (24.6)	176/662 (26.6)	124/479 (25.9)	128/511 (25)
Maternal educational level <high school no./total no. (%)	148/594 (24.9)	165/612 (27.0)	115/471 (24.4)	129/504 (25.6)
Public health insurance only – no./total no. (%)	356/650 (54.8)	348/660 (52.7)	253/479 (52.8)	266/511 (52.1)
Mother married – no./total no. (%)	284/652 (43.6)	308/661 (46.6)	222/479 (46.3)	243/511 (47.6)
Lives with both biological parents – no./total no. (%)†	354/508 (69.7)	364/547 (66.5)	332/478 (69.5)	345/511 (67.5)
Household income < $30,000/year – no./total no.(%) †	247/474 (52.1)	291/528 (55.1)	239/456 (52.4)	272/498 (54.6)
English as primary language – no./total no. (%)‡	402/477 (84.3)	429/513 (83.6)	402/477 (84.3)	427/511 (83.6)
Cesarean section – no./total no. (%)	441/654 (67.4)	442/662 (66.8)	332/479 (69.3)	335/511 (65.6)
Antenatal steroids – no./total no. (%)	633/654 (96.8)	632/661 (95.6)	462/479 (96.5)	487/511 (95.3)
Severe retinopathy of prematurity – no./total no. (%)†	41/475 (8.6)**	91/509 (17.9)**	38/442 (8.6)**	82/471 (17.4)**

Bronchopulmonary dysplasia – no./total no. (%)¶	205/540 (38.0)	237/568 (41.7)	177/479 (37.0)	203/511 (39.7)
Intraventricular hemorrhage grade 3 or 4 or Periventricular leukomalacia – no./total no. (%)	98/630 (15.6)	100/640 (15.6)	56/478 (11.7)	60/510 (11.8)
Necrotizing enterocolitis – no./total no. (%)	76/641 (11.9)	70/649 (10.8)	42/479 (8.8)	44/511 (8.6)
Late onset sepsis/meningitis – no./total no. (%)	228/624 (36.5)	226/634 (35.6)	155/479 (32.4)	166/511 (32.5)
Post natal steroids – no./total no. (%)	61/636 (9.6)	69/644 (10.7)	41/477 (8.6)	48/507 (9.5)
CPAP – no./total no. (%)	336/654 (51.4)	327/662 (49.4)	254/479(53.0)	257/511 (50.3)
Surfactant – no./total no. (%)	318/654 (48.6)	335/662 (50.6)	225/479 (47.0)	254/511 (49.7)

*p<0.01, **p<0.001

† Available only for infant who survived to discharge or transfer

‡ Only available at 18-22 months corrected age

¶ Among survivors to 36 weeks postmenstrual age

Table 2. Primary Outcomes at 18-22 Months Corrected Age

Outcome	Lower Oxygen Saturation N=654	Higher Oxygen Saturation N=662	Adjusted Relative Risk	p value
Outcome determined for death or NDI – no./total no. (%)	612/654 (93.6)	622/662 (94)	1 (0.97, 1.03)	0.79
Neurodevelopmental impairment or death – no./total no. (%)	185/612 (30.2)	171/622 (27.5)	1.12 (0.94, 1.32)	0.21
Died by 18-22 months – no./total no. (%)	140/633 (22.1)	118/648 (18.2)	1.25 (1, 1.55)	0.046
Survivors at follow-up				
Neurodevelopmental impairment – no./total no. (%)	45/472 (9.5)	53/504 (10.5)	0.87 (0.6, 1.28)	0.49
Bayley III cognitive composite score < 70 – no./total no. (%)	34/471 (7.2)	38/503 (7.6)	0.91 (0.58, 1.43)	0.69
Gross motor function level ≥ 2 – no./total no. (%)	26/479 (5.4)	23/511 (4.5)	1.17 (0.68, 2.01)	0.56
Moderate/severe cerebral palsy – no./total no. (%)	20/479 (4.2)	20/511 (3.9)	1 (0.54, 1.83)	>0.99
Blindness – no./total no. (%)	5/479 (1)	6/511 (1.2)	0.9 (0.28. 2.9)	0.86
Hearing Impairment – no./total no. (%)	12/479 (2.5)	12/511 (2.3)	1.16 (0.54, 2.49)	0.70

Table 3. Other Outcomes at 18 to 22 months corrected age by Group

Outcome	Lower Oxygen Saturation (N=479)	Higher Oxygen Saturation (N=510)	Relative Risk for Lower vs. Higher Oxygen Saturation (95% CI)	Adjusted difference in means (95% CI)	Adjusted P-value
Bayley Scales of Infant Development III					
Cognitive composite < 70	34/471 (7.2)	38/503 (7.6)	0.91 (0.58, 1.43)		0.69
Cognitive composite <85	105/471 (22.3)	132/503 (26.2)	0.85 (0.68, 1.07)		0.16
Adjusted mean cognitive composite scores ± standard error	91.2 ± 0.8	90.5 ± 0.7		0.7 (-1.2, 2.5)	0.48
Median cognitive composite scores (interquartile range)	90 (85, 100)	90 (80, 100)			

Neurologic findings				
Mild cerebral palsy vs. none	23/459 (5.0)	21/491 (4.3)	1.16 (0.66, 2.02)	0.61
Moderate cerebral palsy vs. none	11/447 (2.5)	10/480 (2.1)	1.19 (0.52, 2.72)	0.68
Severe cerebral palsy vs. none	9/445 (2.0)	10/480 (2.1)	0.95 (0.39, 2.27)	0.90
Any cerebral palsy	43/479 (9.0)	41/511 (8.0)	1.12 (0.76, 1.66)	0.57
Any abnormal neurologic exam	108/479 (22.5)	114/511 (22.3)	1.02 (0.82, 1.28)	0.84
Vision/Eye findings				
Strabismus	46/478 (9.6)	41/510 (8)	1.2 (0.8, 1.8)	0.38
Nystagmus	22/479 (4.6)	13/510 (2.5)	1.81 (0.89, 3.69)	0.10
Tracks 180 degrees	462/476 (97.1)	432/507 (97.2)	1 (0.98, 1.02)	0.93
Corrective lenses both eyes vs. normal	21/468 (4.5)	20/493 (4.1)	1.15 (0.63, 2.1)	0.65
Blind, some function, both eyes vs. normal	3/450 (0.7)	2/475 (0.4)	1.57 (0.27, 8.96)	0.61
Blind, no useful vision, both eyes vs. normal	2/449 (0.4)	4/477 (0.8)	0.54 (0.1, 2.96)	0.48
Other abnormal eye findings vs. normal	6/453 (1.3)	12/485 (2.5)	0.55 (0.21, 1.46)	0.23
Eye surgery	31/477 (6.5)	67/509 (13.2)	0.53 (0.35, 0.78)	0.001

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Das, Abhik"
Subject: RE: Two papers
Date: Wednesday, February 08, 2012 10:48:00 AM

I have probably sent at least a dozen reminders to them to get moving on the papers. I will forward Marie the last version of Myriam's paper.

Rose

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From: Das, Abhik [mailto:adas@rti.org]
Sent: Wednesday, February 08, 2012 10:48 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: Two papers

FYI, Marie had previously told me that both these first authors are rather uncommunicative, and I am not even sure whether they had her review all the numbers one final time for their final draft!

Thanks

Abhik

From: Gantz, Marie
Sent: Wednesday, February 08, 2012 10:45 AM
To: 'Wally Carlo, M.D.'; Higgins, Rosemary (NIH/NICHD) [E]; Myriam Peralta, M.D.; Vaucher, Yvonne; nfiner@ucsd.edu; Das, Abhik
Subject: RE: Two papers

Congratulations to everyone for getting these papers submitted.

Myriam, can you please send me the final version of your paper?

Thanks,
Marie

Marie Gantz, Ph.D.

Senior Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Wednesday, February 08, 2012 9:58 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Myriam Peralta, M.D.; Vaucher, Yvonne; nfiner@ucsd.edu; Das, Abhik; Gantz, Marie
Subject: RE: Two papers

Great! We will do Myriam's today.

Wally

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Director, Newborn Nurseries
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From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, February 08, 2012 8:57 AM
To: Myriam Peralta, M.D.; 'Vaucher, Yvonne'; nfiner@ucsd.edu; Wally Carlo, M.D.; 'Das, Abhik'; Gantz, Marie
Subject: FW: Two papers

I have communicated with Dr. Solomon at NEJM – see below – let's upload the papers!!
thanks
Rose

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From: Solomon, Caren, M.D. [mailto:csolomon@nejm.org]
Sent: Wednesday, February 08, 2012 9:56 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Two papers

Thanks for letting me know. We look forward to reading them.

Caren

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, February 08, 2012 9:03 AM
To: Solomon, Caren, M.D.
Subject: Two papers

Hi Dr. Solomon,
The NICHD Neonatal Research Network has completed 18-22 month follow up on the SUPPORT trial cohort [NEJM 2010; 362(21):1959-69 and 362(21):1970-9] and will be submitting the following two papers to The Journal this week:

Neurodevelopmental Outcome of Extremely Preterm Infants in a Trial of Different Oxygen Saturation Targets (M. Peralta et al) and

Early CPAP versus Surfactant in Extremely Preterm Infants: Neurodevelopmental Outcomes in Early Childhood (Y Vaucher et al).

Your serious consideration is appreciated.

Rose

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Vaucher, Yvonne"; "nfiner@ucsd.edu"; "Myriam Peralta, M.D."
Cc: "wacarlo@uab.edu"; "Miriam Adhikari"; "Gantz, Marie"
Subject: FW: SUPPORT FU PAPER
Date: Wednesday, February 08, 2012 8:54:00 AM
Attachments: Vaucher SUPPORT FU CPAP PAPERTo NEJM020712.docx

Please submit before you leave. I will email Dr. Solomon and let her know both papers are coming in this week. Please let me know when you submit

Thanks for this immense effort!!

Rose

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From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]
Sent: Tuesday, February 07, 2012 6:13 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Finer, Neil
Subject: RE: SUPPORT FU PAPER

Rose,

Final paper to go to NEJM is attached.

Comments of Reviewer 2 are addressed.
Trial cohort data was removed from Table 1 and paper.
The differences between gestational age strata in outcomes was changed from "less likely to be normal" to " more likely to have NDI, CP, GMFCS >/= 2,cognitive delay and hearing impairment" for which we have the p values as well as the % for each GA stratum.
Order of variables in table 2 changed to match paper .
Statistics are 2-sided as stated in the methods
Changed the last sentence to match the hypothesis ("Early CPAP ....did not decrease the risk of NDI)"
I did not change the patient flow diagram.

Reviewer 1 raised methodologic issues which cannot be changed as they are inherent in the SUPPORT

design (e.g., hypothesis, overlap due to % of CPAP who were intubated later on clinical grounds)
Titles should match; they are "bland" but is descriptive.
We were asked to submit two papers though the question about interaction is a good one.
Deaths remain to be completely analyzed which we should do for PAS as that is a major point of interest for the audience.
I changed the wording from "fewer deaths" to simply give the statistics (%, CI and RR, p values) for both Death and NDI.
We have to assume that the reader read (or will read) the primary SUPPORT paper.

I am sure the NEJM will have much to say.

I am leaving to work in (b)(6) for 6 weeks tomorrow. I will return on March 24th. Basically we have most of the slides prepared from the Hot Topics presentation. We will need to look at the deaths and should be prepared to address the question of interactions between the arms.

Thanks for all your encouragement!

Yvonne

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, February 07, 2012 6:39 AM
To: Vaucher, Yvonne
Cc: Finer, Neil
Subject: RE: SUPPORT FU PAPER

Yvonne
Can we get the final manuscript – Myriam is ready to submit hers

Thanks
Rose

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From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]
Sent: Thursday, February 02, 2012 1:42 PM
To: Higgins, Rosemary (NIH/NICHD) [E]

Subject: RE: SUPPORT FU PAPER

Yes

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, February 02, 2012 10:27 AM
To: Vaucher, Yvonne
Subject: RE: SUPPORT FU PAPER

Ok
Can you submit before leaving??
Thanks
Rose

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From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]
Sent: Thursday, February 02, 2012 1:26 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT FU PAPER

Will try to get this to you tomorrow. Am in the midst o preparing to leave for (b)(6) next week.

Yvonne

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, February 02, 2012 7:32 AM
To: Vaucher, Yvonne
Cc: Finer, Neil
Subject: SUPPORT FU PAPER

Yvonne –
Are you close on the SUPPORT FU paper for submission?

let me know and thanks for all the hard work!!
Rose

Rosemary D. Higgins, MD

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Early CPAP versus Surfactant in Extremely Preterm Infants: Neurodevelopmental Outcomes in Early Childhood

Yvonne E. Vaucher, MD MPH[1]; Myriam Peralta-Carcelen, MD MPH[2]; Neil N. Finer, MD[1]; Waldemar A. Carlo, MD[2]; Michele C. Walsh, MD MS[3]; Marie G. Gantz, PhD[4]; Abbot R. Laptook, MD[5]; Bradley A. Yoder, MD[6]; Roger G. Faix, MD[6]; Abhik Das, PhD[7]; Kurt Schibler, MD[8]; Wade Rich, RRT[2]; Nancy S. Newman, RN[4]; Betty R. Vohr, MD[5]; Kimberly Yolton, PhD[8]; Roy J. Heyne, MD[9]; Deanne E. Wilson-Costello, MD[4]; Patricia W. Evans, MD[10]; Ricki F. Goldstein, MD[11]; Michael J. Acarregui, MD[12]; Ira Adams-Chapman, MD[13]; Athina Pappas, MD[14]; Susan R. Hintz, MD MS Epi[15]; Anna M. Dusick, MD FAAP[16]; Elisabeth C. McGowan, MD[17]; Richard A. Ehrenkranz, MD[18]; Anna Bodnar, MD[6]; Charles R. Bauer, MD[19]; Janell Fuller, MD[20]; T. Michael O'Shea, MD MPH[21]; Gary J. Myers, MD[22]; Rosemary D. Higgins, MD[23] for the SUPPORT Study Group of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network

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ABSTRACT

BACKGROUND: The randomized controlled SUPPORT trial demonstrated that treatment with early CPAP is an alternative to early intubation with surfactant administration, resulting in similar rates of death or BPD in infants born at 24 to 27 weeks gestation. We hypothesized that, compared to early intubation , early CPAP would decrease the composite outcome of death or neurodevelopmental impairment.

METHODS: We followed surviving infants, 24 0/7 to 27 6/7 weeks gestation, randomized in the SUPPORT trial to receive either early CPAP with limited ventilation or intubation with surfactant administration within one hour after birth and conventional ventilation. The primary composite outcome was death or neurodevelopmental impairment (NDI) at 18-22 months corrected age.

RESULTS: Death or NDI was determined for 1234/1316 (93.8%) of infants enrolled in SUPPORT; 93.6% (990/1058) of survivors to hospital discharge were evaluated at 18-22 months corrected age. Death or NDI occurred in 27.9% (173/621) of the CPAP group and in 29.9% (183/613) of the Surfactant group (RR 95% CI 0.93, 0.78.1.1, p=0.39). There were no significant differences between treatment arms in death (CPAP-18.4 vs. Surf-21.9%), NDI (CPAP-10.9 vs. Surfactant-9.1%,) or components of NDI including cognitive score < 70 (CPAP-7.2 vs. Surfactant-7.6%,), moderate/severe cerebral palsy (CPAP-4.1 vs. Surfactant-4.0%), blindness (CPAP-0.8 vs. Surfactant-1.5%) and hearing impairment (CPAP-3.3 vs. Surfactant-1.5%).

CONCLUSION: We found no significant differences in the composite outcome of death or NDI at 18-22 months corrected age between extremely premature infants who were randomized to receive either early CPAP with a limited ventilation strategy or early intubation with surfactant administration and conventional ventilation.

BACKGROUND

Extremely premature infants are at high risk for death and neurosensory or developmental impairment in early childhood. [1-3] The risk of impairment increases with decreasing gestational age, severity of illness and as consequence of neonatal complications including intraventricular hemorrhage or periventricular leukomalacia, symptomatic patent ductus arteriosus, necrotizing enterocolitis, sepsis, prolonged ventilation, bronchopulmonary dysplasia and severe retinopathy of prematurity. [4-12] Although surfactant administration decreases both death and BPD, randomized controlled trials of respiratory interventions including high frequency oscillatory ventilation, high frequency jet ventilation, and inhaled nitric oxide have failed to consistently decrease mortality and morbidity or improve developmental outcome. [13-17]

The recent, multicenter, randomized controlled Surfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT) demonstrated that treatment with non-invasive continuous positive airway pressure (CPAP) shortly after birth is an alternative to surfactant administration after intubation and results in similar rates of death or BPD in extremely premature infants born at 24 0/7 to 27 6/7 weeks gestation. [18] Compared with randomization to surfactant, randomization to early CPAP resulted in less frequent need for postnatal steroids and shorter duration of mechanical ventilation. Both treatment groups had similar rates of air leak, severe intraventricular hemorrhage and other major outcomes. Mortality was lower in the most immature, 24-25 week gestation, stratum of the CPAP arm.

The SUPPORT trial in extremely low birth weight (ELBW) infants was powered to have adequate sample size to evaluate early childhood neurodevelopmental outcome of enrolled infants. We hypothesized that compared to randomization to treatment with surfactant administration after intubation, randomization to early, non-invasive CPAP and a limited ventilation strategy would decrease the rate of a composite outcome of death or neurodevelopmental impairment at 18-22 months corrected age.

METHODS

Study Design

1316 extremely preterm infants (24 weeks 0 days to 27 weeks 6 days) born between February 2005 and February 2009 at 20 centers in the United States participating in the Neonatal Research Network (NRN) of the Eunice Kennedy Shriver National Institute of Child Health and Human Development were enrolled prior to delivery in the randomized controlled SUPPORT trial. Permuted block randomization was used, with stratification according to center and gestational age (24 weeks 0 days to 25 weeks 6 days or 26 weeks 0 days to 27 weeks 6 days), and multiple births were randomized to the same treatment group. The infants were randomly assigned in the delivery room to receive either CPAP immediately following delivery and a limited ventilation strategy if subsequent intubation was required or intubation with surfactant administration within an hour after birth and subsequent conventional ventilation. Using a 2-by-2 factorial design, participants were also randomly assigned to a target oxygen saturation of 85% to 89% (lower oxygen saturation group) or 91 to 95% (higher oxygenation group). Procedures for enrollment, intervention, and data collection have been previously reported.[18] The study was approved by the institutional review board at each participating site and at RTI International, the independent data coordinating center for the Neonatal Research Network. Written informed consent was obtained from the parent or guardian of each child before delivery.

Assessments

A comprehensive neurodevelopmental assessment was performed on survivors at 18-22 months of age, corrected for prematurity (CA), by neurologic examiners and neurodevelopmental testers who were unaware of the treatment assignments and were annually evaluated for testing reliability during a 2-day workshop. Developmental function was assessed using the Bayley Scales of Infant and Toddler Development, 3rd ed. (BSID-III).[19] Cognitive Composite Scores are reported as a standardized score with a mean of 100 and a standard deviation of 15. Examiners recorded the presence of cerebral palsy defined as a nonprogressive disorder of the central nervous system and characterized by abnormal muscle tone in at least one arm or leg associated with abnormal control of movement or posture with delayed attainment of motor milestones.[20] The modified Gross Motor Function Classification System (GMFCS) was used to classify the gross motor performance using a range from 0 (normal) to 5 (most impaired).[21] Moderate to severe cerebral palsy was defined by a GMFCS ≥2 plus an abnormal exam as stated above. Hearing loss defined as the inability to understand directions of the examiner and communicate with or without amplification and visual impairment defined as vision < 20-200) were determined based on examination and parental report.

Certified research nurses collected demographic and neonatal outcome data using standard NRN definitions. Demographic and outcome data collected included gestational age, birthweight, gender, multiple gestation, race/ethnicity, history of medical or surgical necrotizing enterocolitis (modified Bell's Stage ≥ 2), Grades 3-4 intraventricular hemorrhage (IVH) or periventricular leukomalacia (PVL), late onset sepsis, retinopathy of prematurity (ROP), bronchopulmonary dysplasia (BPD), use of postnatal steroids. Socioeconomic variables included insurance status, maternal marital status, maternal education, household income, language spoken at home, and whether the child was living with biological parents. Outcomes following NICU discharge, including rehospitalizations, interim medical history, surgery, and medications, were recorded at 18-22 month visit. Socioeconomic data were updated during the 18-22 month visit and were used if data from the neonatal period were not available.

Outcome

The primary outcome at follow up for this trial was the composite of death or neurodevelopmental impairment at 18 to 22 months corrected age. This composite outcome was selected because infants who died before 18 months could not be classified as having neurodevelopmental impairment, and death is a competing outcome to the latter. Neurodevelopmental impairment was defined as having any of the following: BSID III cognitive composite score less than 70, GMFCS ≥ 2, presence of moderate or severe cerebral palsy, permanent hearing or bilateral visual impairment.

Statistical Analysis

Pre-specified outcomes at 18 to 22 months corrected age were mortality or NDI, NDI, cerebral palsy, blindness in at least one eye. The sample size calculations were based on NRN data on infants born in the year 2000 which included the rate of death or neurodevelopmental impairment at 18-22 months corrected age. Details regarding sample size calculations for the SUPPORT trial have been previously reported.[18] Exploratory secondary outcomes at 18 to 22 months corrected age were death and components of NDI (i.e., cognitive composite score < 70, GMFCS ≥ 2, moderate/severe cerebral palsy, bilateral blindness and bilateral hearing impairment).

Data were entered in standard forms and were transmitted to RTI International which stored, managed and analyzed the data for this study. All analyses were performed according to the intention-to-treat principle. Unadjusted comparisons of demographic and birth characteristics between treatment groups were conducted using chi-square tests for categorical variables and t tests for continuous variables. The primary analyses

focused on the percentage of infants in each group for whom the primary outcome of death or NDI at 18-22 months corrected age could be assigned. Analysis of this and all other categorical outcomes was performed using robust Poisson regression in a generalized-estimating-equation model to obtain adjusted relative risks with 95% confidence intervals. The denominator that was used to calculate the rate of each outcome was the number of infants for whom that outcome was known. Continuous outcomes were analyzed using mixed-effects linear models to obtain adjusted means and standard errors.

Analyses of all neonatal and 18-22 month outcomes were adjusted, as prespecified, for gestational-age strata, center, and familial clustering because multiple births were assigned to the same treatment group. Two-sided p values of less than 0.05 were considered to indicate statistical significance, and no adjustments have been made for multiple comparisons.

RESULTS

Two hundred fifty-eight children were known to have died before 18-22 months (Figure). Sixty-eight children of the remaining 1058 (6.4%) were lost to follow-up; the survival status of 35/68 of these children was unknown. A neurodevelopmental assessment at 18-22 months corrected age was performed for 990/1058 (93.6%) children. Of the 990 children seen for evaluation, NDI was determined for 976 children; 14 children were seen but had an incomplete evaluation that precluded assigning a NDI status. Ultimately, the pre-specified outcome, death or NDI, was determined for 93.8% (1234/1316) of SUPPORT children. The mean corrected age at neurodevelopmental assessment was similar for both treatment arms (CPAP 19.9 ± 2.4 months vs. Surf 20.1 ± 2.7 months, unadjusted p=0.31). There was no difference in the follow-up rate between the CPAP and Surfactant arms (93.7 vs. 93.4%) of the trial.

Compared with mothers of the 990 children who had a neurodevelopmental assessment at 18-22 months, mothers of the 68 children lost to follow-up were less likely to be married (31 vs. 47%, p=0.01), and more likely to have only public insurance (69 vs. 52%, p=0.008). No other demographic variables or neonatal characteristics were significantly different between the groups.

Follow-up Cohort: (Table 1) Almost all mothers (96%) received antenatal steroids. Thirty-four percent of infants in the CPAP arm were intubated in the delivery room and 67% ultimately received surfactant and ventilation. Compared to the Surfactant arm, infants in the CPAP arm with follow-up at 18-22 months were significantly more likely to have had medical or surgical NEC and less likely to have been exposed to postnatal steroids . Other demographic characteristics and neonatal outcomes were similar in infants in the Surfactant and CPAP arms.

Primary neurodevelopmental outcome: (Table 2) The composite outcome of death or NDI at 18-22 months corrected age was not a significantly different between the CPAP and surfactant arms (27.9 vs. 29.9%, RR 0.93 (95% CI 0.78, 1.1), adjusted p=0.38). There were no statistically significant differences in the incidence of either death [18.4 vs. 21.9 %, RR 0.83 (95% CI 0.67, 1.04) adjusted p=0.10] or NDI [10.9 vs. 9.1%, (95% CI 0.0.79, 1.71, RR1.16, p=0.44] between the CPAP and Surfactant arms.

Components of NDI: (Table 2) The incidences of cognitive impairment (BSID-III cognitive composite score < 70 (7.2% vs. 7.6%), gross motor function level ≥ 2 (5.1 vs. 4.8%), moderate/severe cerebral palsy (4.1 vs. 4.0%), and blindness (0.8 vs. 1.5%) among survivors were similar in the CPAP and Surfactant treatment groups. There was a higher incidence of hearing impairment in the early CPAP treatment arm compared to the surfactant treatment arm but the difference was not statistically significant (3.3 vs. 1.5%, adjusted p=.06). Overall 24

infants had hearing loss, 13 of whom had bilateral hearing aids. There were no significant differences in composite outcomes of death or individual NDI components between the CPAP and Surfactant arms (Table 3).

Other neurodevelopmental outcomes: Mean BSID-III composite cognitive scores were similar in both CPAP and Surfactant arms (adjusted means ± standard error 91.3 ± 0.7 vs. 90.4 ± 0.8). Sixty percent of all children seen at 18-22 months corrected age (CPAP 59.7% and Surfactant 59.6%) had normal neuromotor, normal neurosensory and normal developmental (i.e. BSID-III cognitive composite score ≥ 85) evaluations.

Comparisons of outcome between gestational age strata: (Tables 2 and 3)
The difference in death before 18-22 months in the CPAP and surfactant arms was statistically significant in the lower 24 0/7 to 25 6/7 weeks gestation stratum [26.4 vs. 35.5%, adjusted p=0.02, RR 0.74 (95%CI 0.57,0.96)], but not in the higher gestational age stratum (12.3 vs. 11.8%). There were no significant differences in the composite outcome of *death or NDI* at 18-22 months corrected age between the CPAP and surfactant within either of the two gestational age strata (40.1 vs. 44.5% for 24 0/7-25 6/7 weeks gestation; 18.3 vs. 18.7% for 26 0/7 to 27 6/7 weeks gestation). Neither were there significant differences between the CPAP and Surfactant arms in the incidence of *NDI* alone within either of the two gestational age strata (18.1 vs. 12.5, adjusted p=0.22 for 24 0/7-25 6/7 weeks gestation; 6.3 vs. 7.2%, adjusted p=0.81 for 26 0/7-27 6/7 weeks gestation. Within each gestational age stratum the mean BSID-III composite *cognitive scores* were similar in both treatment groups (CPAP 89.2 ± 1.1 vs. Surfactant 88.1 ± 1.2 for 24 0/7-25 6/7 weeks gestation; CPAP 93.4 ± 0.9 vs. Surfactant 92.6 ± 0.9 for 26 0/7 to 27 6/7 weeks gestation, adjusted mean ± standard error).

Although neurodevelopmental outcomes were similar between treatment arms within each gestational age stratum, children in the lower gestational age stratum were at higher risk of adverse outcome. Compared to those in the 26 0/7-27 6/7 stratum, children in the 24 0/7 to 25 6/7 week gestational age stratum were more likely to have NDI (15.5% vs. 6.7%, p<0.0001), to have a cognitive score < 70 (10.7% vs. 5.4%, p<0.0001), to have a GMFCS ≥2 (7% vs. 3.7%, p=0.023), to have moderate to severe cerebral palsy (5.9% vs. 2.9%, p=0.02), and to be hearing impaired (3.8% vs. 1.6%, p=0.035).

DISCUSSION:
We report the neurodevelopmental outcome in early childhood at 18-22 months corrected age for extremely premature children, 24-27 weeks gestation, enrolled in the SUPPORT trial. There was no significant difference in the primary, pre-specified composite outcome of death or NDI at 18-22 months corrected age between those extremely premature infants randomized to treatment with early CPAP vs. those randomized to treatment with early intubation and surfactant administration. Neither were there significant differences between survivors in the CPAP and Surfactant arms in NDI or its components of severe cognitive impairment (cognitive score < 70), moderate/severe cerebral palsy, moderate/severe motor impairment (GMFSC ≥2), and bilateral blindness, or in mean composite cognitive BSID-III scores.

As reported in previous studies, the most immature infants (24 to 25 weeks gestation) in both CPAP and Surfactant arms were less likely to be normal and were at higher risk for severe cognitive impairment, abnormal gross motor function, moderate/severe cerebral palsy and hearing impairment. [22-24]

Bronchopulmonary dysplasia and longer duration of ventilation are associated with an increased risk of adverse neurodevelopmental outcome. [4,8-10] Although infants in the CPAP arm had significantly fewer days of ventilation and less often received postnatal steroids compared to the surfactant treated arm, the incidence of physiologic bronchopulmonary dysplasia was similar in both groups before discharge.

The strengths of this study include the large number of extremely premature infants enrolled, sufficient power to detect a clinically significant difference in the pre-specified outcome of death or neurodevelopmental impairment, the very high percentage of participants who were followed and evaluated in early childhood, and the comprehensive and standardized neurodevelopmental evaluation performed on survivors. One third of infants in the CPAP arm were intubated in the delivery room and two thirds ultimately received surfactant treatment and limited ventilation for clinical indications which may have blunted any difference in neurodevelopmental outcomes between the two groups. In addition, an adverse effect on neurodevelopmental outcome associated with the increased incidence of NEC in the CPAP arm may have counterbalanced adverse outcomes associated with the longer duration of ventilation and the increased need for supplemental oxygen and post-natal steroids in the surfactant treatment arm. The generalizability of this study may be limited by the need for antenatal consent which resulted in a trial cohort with higher socioeconomic status and receipt of antenatal steroids than the entire eligible cohort.[25]

In summary, we found no significant differences in the composite outcome of death or NDI, or in any of the individual components of NDI among survivors to 18-22 months corrected age between extremely preterm infants who were randomized at delivery to either early CPAP with a limited ventilation strategy or early intubation with surfactant administration followed by conventional ventilation. In this study early CPAP, an alternative respiratory management strategy for the extremely premature infant, did not decrease the composite risk of death or neurodevelopmental impairment in early childhood.

Acknowledgements

The National Institutes of Health, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), and the National Heart, Lung, and Blood Institute (NHLBI) provided grant support for the Neonatal Research Network's SUPPORT Trial.

Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Drs. Abhik Das (DCC Principal Investigator) and Marie Gantz (DCC Statistician) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study. The following investigators, in addition to those listed as authors, participated in this study:

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Figure : Patient Flow diagram

Table 1: Demographic and neonatal characteristics of trial and follow-up cohorts

Table 2: Pre-specified outcomes and components of NDI for entire cohort and by gestational age strata

Table 3: Death and components of NDI for entire cohort and by gestational age strata

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Figure: Patient Flow Diagram

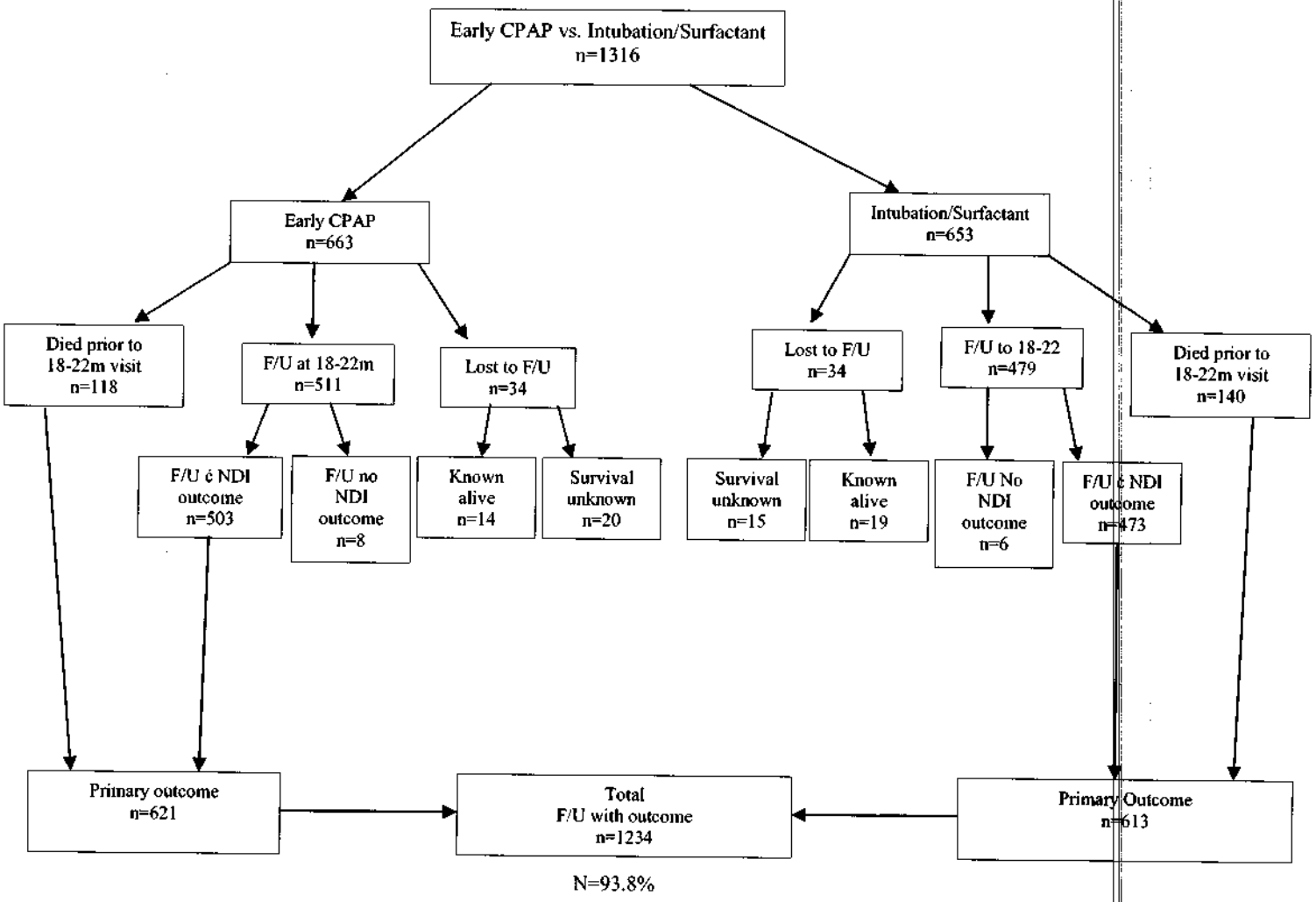

Table 1: Demographics and Characteristics of Trial Cohort and Follow-up Cohorts

	Follow-up Cohort	
	CPAP	Surfactant
	N=511	N=479
Birth weight (grams, Mean ± SD)	849±186	852±193
Gestational age (weeks, Mean ± SD)	26.3±1.1	26.3±1.1
Small for gestational age < 10-no./total no.(%)	23/511(4.5)	32/479(6.7)
Male-no./total no.(%)	256/511(50.1)	266/479(55.5)
Race		
Non-Hispanic White-no./total no.(%)	196/511(38.4)	200/479(41.8)
Non-Hispanic Black-no./total no.(%)	200/511(39.1)	177/479(37)
Hispanic-no./total no.(%)	98/511(19.2)	85/479(17.7)
Other or unknown-no./total no.(%)	17/511(3.3)	17/479(3.5)
Multiples-no./total no.(%)	138/511(27)	114/479(23.8)
Antenatal steroids(any)-no./total no.(%)	493/511(96.5)	456/479(95.2)
Cesarean section-no./total no.(%)	352/511(68.9)	315/479(65.8)
Public health insurance only-no./total no.(%)	262/511(51.3)	257/479(53.7)
Mother married-no./total no.(%)	244/511(47.7)	221/479(46.1)

With both biological parents†-no./total no.(%)	348/510(68.2)	329/479(68.7)
Maternal education < 12-no./total no.(%)	128/506(25.3)	116/469(24.7)
Income < $30,000/year†-no./total no.(%)	260/493(52.7)	251/461(54.4)
English as primary language at FUP -no./total no.(%)	426/510(83.5)	403/478(84.3)
Severe ROP in survivors to discharge-no./total no.(%)	62/479(12.9)	58/434(13.4)
Bronchopulmonary dysplasia in survivors to 36 weeks gestational age-no./total no.(%)	193/511(37.8)	187/479(39)
IVH grade 3-4/PVL-no./total no.(%)	70/510(13.7)	46/478(9.6)
NEC-stage ≥2 -no./total no.(%)	56/511(11)	30/479(6.3)**
Late onset sepsis/meningitis-no./total no.(%)	167/511(32.7)	154/479(32.2)
Postnatal steroids-no./total no.(%)	34/508(6.7)	55/476(11.6)**
Died before discharge-no./total no.(%)		

†Not available for infants who did not survive to discharge

p<0.02,*p<0.001

Tests comparing neonatal outcomes (i.e., Severe ROP through Died before discharge) adjusted for stratification factors (study center and gestational age group) and familial clustering

Table 2: Death and NDI for entire cohort and gestational age strata*

CPAP vs. Surfactant (All)	CPAP	Surfactant	RR	p
Death or NDI-no./total no.(%)	173/621(27.9)	183/613(29.9)	0.93(0.78,1.1)	0.38
Death before 18-22 mo CA-no./total no.(%)	118/643(18.4)	140/638(21.9)	0.83(0.67,1.04)	0.10
Death/NDI determined-no./total no.(%)	621/663(93.7)	613/653(93.9)	1(0.97,1.03)	0.83
NDI-no./total no.(%)	55/503(10.9)	43/473(9.1)	1.16(0.79,1.71)	0.44
BSID-III cognitive score < 70-no./total no.(%)	36/502(7.2)	36/472(7.6)	0.95(0.61,1.5)	0.84
Gross motor function level ≥ 2-no./total no.(%)	26/511(5.1)	23/479(4.8)	0.98(0.57,1.69)	0.95
Moderate/severe cerebral palsy-no./total no.(%)	21/511(4.1)	19/479(4)	0.93(0.51,1.72)	0.82
Blindness, bilateral-no./total no.(%)	4/511(0.8)	7/479(1.5)	0.53(0.16,1.78)	0.31
Hearing impairment-no./total no.(%)	17/511(3.3)	7/479(1.5)	2.27(0.96-5.37)	0.06

b. 24 0/7-25 6/7 weeks Gestational Age	CPAP	Surfactant	RR	p
Death or NDI-no./total no.(%)	109/272(40.1)	118/265(44.5)	0.9 (0.74,1.09)	0.27
Death before 18-22 mo CA-no./total no.(%)	73/277(26.4)	97/273(35.5)	0.74(0.57,0.96)	0.02
Death/NDI determined-no./total no.(%)	272/285(95.4)	265/280(94.6)	1.01(0.97,1.05)	0.68
NDI-no./total no.(%)	36/199(18.1)	21/168(12.5)	1.37(0.83,2.27)	0.22
BSID-III cognitive score < 70-no./total no.(%)	23/198(11.6)	16/167(9.6)	1.16(0.64,2.12)	0.62
Gross motor function level ≥ 2-no./total no.(%)	17/201(8.5)	9/172(5.2)	1.52(0.7,3.29)	0.29
Moderate/severe cerebral palsy-no./total no.(%)	14/201(7.0)	8/172(4.7)	1.32(0.57,3.04)	0.51
Blindness, bilateral -no./total no.(%)	2/201(1.0)	2/172(1.2)	0.86(0.12,6.02)	0.88
Hearing impairment-no./total no.(%)	11/201(5.5)	3/172(1.7)	3.24(0.9,11.71)	0.07

c. <u>26 0/7-27 6/7 weeks Gestational Age</u>	CPAP	Surfactant	RR	p
Death or NDI-no./total no.(%)	64/349(18.3)	65/348(18.7)	0.99(0.72,1.35)	0.93
Death before 18-22 mo CA-no./total no.(%)	45/366(12.3)	43/365(11.8)	1.05(0.71,1.55)	0.82
Death/NDI determined-no./total no.(%)	349/378(92.3)	348/373(93.3)	0.99(0.95,1.03)	0.57
NDI-no./total no.(%)	19/304(6.3)	22/305(7.2)	0.93(0.5,1.72)	0.81
BSID-III cognitive score < 70-no./total no.(%)	13/304(4.3)	20/305(6.6)	0.74(0.36,1.51)	0.41
Gross motor function level ≥ 2-no./total no.(%)	9/310(2.9)	14/307(4.6)	0.61(0.27,1.4)	0.24
Moderate/severe cerebral palsy-no./total no.(%)	7/310(2.3)	11/307(3.6)	0.62(0.24,1.58)	0.31
Blindness, bilateral-no./total no.(%)	2/310(0.6)	5/307(1.6)	0.39(0.08,1.99)	0.26
Hearing impairment-no./total no.(%)	6/310(1.9)	4/307(1.3)	1.53(0.44,5.26)	0.50

*Relative risk and p values adjusted for stratification factors (study center and gestational age group) and familial clustering (except blindness was not adjusted for study center due to small N)

Table 3: Death and Components of NDI for entire cohort and gestational age strata*

a. CPAP vs. Surfactant (All)	CPAP	Surfactant	RR	p
Death or cognitive composite<70-no./total no.(%)	154/620(24.8)	176/612(28.8)	0.86(0.72,1.03)	0.11
Death or GMF level ≥2-no./total no.(%)	144/629(22.9)	163/619(26.3)	0.87(0.72,1.05)	0.16
Death or moderate/severe CP-no./total no.(%)	139/629(22.1)	159/619(25.7)	0.86(0.71,1.05)	0.14
Death or blind in both eyes-no./total no.(%)	122/629(19.4)	147/619(23.7)	0.82(0.67,1.02)	0.07
Death or hearing impairment-no./total no.(%)	135/629(21.5)	147/619(23.7)	0.9(0.74,1.11)	0.33
b. 24 0/7-25 6/7 weeks Gestational Age				
Death or cognitive composite<70-no./total no.(%)	96/271(35.4)	113/264(42.8)	0.83(0.67,1.02)	0.08
Death or GMF level ≥2-no./total no.(%)	90/274(32.8)	106/269(39.4)	0.84(0.67,1.04)	0.12
Death or moderate/severe CP-no./total no.(%)	87/274(31.8)	105/269(39)	0.82(0.65,1.02)	0.08
Death or blind in both eyes-no./total no.(%)	75/274(27.4)	99/269(36.8)	0.75(0.58,0.96)	0.03
Death or hearing impairment-no./total no.(%)	84/274(30.7)	100/269(37.2)	0.83(0.65,1.05)	0.12

c. **26 0/7-27 6/7 weeks Gestational Age**	CPAP	Surfactant	RR	p
Death or cognitive composite<70-no./total no.(%)	58/349(16.6)	63/348(18.1)	0.93(0.67,1.29)	0.67
Death or GMF level ≥2-no./total no.(%)	54/355(15.2)	57/350(16.3)	0.94(0.67,1.33)	0.74
Death or moderate/severe CP-no./total no.(%)	52/355(14.6)	54/350(15.4)	0.96(0.68,1.36)	0.82
Death or blind in both eyes-no./total no.(%)	47/355(13.2)	48/350(13.7)	0.97(0.67,1.42)	0.89
Death or hearing impairment-no./total no.(%)	51/355(14.4)	47/350(13.4)	1.07(0.74,1.55)	0.71

*Relative risk and p values adjusted for stratification factors (study center and gestational age group) and familial clustering

From: Vaucher, Yvonne
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Finer, Neil
Subject: Effect of Antenatal Enrollment on Neurodevelopmental Outcome proposal
Date: Tuesday, February 07, 2012 6:17:50 PM
Attachments: Comparison ND outcome enrolled vs eligible_nonenrolled SUPPORT trial children at 18_22moRevYEV020712.docx

Rose,

Here is the revised antenatal enrollment proposal.

Yvonne

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Proposal to compare early childhood neurodevelopmental outcome of 24-25 week gestation ELBW children enrolled vs. Those not-enrolled in SUPPORT Trial

Authors: Yvonne Vaucher, Susan Hintz, Wade Rich

RATIONALE

Neurodevelopmental outcome results from the SUPPORT trial demonstrate that children born at 24-27 week gestation are at high risk for adverse neurodevelopmental outcome including NDI, MDI < 70, cerebral palsy and deafness compared to those born at 26-27 week gestation. These results support the findings of prior studies of ELBW or ELGAN children [1-4].

An important question for any multicenter trial including neurodevelopmental follow-up is whether the sample studied is representative and therefore generalizable to the larger population. Selection bias may arise during study enrollment or through lack of data for those who were lost to follow-up. Concerning the latter, the SUPPORT trial follow-up rate of 94% was outstanding, and as such, the bias resulting from loss to follow-up is likely quite small. However, the need for antenatal consent in the SUPPORT trial resulted in higher rates of adverse demographic, clinical and neonatal outcome factors in the eligible, non-enrolled group (N=3053)compared with the enrolled group (N=1316). [5, 6] For example the rate of resuscitation at delivery, BPD, severe IVH (Grades 3-4) and death were all significantly higher in the eligible, non-enrolled group.

It is important, therefore, to determine whether enrollment selection bias inherent in the need to obtain antenatal consent which was associated with more adverse demographic characteristics and neonatal outcomes is also associated with more adverse neurodevelopmental outcome in children who were eligible but not enrolled in trial, thereby reducing the generalizability of the study results. Alternatively it is possible that the effect of extremely low gestational age alone might predominate such that the incrementally increased risk associated with the higher rate of adverse demographic and neonatal outcome factors in the non-enrolled group would not be evident.

The SUPPORT trial included a very large group of extremely premature children born in the US at ≤ 27 weeks gestation for whom the composite outcome of death or NDI at 18-24 months adjusted age was determined for 93.7% (1234/1316). This group provides a unique opportunity to examine the effect of enrollment selection bias on early childhood neurodevelopmental outcome in children who are at the high neurodevelopmental risk. The initial step of determining the maternal and neonatal outcome biases has already been accomplished. [5, 6]The next logical step is to determine whether there is an associated neurodevelopmental outcome bias evident at 18-22 months corrected age. This short-term outcome information will also inform results from the longer term outcome study planned for SUPPORT children at 7 years.

We therefore propose to compare the frequency of death and the neurodevelopmental outcome of surviving 24-26 weeks gestation children at 18-22 months corrected age born between February 2005 and February 2009 who were eligible and enrolled in the SUPPORT trial to similar outcomes of

surviving 24-26 week gestation children who born during the same time period and who were eligible but were not enrolled in the SUPPORT trial.

HYPOTHESES

We hypothesize that:

1) the incidence of death and therefore the composite outcome of death or NDI will be higher in the eligible/non-enrolled group compared to the eligible/enrolled group
2) among survivors to 18-22 month follow up, the neurodevelopmental outcome of the eligible/enrolled vs. eligible/non-enrolled groups will not be significantly different

METHODS

This study would be a secondary, post-hoc, subgroup analysis of death and neurodevelopmental outcome for the extremely premature children born at 24-26 weeks gestation and enrolled in the SUPPORT trial. The outcome data for these children would be compared with that of the 24-26 week cohort , who were born during the enrollment period of the SUPPORT trial (2/2005 to 2/2009), were eligible for, but not enrolled in, the SUPPORT trial, and who were included in the NRN GDB. Comprehensive neurodevelopmental outcome data for both groups were prospectively collected at 18-22 months adjusted age, were sent to RTI and recorded in the GDB which is maintained by RTI. We will not include the outcome for 27 week gestation infants as these infants were excluded from the GDB beginning in 1/2008 when the admission criteria for the GDB was changed from birthweight < 1000 g to gestational age < 27 weeks.

Potential date limiters for developmental outcome results: All children enrolled in the SUPPORT trial (2/2005 to 2/2009) were assessed using the Bayley III exam. However, eligible/non-enrolled children in the GDB born before 1/2006 were evaluated using the Bayley II exam. Due to inherent differences in test design and construction, the rate of developmental impairment is substantially lower using the Bayley III (composite cognitive score < 70) when compared to the Bayley II (MDI or PDI < 70), thereby substantially reducing the rate of NDI which is a composite of developmental /cognitive, neuromotor and neurosensory outcomes. Unfortunately it is not possible to adjust for these differences between the Bayley II and Bayley III developmental scores. Due to this problem we may need to limit the time period for developmental comparison between the two groups to only those children born between 1/2006-2/2009, all of whom would been evaluated using the Bayley III. The rates of cerebral palsy, functional motor score (GMFCS) or blindness (vision <20-200) would not be affected as the assessment and definitions for these outcomes were the same throughout the study period for both groups. Although the definition of hearing impairment was changed from bilateral amplification for permanent deafness to permanent hearing loss ± amplification in 2006, the prior definition could be used for both groups .

Sample size: We will determine by week gestation and year of birth how many of the eligible/enrolled vs. eligible/non-enrolled in the GDB born at 24 0/7 to 26 6/7 weeks gestation from 2/2005 to 2/2009 had a developmental assessment using either the Bayley II or Bayley III at 18-22 month corrected age.

From this information we can then determine the available sample size and the magnitude of difference in neurodevelopmental outcomes which could be detected given a power of 80% and a two-sided alpha of < 0.05.

Lost-to Follow-Up (LTFU): The demographics and neonatal outcomes of LTFU vs. those who received follow-up at 18-22 moths will be compared within and between eligible/enrolled and eligible/non-enrolled groups. We anticipate that although the LTFU rate for the eligible/non-enrolled group will be greater than for eligible/enrolled children followed in the SUPPORT trial; it will be at ≥85%.

Outcome variables: Death, NDI (developmental /cognitive score < 70, GMFCS ≥2, moderate-severe cerebral palsy, blindness (vision < 20-200); deafness (permanent hearing impairment with amplification), individual components of NDI, developmental/cognitive score < 80 and <85, standardized cognitive score

Analyses: Comparative outcomes will include death before 18 to 22 months adjusted age, composite NDI, death or NDI and the individual outcomes included in the composite NDI (cognitive, cerebral palsy, GMFCS ≥ 2, blindness and deafness). We will also compare the standardized Bayley III cognitive scores and the proportions of the cognitive score< 80 and < 85. Outcomes will be compared for groups as a whole (24-26 weeks gestation) and for week gestation as the most immature infants (24-25 weeks gestation) enrolled in the SUPPORT trial were at significantly higher neurodevelopmental risk compared to the 26-27 weeks gestation infants. Unadjusted comparisons of demographic and treat neonatal characteristics between the groups will be conducted using chi-square test for categorical and t-tests for continuous variables. Analyses of categorical outcomes will be performed using robust Poisson regression in a general-estimating model to obtain adjusted relative risks with 95% confidence intervals. Analyses will be adjusted for center and familial clustering.

Linear and logistic regression models will be developed to examine the independent association of trial enrollment with death, composite NDI and individual neurodevelopmental outcomes. Factors in the regression model will include those demographic (gestational age, birthweight, race/ethnicity, maternal education, insurance status, prenatal care, antenatal steroids) and neonatal factors [Apgar < 3 at 1 and 5 minutes, delivery room resuscitation (chest compressions, epinephrine), oxygen at 36 wk(BPD), Grades 3-4 IVH or PVL]which were previously shown to be significantly different between the eligible/enrolled and eligible/non-enrolled groups [5,6]. When collinearity is present (e.g., birthweight/ gestational age; chest compressions/epinepherine), the most powerful predictor will be used in the final regression model.

Two-sided p values < 0.05 will be considered statistically significant.

RESULTS

Figure: Consort/Patient flow diagram: Enrolled vs. eligible/non-enrolled for death, follow up, lost-to-follow up, neurodevelopmental assessment determined

Tables: Comparisons of enrolled and eligible/non-enrolled groups

1. Demographic and neonatal factors for LTFU
2. Demographic and neonatal clinical outcomes
3. Death, NDI, death or NDI, individual components of NDI (cognitive < 70, GMFCS ≥2, moderate-severe CP, bilateral blindness, permanent hearing impairment) for each group as a whole and by week gestation
4. Comparison of additional developmental and neuromotor outcomes (i.e., Bayley III standardized composite cognitive score and proportion <80, >85; abnormal neurologic exam, normal, mild, moderate-severe CP for each group as a whole and by week gestation.
5. Adjusted odds ratios for factors (antenatal, neonatal) independently associated with differences in neurodevelopmental outcome.

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1. Raz, S., et al., *Extreme prematurity and neuropsychological outcome in the preschool years.* J Int Neuropsychol Soc, 2010. **16**(1): p. 169-79.
2. Leversen, K.T., et al., *Prediction of neurodevelopmental and sensory outcome at 5 years in Norwegian children born extremely preterm.* Pediatrics, 2011. **127**(3): p. e630-8.
3. Tyson, J.E., et al., *Intensive care for extreme prematurity--moving beyond gestational age.* N Engl J Med, 2008. **358**(16): p. 1672-81.
4. Wood, N.S., et al., *Neurologic and developmental disability after extremely preterm birth. EPICure Study Group.* N Engl J Med, 2000. **343**(6): p. 378-84.
5. Rich, W.D., et al., *Antenatal consent in the SUPPORT trial: challenges, costs, and representative enrollment.* Pediatrics, 2010. **126**(1): p. e215-21.
6. Rich, W., *Enrollment of ELBW Infants in a clinical research study may not be representative.* Pediatrics. **in press**.

n.b. Before January 2008 the criteria for GDB enrollment was birthweight <1000g; since January 2008 it has been a gestational age < 27 weeks.

The transition from administration of the Bayley II to the Bayley III at 18-22 months for GDB children occurred in 2/2007 for all those born in 2006.]

From: Vaucher, Yvonne
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Finer, Neil
Subject: RE: SUPPORT FU PAPER
Date: Tuesday, February 07, 2012 6:13:29 PM
Attachments: Vaucher SUPPORT FU CPAP PAPERTo NEJM020712.docx

Rose,

Final paper to go to NEJM is attached.

Comments of Reviewer 2 are addressed.
Trial cohort data was removed from Table 1 and paper.
The differences between gestational age strata in outcomes was changed from "less likely to be normal" to " more likely to have NDI, CP, GMFCS >/= 2,cognitive delay and hearing impairment" for which we have the p values as well as the % for each GA stratum.
Order of variables in table 2 changed to match paper .
Statistics are 2-sided as stated in the methods
Changed the last sentence to match the hypothesis ("Early CPAP ....did not decrease the risk of NDI)"
I did not change the patient flow diagram.

Reviewer 1 raised methodologic issues which cannot be changed as they are inherent in the SUPPORT
design (e.g., hypothesis, overlap due to % of CPAP who were intubated later on clinical grounds)
Titles should match; they are "bland" but is descriptive.
We were asked to submit two papers though the question about interaction is a good one.
Deaths remain to be completely analyzed which we should do for PAS as that is a major point of interest for the audience.
I changed the wording from "fewer deaths" to simply give the statistics (%, CI and RR, p values) for both Death and NDI.
We have to assume that the reader read (or will read) the primary SUPPORT paper.

I am sure the NEJM will have much to say.

I am leaving to work in (b)(6) for 6 weeks tomorrow. I will return on March 24th. Basically we have most of the slides prepared from the Hot Topics presentation. We will need to look at the deaths and should be prepared to address the question of interactions between the arms.

Thanks for all your encouragement!

Yvonne

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, February 07, 2012 6:39 AM
To: Vaucher, Yvonne
Cc: Finer, Neil

Subject: RE: SUPPORT FU PAPER

Yvonne
Can we get the final manuscript – Myriam is ready to submit hers

Thanks
Rose

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From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]
Sent: Thursday, February 02, 2012 1:42 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT FU PAPER

Yes

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, February 02, 2012 10:27 AM
To: Vaucher, Yvonne
Subject: RE: SUPPORT FU PAPER

Ok
Can you submit before leaving??
Thanks
Rose

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From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]
Sent: Thursday, February 02, 2012 1:26 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT FU PAPER

Will try to get this to you tomorrow. Am in the midst o preparing to leave for (b)(6) next week.

Yvonne

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, February 02, 2012 7:32 AM
To: Vaucher, Yvonne
Cc: Finer, Neil
Subject: SUPPORT FU PAPER

Yvonne –
Are you close on the SUPPORT FU paper for submission?

let me know and thanks for all the hard work!!
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
6100 Executive Blvd., Room 4B03
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Early CPAP versus Surfactant in Extremely Preterm Infants: Neurodevelopmental Outcomes in Early Childhood

Yvonne E. Vaucher, MD MPH[1]; Myriam Peralta-Carcelen, MD MPH[2]; Neil N. Finer, MD[1]; Waldemar A. Carlo, MD[2]; Michele C. Walsh, MD MS[3]; Marie G. Gantz, PhD[4]; Abbot R. Laptook, MD[5]; Bradley A. Yoder, MD[6]; Roger G. Faix, MD[6]; Abhik Das, PhD[7]; Kurt Schibler, MD[8]; Wade Rich, RRT[2]; Nancy S. Newman, RN[4]; Betty R. Vohr, MD[5]; Kimberly Yolton, PhD[8]; Roy J. Heyne, MD[9]; Deanne E. Wilson-Costello, MD[4]; Patricia W. Evans, MD[10]; Ricki F. Goldstein, MD[11]; Michael J. Acarregui, MD[12]; Ira Adams-Chapman, MD[13]; Athina Pappas, MD[14]; Susan R. Hintz, MD MS Epi[15]; Anna M. Dusick, MD FAAP[16]; Elisabeth C. McGowan, MD[17]; Richard A. Ehrenkranz, MD[18]; Anna Bodnar, MD[6]; Charles R. Bauer, MD[19]; Janell Fuller, MD[20]; T. Michael O'Shea, MD MPH[21]; Gary J. Myers, MD[22]; Rosemary D. Higgins, MD[23] for the SUPPORT Study Group of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network

Corresponding author and reprints:

Yvonne E. Vaucher, M.D., M.P.H. Telephone: 619-543-3759

[1] University of California at San Diego, San Diego, CA
[2] Division of Neonatology, University of Alabama at Birmingham, Birmingham, AL
[3] Department of Pediatrics, Rainbow Babies & Children's Hospital, Case Western Reserve University, Cleveland, OH
[4] Statistics and Epidemiology Unit, RTI International, Research Triangle Park, NC
[5] Department of Pediatrics, Women & Infants Hospital, Brown University, Providence, RI
[6] Department of Pediatrics, Division of Neonatology, University of Utah School of Medicine, Salt Lake City, UT
[7] Statistics and Epidemiology Unit, RTI International, Rockville, MD
[8] Department of Pediatrics, Cincinnati Children's Hospital Medical Center and University of Cincinnati, Cincinnati, OH
[9] Department of Pediatrics, University of Texas Southwestern Medical Center, Dallas, TX
[10] Department of Pediatrics, University of Texas Medical School at Houston, Houston, TX
[11] Department of Pediatrics, Duke University, Durham, NC
[12] Department of Pediatrics, University of Iowa, Iowa City, IA (current affiliation Children's Hospital at Providence, Anchorage, AK)
[13] Emory University School of Medicine, Department of Pediatrics, and Children's Healthcare of Atlanta, Atlanta, GA
[14] Department of Pediatrics, Wayne State University, Detroit, MI
[15] Department of Pediatrics, Division of Neonatal and Developmental Medicine, Stanford University School of Medicine and Lucile Packard Children's Hospital, Palo Alto, CA
[16] Department of Pediatrics, Indiana University School of Medicine, Indianapolis, IN
[17] Department of Pediatrics, Division of Newborn Medicine, Floating Hospital for Children, Tufts Medical Center, Boston, MA
[18] Department of Pediatrics, Yale University School of Medicine, New Haven, CT
[19] University of Miami Miller School of Medicine, Miami, FL
[20] University of New Mexico Health Sciences Center, Albuquerque, NM
[21] Wake Forest University School of Medicine, Winston-Salem, NC
[22] Department of Pediatrics, University of Rochester Medical Center, Rochester, NY
[23] *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD

University of California, San Diego

Division of Neonatology

200 West Arbor Drive

San Diego, CA, 92013

Fax: 619-543-3812

Email:yvaucher@ucsd.edu

are any changes please notify the Society in writing so that this information will appear correctly in the final program.

Presenter Name: **Marie Gantz**
Abstract Title: **Enrollment Propensity Weighting to Assess the Generalizability of a Randomized Clinical Trial**
Affiliation: **RTI International**

Changes or updates may be sent via email to tkeppler@fernley.com. Additionally, if there are unfortunate circumstances which result in you being unable to present your abstract, please notify me via email by no later than March 2, 2012.

Once again, congratulations, and we look forward to seeing you in Miami.

Sincerely,

Trish Keppler

Trish Keppler, CMP
SCT Meeting Manager

100 N. 20TH STREET, SUITE 400 • PHILADELPHIA, PA USA 19103
T: +1 215-320-3878 • F: +1 215-564-2175 • HTTP://WWW.SCTWEB.ORG • E-MAIL: SCT@FERNLEY.COM

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Vaucher, Yvonne"
Cc: "Cunningham, Meg"; Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: 2012 PAS Abstract Notification (#750265)
Date: Tuesday, February 07, 2012 2:03:00 PM

Congratulations!!
Also - let me know about the paper for NEJM so we can get both submitted.

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
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For overnight delivery use Rockville, MD 20852
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301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

-----Original Message-----
From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]
Sent: Tuesday, February 07, 2012 2:00 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: 2012 PAS Abstract Notification (#750265)

-----Original Message-----
From: Pediatric Academic Societies - Marathon Multimedia [mailto:support@marathonmultimedia.com]
Sent: Tuesday, February 07, 2012 8:30 AM
To: Vaucher, Yvonne
Cc: campaign@marathonmultimedia.com
Subject: 2012 PAS Abstract Notification (#750265)

Dear Dr. Vaucher:

Thank you for submitting your abstract entitled "Neurodevelopmental Outcome of Extremely Premature Infants Enrolled in the SUPPORT Trial: Early CPAP Versus Intubation with Surfactant Administration", abstract #750265, to the 2012 Pediatric Academic Societies' Annual Meeting, April 28-May 1, 2012, in Boston, Massachusetts. We are pleased to inform you that your abstract has been selected for a Platform Presentation.

For your official acceptance letter, which contains the PAS publication number and presentation instructions, please go to the following website. You will not receive this information via mail.

Website: http://www.call4abstracts.com/pas
Username: (b)(6)
Password: (b)(6)

If you have any questions, please feel free to contact Marathon Multimedia Technical Support at 507-333-1000, support@marathonmultimedia.com. If you have any questions regarding the presentation itself after viewing your acceptance letter, please contact me at mbrown@marathonmultimedia.com.

Sincerely,
The Pediatric Academic Societies

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Kennedy, Kathleen A"; "Wrage, Lisa Ann (wrage@rti.org)"; "dale_phelps@urmc.rochester.edu"; Archer, Stephanie (NIH/NICHD) [E]; "wcarlo@peds.uab.edu"; "Das, Abhik"; "Roger.Faix@hsc.utah.edu"; "nfiner@ucsd.edu"; "Gantz, Marie"; "alaptook@WIHRI.org"; "nxs5@cwru.edu"; "wrich@ucsd.edu"; "kurt.schibler@cchmc.org"; "Michele.Walsh@UHhospitals.org"; "Bradley.Yoder@hsc.utah.edu"
Cc: Archer, Stephanie (NIH/NICHD) [E]; "Cunningham, Meg"
Subject: RE: 2012 PAS Abstract Notification (#750344)
Date: Tuesday, February 07, 2012 1:57:00 PM

Congratulations!!
Rose

Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network
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301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

-----Original Message-----
From: Kennedy, Kathleen A [mailto:Kathleen.A.Kennedy@uth.tmc.edu]
Sent: Tuesday, February 07, 2012 1:53 PM
To: Wrage, Lisa Ann (wrage@rti.org); dale_phelps@urmc.rochester.edu; Archer, Stephanie (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; wcarlo@peds.uab.edu; Das, Abhik; Roger.Faix@hsc.utah.edu; nfiner@ucsd.edu; Gantz, Marie; alaptook@WIHRI.org; nxs5@cwru.edu; wrich@ucsd.edu; kurt.schibler@cchmc.org; Michele.Walsh@UHhospitals.org; Bradley.Yoder@hsc.utah.edu
Subject: FW: 2012 PAS Abstract Notification (#750344)

See below. The ROP Screening Secondary Study has been accepted as a poster (to be presented on Sunday).

Kathleen A. Kennedy, MD, MPH
Richard W. Mithoff Professor of Pediatrics
Director, MS in Clinical Research Degree Program
UT-Houston Medical School
6431 Fannin, Suite 2.106
Houston, TX 77030
713 500-6708

-----Original Message-----
From: Pediatric Academic Societies - Marathon Multimedia [mailto:support@marathonmultimedia.com]
Sent: Tuesday, February 07, 2012 10:43 AM
To: Kennedy, Kathleen A
Cc: campaign@marathonmultimedia.com
Subject: 2012 PAS Abstract Notification (#750344)

Dear Dr. Kennedy:

Thank you for submitting your abstract entitled "Evaluating Retinopathy of Prematurity (ROP) Screening

Guidelines for 24-27 Week Gestational Age (GA) Infants", abstract #750344, to the 2012 Pediatric Academic Societies' Annual Meeting, April 28-May 1, 2012, in Boston, Massachusetts. We are pleased to inform you that your abstract has been selected for a Poster Presentation.

For your official acceptance letter, which contains the PAS publication number and presentation instructions, please go to the following website. You will not receive this information via mail.

Website: http://www.call4abstracts.com/pas
Username: kkennedy
Password: sadie

If you have any questions, please feel free to contact Marathon Multimedia Technical Support at 507-333-1000, support@marathonmultimedia.com. If you have any questions regarding the presentation itself after viewing your acceptance letter, please contact me at mbrown@marathonmultimedia.com.

Sincerely,
The Pediatric Academic Societies

From: Navarrete, Cristina
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Duara, Shahnaz
Subject: RE: PAS abstract notifications
Date: Tuesday, February 07, 2012 1:06:21 PM
Attachments: 2012 PAS Notification Letter_Growth Sec.pdf
PAS 2012 - Growth Outcome SUPPORT.pdf

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]
Sent: Tuesday, February 07, 2012 11:47 AM
To: 'Beau Batton'; 'Phelps, Dale'; 'Myriam Peralta, M.D.'; 'Vaucher, Yvonne'; 'Susan Hintz'; Navarrete, Cristina; 'Erika Fernandez'; 'John Kelleher, M.D.'; Kathleen Kennedy; Laptook, Abbot; Pappas, Athina; 'Vohr, Betty'
Cc: Archer, Stephanie (NIH/NICHD) [E]; Meg Cunningham
Subject: PAS abstract notifications

Please forward your PAS abstract notifications to us – we are assembling a schedule for the network

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network
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BOSTON PAS 2012

PEDIATRIC ACADEMIC SOCIETIES
ANNUAL MEETING APRIL 28 - MAY 1

PAS PROGRAM OFFICE
3400 Research Forest Dr., Ste. B7
The Woodlands, TX 77381
Phone: (281) 419-0052 * Email: info@pas-meeting.org * www.pas-meeting.org

February 6, 2012

Cristina Navarrete
Pediatrics/Neonatology University of Miami/Jackson Memorial Hospital
1611 NW 12th Ave (Rm C740)
Miami FL 33136

RE: Growth Outcomes of Preterm Infants Exposed to Different Oxygen Saturation Target Ranges from Birth (Abstract #: 752262)

Dear Dr. Cristina Navarrete:

The abstract listed below has been selected for a PLATFORM PRESENTATION at the 2012 Pediatric Academic Societies' Annual Meeting in Boston, Massachusetts, April 28 – May 1. On behalf of the PAS Program Committee, we would like to thank you for your submission and extend our congratulations!

ABSTRACT TITLE: Growth Outcomes of Preterm Infants Exposed to Different Oxygen Saturation Target Ranges from Birth

FIRST AUTHOR: Cristina Navarrete

PUBLICATION NUMBER: 2755.5

SESSION**: 2755 – Neonatal – Patient-Oriented Research: Neonatal Nutrition

SESSION DATE & TIME: Sunday, April 29, 2012, 1:00 pm-3:00 pm

ROOM: Ballroom B (Hynes Convention Center)

PRESENTATION TIME: 2:00 pm (10-minute oral presentation followed by 5 minutes of discussion)

**In some cases, abstracts were moved from the author-designated theme or subspecialty to another to enhance scientific interchange. If you have questions about your abstract, please email info@pas-meeting.org or call the phone number listed above.

AUDIO VISUAL AIDS!!
Carefully read and follow the PAS audiovisual and speaker guidelines available at our website at www.pas-meeting.org. These guidelines outline computer formats and other important details related to a successful presentation. All presentations must be uploaded to the PAS Meeting server either via email or mail prior to the meeting (preferred) -or- hand carried on flash drive, diskette or CD and checked into the speaker ready room at least 24 hours in advance of presentation. All presenters are required to check in at the Speaker Ready Room (Main Lobby Cafeteria Room) at least six hours in advance to view their uploaded presentation. All presentations are in PowerPoint format.

For onsite assistance inquire at the PAS Information Desk at the Hynes Convention Center. Please be sure to read and adhere to the "Presenter Policies" available here: http://www.pas-meeting.org/2012Boston/CME/Index.asp. Feel free to review and update your disclosures here: http://www.call4abstracts.com/pas_disclosure/.

Once again, congratulations! We look forward to welcoming you to Boston, Massachusetts.

Sincerely,
The Pediatric Academic Societies

Meeting Registration And Housing
Abstract presenters are encouraged to register for the meeting. If you have not already registered at a reduced rate, please go to [illegible] website to register and secure housing. Register by March 1, 2012 for substantial savings. The final deadline for meeting registration is April 20, 2012. The deadline for housing reservations is March 30, 2012. We strongly encourage you to register and secure housing right away.

4-12311

Please select Print from the file menu to print your Abstract.

First Author: Cristina T Navarrete, MD
Responsible Author: Cristina T Navarrete, MD
Presenting Author: Cristina T Navarrete, MD
Contact Person: Cristina T Navarrete, MD

Filename: 752262

2012 PAS Annual Meeting

Subspecialty: Neonatology - General
Theme: Neonatal Medicine: Clinical Trials

Contact Author: Cristina T Navarrete, MD
Department/Institution/Address: Pediatrics/Neonatology, University of Miami/Jackson Memorial Hospital, 1611 NW 12th Ave (Rm C740), Miami, FL, 33136, United States
Phone: 305-5856408 **Fax:** 305-5456581 **E-mail:** cnavarrete@med.miami.edu

Reponsible Author: Cristina T Navarrete, MD
Department/Institution/Address: Pediatrics/Neonatology, University of Miami/Jackson Memorial Hospital, 1611 NW 12th Ave (C740), Miami, FL, 33136, United States
Phone: 305-5856408 **Fax:**
Responsible Author E-mail: cnavarrete@med.miami.edu
Responsible Author Declaration: As the responsible author, I confirm that the individual listed as the sponsor has been contacted and given the opportunity to review the abstract and has subsequently agreed to sponsor this abstract.

Presenting Author: Cristina T Navarrete, MD
Department/Institution/Address: University of Miami/Jackson Memorial Hospital, 1611 NW 12th Ave (C740), Miami, FL, 33136, United States
Phone: 305-5856408 **Fax:**
Presenting Author E-mail: cnavarrete@med.miami.edu
The presenting author is member of these Alliance Societies:
Is Presenting Author a Trainee? No, Not a Trainee
Presenter Copyright Declaration:
I certify that any material I will use, display, distribute, reproduce or have reproduced or distributed in connection with my above noted presentation for which I do not have permission to use, is my original work and/or is public information or another type of material which does not require securing permission from another party to use, display, distribute, reproduce or have reproduced or distributed.

QUESTIONNAIRE INFORMATION

Eastern Society for Pediatric Research: No, Do not consider this abstract for the Eastern SPR
Pediatric Hospital Medicine: No, Do not consider this abstract for presentation at the Pediatric Hospital Medicine, July 19-22, 2012
Research Type: Clinical
Presentation Sabbath Conflict on: N/A
APA Special Interest Groups, Committees or Regions: None

AWARDS APPLIED FOR:

No awards selected

SPONSOR INFORMATION

Sponsoring Member for PAS/ASPR abstract:
Sponsor Name: Shahnaz Duara, MD
Email: sduara@med.miami.edu
Is the Sponsor an Author? Yes
Sponsoring Societies:
American Academy of Pediatrics

Society for Pediatric Research

Title: Growth Outcomes of Preterm Infants Exposed to Different Oxygen Saturation Target Ranges from Birth

Cristina T Navarrete, MD[1], Shahnaz Duara, MD[1] and Rosemary D Higgins, MD[2]. [1]University of Miami, Miami, FL, United States and [2]the SUPPORT Subcommittee of the NICHD Neonatal Research Network, Rockville, MD, United States

Background: Post-natal growth restriction is a major morbidity in preterm infants. Perturbations in oxygenation may influence somatic growth; a recent study showed that infants exposed to higher oxygen saturation (SpO2) targets experience poorer growth (Tin, Arch Child Dis FN 2001). The Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial (SUPPORT) showed that a lower target range of SpO2 from birth, as compared with a higher range, resulted in less retinopathy of prematurity in survivors but an increase in mortality (Carlo, NEJM 2010).

Objective: To test the hypotheses that infants kept in the low SpO2 target range from birth will have better growth trajectories and better growth at 36 weeks and at 18-22 months corrected age (fewer babies <10th %ile for weight).

Design/Methods: A sub-cohort of 810 preterm infants enrolled in SUPPORT (n=1,316), randomized at birth to low (85-89%, n=402, GA 26.2 ± 1.1wks, BW 838.6 ± 186 gm) or high (91-95%, n=408, GA 26.2 ± 1.1wks, BW 839.6 ± 191gm) SpO2 target range was studied. Anthropometric measures were obtained at birth, postnatal days 7, 14, 21, and 28; 32 and 36 weeks post-menstrual age, and at 18-22 months corrected age. Longitudinal growth trajectories were constructed for each target group using the means of each measure per time point. Poor growth (weight, length, head circumference <10th %ile) at 36 weeks and 18-22 months was analyzed using robust Poisson regression.

Results: Growth trajectories for Wt, L, and HC showed no differences in growth between the low and high SpO2 assignment groups. There was no difference in mortality by 36 weeks and the rate of poor growth at 36 wks and at 18-22 month was not different for any measure.

Growth Outcomes by Assigned Groups

	Low SpO2 (n=402)	High SpO2 (n=408)	p-value
n (%) death by 36wk	69 (17.2)	60 (14.7)	0.32
n /N(%) with Wt <10th %ile at 36wk	155/333 (46.6)	172/342 (50.3)	0.30
n /N(%) with Wt <10th %ile at 18-22m	48/296 (16.2)	45/313 (14.4)	0.49
n /N(%) with L <10th %ile at 36wk	203/314 (64.7)	218/315 (69.2)	0.21
n /N(%) with L <10th %ile at 18-22m	79/296 (26.7)	98/313 (31.3)	0.28
n /N(%) with HC <10th %ile at 36wk	124/319 (38.9)	130/325 (40.0)	0.87
n /N(%) with HC <10th %ile at 18-22m	46/296 (15.5)	49/313 (15.7)	0.92

Conclusions: Early oxygen saturation target assignment did not impact on growth in a large subgroup of infants enrolled in the SUPPORT Trial.

Other Previews:

Abstract Disclosure Info: Disclosures

Close Window

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Vaucher, Yvonne"
Subject: RE: SUPPORT FU PAPER
Date: Thursday, February 02, 2012 1:44:00 PM

Spectacular

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
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301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]
Sent: Thursday, February 02, 2012 1:42 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT FU PAPER

Yes

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, February 02, 2012 10:27 AM
To: Vaucher, Yvonne
Subject: RE: SUPPORT FU PAPER

Ok
Can you submit before leaving??
Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
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301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]
Sent: Thursday, February 02, 2012 1:26 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT FU PAPER

Will try to get this to you tomorrow. Am in the midst o preparing to leave for (b)(6) next week.

Yvonne

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, February 02, 2012 7:32 AM
To: Vaucher, Yvonne
Cc: Finer, Neil
Subject: SUPPORT FU PAPER

Yvonne –
Are you close on the SUPPORT FU paper for submission?

let me know and thanks for all the hard work!!
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
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301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Myriam Peralta, M.D."
Cc: "Wally Carlo, M.D."
Subject: RE: Support 1_23_2012
Date: Thursday, February 02, 2012 9:12:00 AM

Myriam
I am good with this version. I suggest getting the format right for NEJM (i.e. references as numbers as opposed to citations) and let's get it submitted. I will also ask Yvonne for an update.

Thanks for all the effort
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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higginsr@mail.nih.gov

From: Myriam Peralta, M.D. [mailto:MPeralta@peds.uab.edu]
Sent: Friday, January 27, 2012 5:46 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Wally Carlo, M.D.
Subject: Support 1_23_2012

Rose I included the review with responses, and make a few changes in the manuscript, please let me know what do you think, I will review this more this weekend and try to get it ready for the final review to send to authors next week and send out let me know thanks

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Wally Carlo, M.D."
Subject: RE: Review paper on O2 sats
Date: Wednesday, February 01, 2012 2:02:00 PM

I cannot be a co-author if that is the message.

Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Wednesday, February 01, 2012 1:43 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Review paper on O2 sats

Rose.

They want me to make practice recommendations. Would you be ok recommending O2 targeting of 91 to 95%?

Wally

-----Original message-----
From: "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>
To: "'Wally Carlo, M.D.'" <WCarlo@peds.uab.edu>
Sent: Wed, Feb 1, 2012 18:38:34 GMT+00:00
Subject: RE: Review paper on O2 sats

Wally
I don't need to be an author, but if you would like me to be one, I certainly can – I need some time for clearance and we can't state things like practice should be....

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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CDBPM, NIH
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301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Sunday, January 29, 2012 2:05 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Review paper on O2 sats

Hi Rose:

I have been asked by Paulo Manzoni to write a brief review on O2 saturation targets to be published in Early Human Development as part of a talk I will give in Italy in May.

I was wondering if you want to be a co-author as it will be largely like the other review we published together. Also, do we have to get this cleared by the NRN Publication Subc?

Wally

From: Buchanan, Lisa (HHS/OASH)
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Borror, Kristina C (HHS/OASH)
Subject: RE: "SUPPORT Trial" (HHS Protocol 2U10HD034216)
Date: Wednesday, February 01, 2012 1:54:20 PM

Hi Rose,

Got it. Thanks again.

Lisa

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, February 01, 2012 1:31 PM
To: Buchanan, Lisa (HHS/OASH)
Cc: Borror, Kristina C (HHS/OASH)
Subject: RE: "SUPPORT Trial" (HHS Protocol 2U10HD034216)

Hi,
These were sent and we have confirmed with FED EX that they were delivered – can you confirm that you have them??
Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Buchanan, Lisa (HHS/OASH)
Sent: Monday, January 09, 2012 11:40 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Borror, Kristina C (HHS/OASH)
Subject: "SUPPORT Trial" (HHS Protocol 2U10HD034216)

Good morning Dr. Higgins,

I am reviewing responses' to allegations of noncompliance with Department of Health and Human Services (HHS) regulations for the protection of human research subjects (45 CFR Part 46) involving the above-referenced research. OHRP has only opened its investigation with the University of Alabama. However, we would like to review the informed consent documents for all of the sites (~20). The data coordinating center, RTI,

recommended that we contact you for this information. (See email below.) Would it be possible for you to provide copies of all the most recent IRB-approved informed consent documents from the different sites in the SUPPORT study?

Please feel free to contact me if you have any questions regarding this request.

Thanks,
Lisa

Lisa Buchanan, MAOM
Public Health Analyst, Division of Compliance Oversight
Office for Human Research Protections
Department of Health and Human Services
1101 Wootton Parkway, Suite 200
Rockville, MD 20852
Ph: 240-453-8298
Fax: 240-453-6909

From: Borasky, David [mailto:dborasky@rti.org]
Sent: Thursday, August 04, 2011 12:19 PM
To: Borror, Kristina C (HHS/OASH)
Cc: Caddell, Juesta M.
Subject: RE: clarification requested

Hi Kristina –

We had a chance to discuss your request with the RTI DCC folks this morning and how RTI may be able to help facilitate this for OHRP.

As I mentioned this morning, the RTI IRB does not require the DCC to provide RTI IRB with copies of the approved informed consent documents for each site. I did confirm that the DCC requires sites to submit copies of study approval notices to the DCC, but they do not require submission of copies of site-level informed consent documents to the DCC. Some site do include them with the approval notices, but this is not done consistently and may not be done every time a consent document is amended at the site level. Therefore, the DCC's records for site-level consent documents are incomplete.

The RTI IRB and the Neonatal Research Network DCC appreciate your desire to expeditiously obtain site-level informed consent documents for the SUPPORT Trial. We believe that the best way to facilitate this is to have OHRP submit a formal request to the Neonatal Research Network steering committee via the NICHD project officer Rosemary Higgins (contact information below) to have the RTI Data Coordinating Center collect copies of the final approved consent forms (as well as whether or not this is the initially approved documents or all versions that were used with participants for the duration of the study) for each of the SUPPORT Trial sites for transmittal to OHRP.

I hope this is a suitable approach.

Best,

Dave

Dr. Higgins contact information:

Rosemary D. Higgins, MD
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****

David Borasky, MPH, CIP
Office of Research Protection
RTI International
3040 Cornwallis Rd
RTP, NC 27709
USA

Phone: 919-316-3903
Fax: 919-316-3897
E-mail: dborasky@rti.org

From: Borror, Kristina C (HHS/OASH) [mailto:Kristina.Borror@hhs.gov]
Sent: Friday, July 29, 2011 4:23 PM
To: Borasky, David
Cc: Caddell, Juesta M.
Subject: RE: clarification requested

Dave,
We were wondering if you would be able to get us copies of all the most recent IRB-approved informed consent documents from the different sites in the SUPPRT study. Is that possible?
Thanks for your assistance.
Kristina

From: Borasky, David [mailto:dborasky@rti.org]
Sent: Monday, July 25, 2011 1:13 PM
To: Borror, Kristina C (HHS/OASH)
Cc: Caddell, Juesta M.
Subject: RE: clarification requested

Thank you for the quick response Kristina.

RTI was not engaged in the conduct of the SUPPORT clinical protocol nor would have

been considered the IRB of record. RTI serves as the network data coordinating center for all sites, and in this role received coded data for analysis.

Therefore, as per your email, we will not submit a response to the letter dated July 18, 2011.

Regards,

Dave

****

David Borasky, MPH, CIP
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RTI International
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RTP, NC 27709
USA

Phone: 919-316-3903
Fax: 919-316-3897
E-mail: dborasky@rti.org

From: Borror, Kristina C (HHS/OASH) [mailto:Kristina.Borror@hhs.gov]
Sent: Monday, July 25, 2011 1:00 PM
To: Borasky, David
Cc: Caddell, Juesta M.
Subject: RE: clarification requested

Dave,
If RTI is not engaged in the research, we do not require any additional information at this time. We'll let you know if we need anything else.

Kristina C. Borror, Ph.D.
Director
Division of Compliance Oversight
Office for Human Research Protections
1101 Wootton Parkway, Suite 200
The Tower Building
Rockville, MD 20852
email: kristina.borror@hhs.gov
Phone: (240) 453-8132
Fax: (240) 453-6909

From: Borasky, David [mailto:dborasky@rti.org]
Sent: Monday, July 25, 2011 11:10 AM
To: Borror, Kristina C (HHS/OASH)
Cc: Caddell, Juesta M.
Subject: clarification requested

Good morning Kristina,

On Friday we (RTI) received a letter from you that was addressed to both our signatory official (Ward Sax) and the SO of UAB (Dr. Marchase) related to the SUPPORT trial.

However, we noticed that the letter's salutation was only addressed to Dr. Marchase.

For the SUPPORT Trial (and for the entire Neonatal Research Network) RTI serves as the data coordinating center and we have no oversight of the clinical research. We receive and analyze coded data, and do not have access to the code linking subjects to identifiers.

Given our role and that we are not in the salutation, we assume that OHRP does not expect a formal response from RTI. Would you please confirm if our assumption is correct, and if not, provide guidance on what OHRP would want RTI to provide given our role with the SUPPORT Trial? I leave on vacation tomorrow, so if you could reply to all I would appreciate it. Juesta Caddell is the Director of our IRB office and is the HPA on our FWA.

Thank you.

Dave

****

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Phone: 919-316-3903
Fax: 919-316-3897
E-mail: dborasky@rti.org

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Das, Abhik"
Subject: SUPPORT pulmonary outcomes
Date: Wednesday, February 01, 2012 12:33:00 PM

Abhik
Any chance for a later breaker on the SUPPORT breathing outcomes??
thanks
Rsoe

Rosemary D. Higgins, MD
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From: Blaisdell, Carol (NIH/NHLBI) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]
Cc: Gail, Dorothy (NIH/NHLBI) [E]
Subject: FW: Division of Lung Diseases staff members receive first-ever partnership award from NICHD
Date: Friday, January 27, 2012 3:08:16 PM

Hi Rose, Cathy
Dr. Shurin was so pleased with the NICHD partnership award to our division, that she posted in on the NHLBI site.
We have had a lot of acknowledgements—so we owe you!!

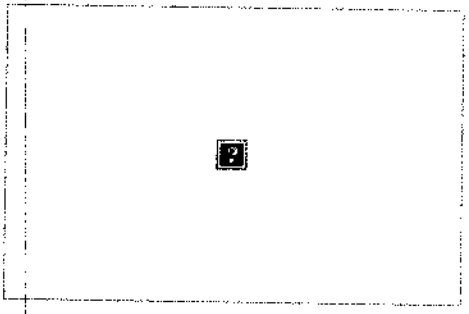
Could we meet with you and Cathy sometime to celebrate our partnership?
You both have been so great to work with and we hope to continue more shared projects.

Carol

Carol J. Blaisdell M.D.
Medical Officer
Lung Development and Pediatrics
Lung Biology and Diseases Branch
Division of Lung Diseases
NHLBI, NIH
301-435-0222

From: The National Heart, Lung, and Blood Institute
Sent: Friday, January 27, 2012 11:02 AM
To: Blaisdell, Carol (NIH/NHLBI) [E]
Subject: Division of Lung Diseases staff members receive first-ever partnership award from NICHD

Message from the NHLBI Director's Office



Division of Lung Diseases staff members receive first-ever partnership award from NICHD

Drs. James Kiley, Carol Blaisdell, Dorothy Gail, and Barry Schmetter of the NHLBI Division of Lung Diseases were selected to receive the first-ever Partnership Award from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD). The team was honored during an awards ceremony at NIH's Lipsett Amphitheater on Jan. 18.

Related links:

- Neonatal Research Network
- Maternal Fetal Medicine Units Network

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)
Date: Friday, January 27, 2012 9:14:00 AM
Attachments: HIC consent version 3.doc
HIC Spanish consent version 3.doc

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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From: Ehrenkranz, Richard [mailto:richard.ehrenkranz@yale.edu]
Sent: Thursday, January 26, 2012 4:35 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)

Rose:
Here they are. I did not see your early email until today; it had been put into my junk inbox.
Richard

Richard A. Ehrenkranz, MD
Department of Pediatrics
Yale University School of Medicine
333 Cedar Street
PO Box 208064
New Haven, CT 06520-8064
tele: 203-688-2320
fax: 203-688-5426

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, January 26, 2012 2:53 PM
To: Ehrenkranz, Richard
Subject: FW: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)

Importance: High

Richard – Can you send me your latest SUPPORT main Trial consent today? Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, January 20, 2012 2:38 PM
To: 'Ehrenkranz, Richard'
Cc: Maddox, Yvonne (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Hirschfeld, Steven (NIH/NICHD) [E]
Subject: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)

Richard-
As you are aware the Neonatal Research Network (NRN) continues to support studies under common protocols, but which require individual institutional IRB review prior to the conduct of these studies at each of the NRN sites. This is to inform you that The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), which provided the Federal support to the NRN, has been requested by the Office of Human Subjects Protection, to provide to the Office the most current consent form approved by your IRB and the corresponding IRB approval for the main SUPPORT Study, including any revisions, as soon as possible. As the NICHD Program Director of the NRN, I am requesting that the most recent consent form with IRB approval for your site for SUPPORT be submitted to me as soon as possible, but no later than January 26, 2012. Thank you for your cooperation.

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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301-435-7909

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301-496-3790 (FAX)
higginsr@mail.nih.gov

NAME:

HOSPITAL UNIT NUMBER:

ADDRESSOGRAPH:

PERMISSION FOR PARTICIPATING IN A RESEARCH PROJECT YALE UNIVERSITY SCHOOL OF MEDICINE-YALE-NEW HAVEN HOSPITAL

Study Title: The SUrfactant Positive Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants (The SUPPORT Trial)

Principal Investigator: Richard A. Ehrenkranz, MD
Co-Investigator: Vineet Bhandari, MD, DM

Funding Source: The National Institute of Child Health and Human Development (NICHD) Neonatal Research Network

Invitation to Participate and Description of Project

You are invited to participate in a research study designed to determine if using continuous positive airway pressure during resuscitation after birth helps decrease the severity of lung disease in premature babies. We will also be looking at the ranges of oxygen saturation that are currently being used with these same babies. You and your baby have been asked to participate because you are less than 28 weeks pregnant and your baby may be born prematurely. The doctors at the Newborn Special Care Unit (NBSCU) at Yale-New Haven Children's Hospital (Y-NHCH); along with 15 other centers across the country, are participating in this project sponsored by the National Institute of Child Health and Human Development.

In order to decide whether or not you wish to be a part of this research study you should know enough about its risks and benefits to make an informed judgment. This consent form gives you detailed information about the research study, which a member of the research team will discuss with you. This discussion should go over all aspects of this research: its purpose, the procedures that will be performed, any risks of the procedures, possible benefits and possible alternative treatments. Once you understand the study, you will be asked if you wish to participate; if so, you will be asked to sign this form.

Description of Procedures

Your baby may be born prematurely and is at risk for a breathing problem called **Respiratory Distress Syndrome (RDS)**. A baby's lungs are made up of tiny lung sacs; each one is suppose to open and close as the baby breathes in and out. Oxygen is supposed to go in and carbon dioxide is supposed to come out. This works well in full term babies and adults; however, in premature babies the lung sacs don't always work this way. Some lung sacs open and close normally; others collapse and stick together when the baby breathes out making it harder for the baby to breathe. Doctors treat this problem by keeping the lungs slightly inflated (or open) between breaths. This is done by maintaining a little air pressure in the lungs after the baby

breathes out (resting pressure), making it easier for the baby to take the next breath. Sometimes a medication called **surfactant** is given to try to help keep the lung sacs expanded. Surfactant is given directly into the lungs via a tube that is inserted into the airway (referred to as intubation).

After your baby is born, if he/she needs help breathing, the doctor or nurse will place a resuscitation mask over the baby's nose and mouth and provide oxygen and manual breaths with a resuscitation bag. The bag is squeezed to force air into the baby's lungs. The bag and mask may be used to give breaths or give just pressure to keep the lungs inflated (open) between breaths. This resting pressure is called continuous positive airway pressure (CPAP) or positive end-expiratory pressure (PEEP). At the present time, there is no recommendation regarding the early use of CPAP/PEEP in the delivery room and then continuing it in the nursery for premature infants. However, some studies have suggested that the use of early CPAP/PEEP may be associated with improved outcomes such as; fewer babies needing to be placed on a breathing machine, less oxygen use in babies at one month of age and longer, and less need for surfactant to be given. This study will begin in the delivery room and will continue into the nursery. It will compare the use of early CPAP/PEEP with early intubation, surfactant treatment, and initiation of mechanical breathing assistance. The purpose of the study is to see if one of these treatment plans reduces the severity of, and perhaps prevents, the development of long-term lung problems in premature infants. Those lung problems are referred to as bronchopulmonary dysplasia (BPD) or chronic lung disease (CLD).

Another part of the study will be looking at the ranges of oxygen saturations that are currently being used with premature infants. Doctors, nurses, and others taking care of your baby use, in routine daily care, a monitor called a **pulse oximeter** that uses a small probe placed on a hand or a foot to non-invasively monitor oxygen provided to help meet the baby's needs. In this part of the study we would like to pinpoint the exact range that should be used to help prevent some of the problems that occur with premature babies such as Retinopathy of Prematurity (ROP). This is when there is abnormal blood vessel growth in the eye. It causes scar tissue to build up around the retina and if it pulls on the retina hard enough it can cause blindness. It is known that the risk of ROP is increased by the prolonged use of supplemental oxygen from observations published in the 1950's, but the benefit of higher versus lower levels of oxygenation in infants, especially for premature infants, is not known. After reviewing how babies in the past were managed, it has been suggested that the use of lower saturation ranges may result in a lower incidence of severe ROP.

If your baby is born before a gestational age of 28 weeks, he/she will randomly (like the flip of a coin) be placed into the Early CPAP/PEEP group **or** the Early Surfactant/Ventilation group. **Both approaches are currently used at Y-NHCH.**

If your baby is randomized to the Early CPAP/PEEP group, he/she will be treated with CPAP/PEEP in the delivery room and will continue to be supported by CPAP/PEEP after admission to the nursery. However, if at any time, your baby's respiratory distress worsens, he/she will be intubated and started on a breathing machine. If this occurs within the first 48 hours of life, he/she will also be given surfactant.

If your baby is randomized to the Early Surfactant/Ventilation Group, he/she will be intubated and started on the breathing machine in the delivery room and will also be given surfactant within the first hour of birth.

For the first 14 days of life, there will be guidelines for the doctors in the nursery to follow. These guidelines help them decide when to place babies on the breathing machines and when to try and take them off the breathing machines. These guidelines also will help decide when to put them on and take them off of CPAP/PEEP. After 14 days of life, your baby's respiratory care will be managed in accordance with standard NBSCU practice.

The babies in this study will also be placed randomly (again, like the flip of a coin) into a group in which lower oxygen saturation (SpO2) values are targeted or into a group in which higher SpO2 values are targeted. As described above, oxygen saturation is measured on a baby with a monitor called a pulse oximeter. It uses a tiny sensor or probe on the hand or foot of the baby to non-invasively measure how saturated the baby's blood is with oxygen. Oximetry is not painful and provides SpO2 measurements 24 hours a day. The babies in the lower range group will have a target SpO2 of 85-89%, while the babies in the higher range group will have a target SpO2 of 91-95%. All of these saturations are considered within the normal range for premature infants. If the SpO2 falls below 85% or goes higher than 95% then the pulse oximeter will alarm so that the doctors and nurses know when to turn your baby's oxygen up or down.

Therefore, if your baby participates in this study, he/she will be assigned to one of 4 groups.

Randomized Intervention	**Low SpO2 85% to 89%**	**High SpO2 91 to 95%**
Early CPAP/PEEP Group	Early CPAP + Low SpO2	Early CPAP + High SpO2
Early Surfactant - Ventilation Group	Surfactant + Low SpO2	Surfactant + High SpO2

Finally, after discharge home your baby will be invited to return to Yale's Newborn Follow-Up Program located at the Yale Child Study Center. The purpose of this program is to perform standardized developmental testing on all infants cared for in the NBSCU with birth weights less than or equal to 1000 grams. Infants who participate in research projects, such as this one, are also invited to be evaluated in this program. Therefore, at 18-22 months corrected age, your baby will receive, as part of this study, a complete exam of his or her muscles, nerves, and mental and motor skills. In addition, before that visit, brief telephone interviews about your baby's health will be done by our Follow-Up staff.

Risks and Inconveniences

The possible risks of using CPAP/PEEP include stomach fullness and a temporary slowing of the heart rate. Another possible risk is collapsing of one or both lungs. Use of CPAP/PEEP at the level used in this study **does not** increase the risk of a collapsed lung (pneumothorax). As with the use of CPAP/PEEP, a possible risk of being intubated for initiation of mechanical ventilation may include a temporary slowing of the heart rate or possibly the collapse of one or both lungs. Another unlikely risk is the possibility of the airway being punctured during insertion of the breathing tube. **Note** that the risks associated with intubation and initiation of mechanical ventilation **are not increased** by participation in this study.

Pulse oximeters are used routinely in thousands of premature infants in NICU's across the country. There is no known risk to your baby from monitoring with the pulse oximeters. There is a small risk of skin breakdown at the site of the pulse oximeter's probe, but that will be minimized by your baby's nurse routinely changing the probe site.

Benefits

Each of the 4 possible treatment combinations is considered to represent the best approach by some units. However, your baby may not receive any direct benefits from participating in this trial.

If this trial identifies treatment strategies that lower the risk of BPD or ROP, clinical management of extremely preterm infants will be influenced and, hopefully, lead to reductions in the incidence of those problems.

Economic Considerations

All of the therapies and procedures used as part of this study, including early CPAP/PEEP, intubation, mechanical ventilation, surfactant therapy, and pulse oximetry, are commonly used to treat infants in the NBSCU with respiratory problems. Since this study will compare standard therapies, you or your insurer will be responsible for the cost of medical care provided by the staff of the NBSCU to your infant.

A $50.00 gift plus expenses (for example for parking or childcare) will be given to you as compensation for your time after your infant completes the Follow-Up visit at 18 to 22 months corrected age.

Treatment Alternatives/Alternatives

If you choose not to enroll your infant in this study your infant will be treated with respiratory support in accordance with treatment commonly followed in the NBSCU. Currently early CPAP/PEEP, intubation, mechanical ventilation, and surfactant therapy are common practices in the NBSCU for extremely low birth weight infants with breathing problems. As described above, participation in this study will compare standard treatment strategies.

Confidentiality

The medical information gathered from this study and your infant's medical record might be reviewed by representatives of the National Institute of Child and Human Development (NICHD), and the Yale University School of Medicine Human Investigation Committee (the committee that reviews, approves and monitors research on humans). The collection and submission of medical information from this study to the NICHD will be done with professional standards of confidentiality. The results of this study may eventually be published and information may be exchanged between medical investigators. However, your infant's name will not be used in any publication which may result from this research.

In Case of Injury

Although it is highly unlikely that your infant will be injured as a result of his/her participation in this study, treatment will be provided for an injury that is a result of this study. You or your insurance carrier will be expected to pay for the costs of this treatment. No additional financial compensation for injury is available. You do not give up any of your legal rights by signing this form.

Volunteer Participation and Withdrawal

Your infant's participation in this study is purely voluntary. You are free not to give your permission for participation, and refusal to do so will in no way affect the care your baby receives in this unit. Whether or not your infant participates, he/she will be cared for according to standards of newborn care. You are free to withdraw your infant from this study at any time and withdrawal from this study will in no way hurt your relationship with the physicians in the NBSCU or with Yale-New Haven Children's Hospital.

Questions

We have used some technical terms in this form. Please feel free to ask about anything you don't understand and to consider this research and the consent form carefully for as long as you feel is necessary before you make a decision.

Authorization

I have read (or someone has read to me) this form and have decided to participate in the project described above. Its general purposes, the particulars of involvement and possible hazards and inconveniences have been explained to my satisfaction. My signature also indicates that I have received a copy of this consent form.

Name of Subject:_____

Signature:_____

Relationship:_____

Date:_____

_____ _____

Signature of Principal Investigator Date

Or

_____ _____

Signature of Person Obtaining Consent Date

If you have further questions about this project or if you have a research-related problem, you may contact the Principal Investigator [Richard A. Ehrenkranz, MD at (203)-688-2320]. If you have any questions concerning your rights as a research subject, you may contact the Human Investigation Committee at (203) 785-4688.

THIS FORM IS NOT VALID UNLESS THE FOLLOWING BOX HAS BEEN COMPLETED IN THE HIC OFFICE

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HIC PROTOCOL #: 0410027163

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Hospital Unit Number:

Addressogragh:

PERMISO PARA LA PARTICIPACIÓN EN UN PROYECTO DE INVESTIGACIÓN ESCUELA DE LA UNIVERSIDAD DE YALE DE LA MEDICINA - HOSPITAL DE YALE NEW HAVEN

Titulo del Estudio: Ensayo Clínico de la Presión Positiva del Surfactante y de la Oximetría de Pulso en Neonatos con un Peso de Nacimiento Extremadamente Bajo (El ensayo SUPPORT).

Investigador Principal: Richard A. Ehrenkranz, MD

Coinvestigador: Vineet Bhandari, MD, DM

Fuente De Financiamiento: Instituto Nacional de la Salud del Niño y de la Red Neonatal Humana de Investigación del Desarrollo (NICHD)

Invitación a Participar y Descripción del Proyecto

Le invitamos a participar en un proyecto de investigación que tiene por objeto averiguar si el uso de la presión positiva continua en las vías respiratorias durante las maniobras de resucitación después del nacimiento disminuye la gravedad de las enfermedades pulmonares en los bebés prematuros. También observaremos el nivel de saturación de oxígeno que se usa actualmente para tratar a estos bebés. Le hemos pedido a su bebé y a usted que participen porque usted está embarazada de menos de 28 semanas y su bebé puede nacer prematuramente. Este estudio está avalado por el Instituto Nacional de la Salud Infantil y del Desarrollo Humano (National Institute of Child Health and Human Development) y en él participan los médicos de la Unidad Especial de Cuidados Neonatales (NBSCU) del Yale-New Haven Children's Hospital (Y-NHCH); junto con otros 15 hospitales por todo el país.

Para decidir si usted desea participar en de este estudio de investigación debe saber bastante sobre sus riesgos y ventajas para poder hacer un juicio informado. Esta forma de consentimiento le da información detallada sobre el estudio de investigación, que un miembro del equipo de investigación discutirá con usted. Esta discusión debe cubrir todos los aspectos de esta investigación: su propósito, los procedimientos que serán realizados, cualquier riesgo de los procedimientos, ventajas posibles y posibles tratamientos alternativos. Una vez que usted entienda el estudio, le preguntarán si usted desea participar; si es así le pedirán firmar esta forma de consentimiento.

Descripcion de los Procedimientos

Su bebé puede nacer prematuramente y corre el riesgo de sufrir un problema respiratorio llamado **Síndrome de Sufrimiento Respiratorio (RDS)**. Los pulmones del bebé están compuestos de diminutos sacos pulmonares, cada uno de éstos debe abrirse y cerrarse cuando el bebé inspira y espira. De manera que el oxígeno debe entrar y el dióxido de carbono salir. Esto es lo que hacen los bebés nacidos a término y los adultos. Sin embargo, en el caso de los bebés prematuros, los sacos pulmonares no siempre funcionan así. Algunos sacos pulmonares se abren y se cierran con normalidad; otros se colapsan o se quedan pegados cuando el bebé respira dificultando su respiración. Los médicos tratan este problema manteniendo los pulmones ligeramente inflados (o abiertos) entre las respiraciones. Esto se hace manteniendo un poco de presión de aire en los pulmones después de que el bebé espira (presión diastólica), facilitándole la siguiente inspiración de aire. A veces se emplea un medicamento llamado **surfactante** que ayuda a mantener los sacos pulmonares dilatados. El surfactante se administra directamente a los pulmones mediante un tubo que se inserta en las vías respiratorias (este procedimiento se denomina intubación).

Después de que nazca su hijo, si él/ella necesita ayuda para respirar, el médico o la enfermera colocarán una mascarilla para resucitación sobre la nariz y la boca del bebé y le suministrarán oxígeno con una bolsa resucitadora de acción manual. Se aprieta la bolsa para introducir aire en los pulmones del bebé. La bolsa y la mascarilla pueden usarse para proporcionar aire o presión para mantener los pulmones inflados (abiertos) entre las respiraciones. Esta presión de descanso se denomina presión positiva continua en las vías respiratorias (CPAP) o presión positiva espiratoria final (PEEP). En la actualidad, no hay recomendaciones sobre la utilización temprana de la CPAP/PEEP en la sala de partos para continuar después en la sala de neonatos prematuros. No obstante, algunos estudios apuntan que el uso temprano de la CPAP/PEEP puede estar relacionado con resultados beneficiosos tales como: el descenso del número de bebés que necesitan una máquina para poder respirar, disminución del uso de oxigeno en bebés que tienen un mes de edad, y descenso del número de casos en los que hay que administrar surfactante. Este estudio empezará en la sala de partos y continuará en la sala de cuidado de neonatos. Compararemos el uso temprano de la CPAP/PEEP con la intubación temprana, el tratamiento con surfactante y el inicio de ayuda respiratoria mecánica. El objeto de este estudio consiste en observar si alguno de estos tratamientos reduce la gravedad de, o tal vez sirva para prevenir, el desarrollo de problemas pulmonares a largo plazo en neonatos prematuros. Estos problemas respiratorios se denominan displasia bronco-pulmonar (BPD) o enfermedad pulmonar crónica (CLD).

En otro apartado de este estudio observaremos los niveles de saturación de oxígeno que se usan actualmente con neonatos prematuros. En el transcurso de una jornada rutinaria, los médicos, enfermeras y el resto del personal que cuida a su bebé usan un monitor llamado oxímetro de pulso que emplea una sonda que se coloca en la mano o en el pie para controlar de forma no invasiva el oxígeno que se le suministra al bebé para satisfacer sus necesidades. En esta parte del estudio nos gustaría determinar el nivel exacto que debería usarse para ayudar a prevenir algunos de los problemas que sufren los bebés prematuros, tales como la retinopatía de la prematuridad (ROP). Ésta procede cuando hay una proliferación anormal de los vasos sanguíneos en el ojo. Esto

causa un crecimiento de tejido cicatrizado alrededor de la retina y si éste se adhiere a la retina con suficiente firmeza, puede causar ceguera. Gracias a una serie de observaciones publicadas en 1950, se sabe que el riesgo de contraer ROP aumenta debido al uso prolongado de suplementos de oxígeno, pero desconocemos cuales son los beneficios de emplear niveles altos de oxigenación comparado a los niveles bajos en los bebés, especialmente en los prematuros. Después de examinar cómo se trataba a los bebés en el pasado, se ha sugerido que el uso de niveles bajos de saturación puede resultar en un descenso de la ROP grave.

Si su bebe ha nacido antes de la edad gestacional de 28 semanas, es posible que de forma aleatoria (como sucede al lanzar una moneda al aire) él/ella sea asignado al grupo de CPAP/PEEP Temprana o de Surfactante Temprano/ Grupo de ventilación. **Ambos procedimientos se emplean actualmente en Y-NHCH.**

Si su bebé queda adscrito aleatoriamente al grupo de CPAP/PEEP Temprana, él/ella será tratado con CPAP/PEEP en la sala de partos y seguirá con este tratamiento en la sala de cuidado de neonatos. No obstante, si en cualquier momento, las dificultades respiratorias de su bebé empeoran, se le intubará y se le conectará a una maquina PARA RESPIRAR. Si esto sucede dentro de las primeras 48 horas de vida del bebé, también se le administrará surfactante.

Si su bebé queda adscrito aleatoriamente al grupo de Surfactante Temprano/ Grupo de ventilación, se le intubará y se le conectará a la máquina PARA RESPIRAR en la sala de partos y también se le administrará surfactante durante su primera hora de vida.

Durante los primeros 14 días de vida, habrá una serie de pautas que los médicos de la unidad de neonatos tendrán que seguir. Estas pautas les ayudarán a decidir cuando hay que conectar a los bebés a las máquinas para respirar y cuando hay que desconectarlos. Estas pautas también les ayudarán a decidir cuando hay que administrar o suprimir la CPAP/PEEP. Transcurridos 14 días de vida, la atención respiratoria de su bebé se manejará según la práctica estándar de la NBSCU.

Los bebés que participen en este estudio también serán asignados aleatoriamente (de nuevo, como si tirásemos una moneda al aire) a un grupo que tendrá como objetivo el alcance de niveles más bajos de saturación de oxígeno (SpO2) o en un grupo que tendrá como objetivo el alcance de niveles más altos de saturación de oxígeno (SpO2). Como hemos mencionado arriba, la saturación del oxígeno en el bebé se mide con un monitor llamado oxímetro de pulso. Emplea un sensor diminuto o una sonda que se coloca en la mano o en el pie del bebe para medir de forma no invasiva el nivel de saturación de oxígeno en la sangre del bebé con oxígeno. La oximetría no es dolorosa y proporciona las medidas de SpO2 durante las 24 horas del día. Los bebés que estén en el grupo de niveles bajos tendrán como objetivo un SpO2 del 85-89%, mientras que los bebés que se encuentre en el grupo de niveles más altos tendrán como objetivo un SpO2 del 91-95%. Se considera que estas saturaciones están dentro de los niveles normales para neonatos prematuros. Si el SpO2 cae por debajo del 85% o sube más del 95%, sonará la alarma del oxímetro de pulso para que los médicos y las enfermeras sepan si tienen que aumentar o disminuir el oxígeno que está recibiendo su bebé.

Por consiguiente, si su bebé participa en este estudio, le asignaremos uno de los siguientes 4 grupos:

Intervención Aleatoria	**Bajo SpO2 85% a 89%**	**Alto SpO2 91 a 95%**
Grupo de CPAP/PEEP Temprana	CPAP Temprana + Bajo SpO2	CPAP Temprana + Alto SpO2
Administración Temprana de Surfactante - Grupo con Ventilación	Surfactante + Bajo SpO2	Surfactante + AltoSpO2

Finalmente, después de haber sido dado de alta invitaremos a su bebé a que vuelva al Programa de Seguimiento de Neonatos de Yale situado en el Yale Child Study Center. Este programa tiene por objeto la realización de pruebas de desarrollo estandarizadas a todos los bebés con un peso de nacimiento inferior o igual a 1.000 (mil) gramos que han recibido tratamiento en la NBSCU. Los recién nacidos que participan en proyectos de investigación, como este, también están invitados a participar en este programa. De manera que como parte de este estudio, cuando su bebé tenga entre 18 a 22 meses de edad, se le hará un examen completo de sus músculos, nervios y de su habilidad mental y motora. Además, antes de esta visita, nuestro personal de seguimiento le hará breves entrevistas por teléfono para interesarse por la salud de su bebé.

Riesgos e Inconveniencias

Los posibles riesgos que se derivan del uso de la CPAP/PEEP incluyen la sensación de estómago lleno y la disminución temporal de la frecuencia cardiaca. Otro riesgo posible es el colapso de uno o de ambos pulmones. El uso de la CPAP/PEPE, en la proporción empleada en este estudio, no aumenta el riesgo de colapso pulmonar (neumotórax). Al igual que sucede con la CPAP/PEEP, un riesgo posible que se deriva de la intubación para iniciar la ventilación mecánica puede consistir en la disminución temporal del ritmo cardiaco o la posibilidad de colapso de uno o de los dos pulmones. Otro riesgo muy remoto es la posibilidad de pinchar las vías respiratorias al insertar el tubo para respirar. Advierta que los riesgos asociados con la intubación y la iniciación de la ventilación mecánica no aumentan al participar en este estudio.

La oximetría de pulso se usa rutinariamente en miles de neonatos prematuros en NICU's de todo el país. El control mediante los oxímetros de pulso no entraña ningún

riesgo conocido para su bebé. Hay un pequeño riesgo de rotura de la piel en el lugar donde se inserta la sonda del oxímetro de pulso, pero esto puede minimizarse si la enfermera de su hijo cambia la sonda de lugar de vez en cuando.

Beneficios

Algunas Unidades consideran que cada una de estas 4 posibles combinaciones de tratamientos representa la mejor alternativa disponible. No obstante, puede ocurrir que su bebé no se beneficie directamente al participar en esta prueba.

Si en este ensayo se identifican líneas de tratamiento que puedan disminuir el riesgo de BPD o ROP, éstas se aplicarán al manejo clínico de casos extremos de neonatos pretérmino, con la esperanza de que se reduzca la incidencia de estos problemas.

Consideraciones Económicas

Todos los tratamientos y procedimientos que se han usado como parte de este estudio, incluyendo CPAP/PEEP temprana, intubación, ventilación mecánica, terapia con surfactante, y oximetría de pulso, son los que se emplean regularmente para tratar a recién nacidos que ingresan en la NBSCU a causa de problemas respiratorios. Como en este estudio compararemos tratamientos estándar, bien usted o su compañía de seguros serán los responsables de abonar el coste de los cuidados médicos que el personal de la NBSCU dispense al pequeño.

Después de que el bebé complete su visita de seguimiento cuando tenga entre 18 y 22 meses de edad, le abonaremos una compensación de 50 (cincuenta) dólares más gastos (por ejemplo el parking o la guardería).

Tratamientos Alternativos /Alternativas

Si usted decide que su bebé no participe en este estudio, el niño recibirá ayuda para respirar mediante los tratamientos que normalmente se emplean en la NBSCU. En la actualidad la CPAP/PEEP temprana, la intubación, la ventilación mecánica, y la terapia con surfactante son prácticas habituales en la NBSCU para recién nacidos con un peso extremadamente bajo que tienen problemas respiratorios. Como hemos mencionado arriba, la participación en este estudio entraña la comparación de estrategias de tratamientos estándar.

Confidencialidad

La información clínica será recogida del la historia medica de su bebé por el personal del estudio del equipo de investigación clínico neonatal de Yale. La información será identificada con un código numérico. La información será enviada con este código al centro neonatal de recolección de datos de las redes de NICHD en el instituto del triángulo de investigación (RTI) en el Parque del Triángulo de la Investigación, en Carolina del Norte. El registro del estudio que contiene el número de código a la identidad de los bebés será guardado bajo llave en la oficina clínica neonatal de investigación de Yale. La información

que identifica directamente a su bebé quedara en Yale. Todos los datos obtenidos con el fin de este estudio serán mantenidos en un archivo protegido por un código secreto, y todos los datos incorporados en la computadora neonatal de la investigación serán accesados solamente utilizando una contraseña.

Representantes de la Comite de la Yale Investigacion Humana (el comite que revisa, aprueba y vigila estudio humano) y la Institucion Nacional de Salud (los patricinadores de este estudio) pueden revisar los documentos del estudio durante procedimientos de intervencion. Estos individuales estan obligados a mantener toda la informacion confidencial.

En caso de una lesión

Si su bebe sufre una lesión al participar en este estudio, se le proporcionara tratamiento médico. Usted o su seguro médico serán responsables por los costos de este tratamiento. No habrá remuneración financiera adicional si surge una lesión. Tampoco se le pagara por el tiempo de trabajo que haya perdido. Usted no renuncia a sus derechos legales al firmar esta hoja de consentimiento.

Participación y retiro voluntario

Sí usted elige no participar, o si usted retira su participación, no se afectara su relación con los doctores o con el Hospital de Niños de Yale-New Haven. También, según lo indicado previamente, si usted retira su participación los datos obtenidos hasta ese momento serán utilizándos. Estos se mantendrán de manera confidencial.

Preguntas

Hemos utilizado algunos términos técnicos en esta forma. Por favor siéntase libre a preguntar cualquier cosa que usted no entienda y considere esta investigación y la hoja de consentimiento cuidadosamente - antes de tomar una decisión.

Autorización

He leído (o alguien me ha leído) esta forma y he decidido participar en el proyecto descrito arriba. Sus propósitos generales, los detalles de la implicación y de peligros posibles y los inconvenientes se han explicado a mi satisfacción. Mi firma también indica que he recibido una copia de esta forma del consentimiento.

Nombre del Sujeto: _____

Firma: _____

Relación: _____

Fecha: _____

_____ _____

Firma del Investigador principal Fecha

_____ _____

Firma de la persona que obtiene consentimiento Fecha

Si usted tiene otras preguntas sobre este proyecto o si usted tiene un problema relacionado – a esta investigación, usted puede llamar el Investigador Principal del estudio, Richard A. Ehrenkranz en (203) 688-2320. Si usted tiene algunas preguntas referentes a los derechos de su bebe como sujeto de la investigación, usted puede llamar al Comité de Investigaciones Humanas de la Universidad de Yale al (203) 785-4688.

ESTA FORMA ES INVÁLIDA A MENOS QUE LA CAJA SIGUIENTE SE HAYA TERMINADO EN LA OFICINA DE HIC.

ESTA FORMA ES VÁLIDO SOLO HASTA:

_____

PROTOCOLO # 27163

INICIALES:

_____

From: Buchanan, Lisa (HHS/OASH)
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Borror, Kristina C (HHS/OASH)
Subject: RE: "SUPPORT Trial" (HHS Protocol 2U10HD034216)
Date: Friday, January 27, 2012 8:02:09 AM

Hi Rose,

Yes. The address below is fine.

Thanks,
Lisa

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, January 25, 2012 4:43 PM
To: Buchanan, Lisa (HHS/OASH)
Cc: Borror, Kristina C (HHS/OASH)
Subject: RE: "SUPPORT Trial" (HHS Protocol 2U10HD034216)

Hi,
We have most of these and are going to send to you on Friday – can I use the address below for Fed EX?

Division of Compliance Oversight
Office for Human Research Protections
1101 Wootton Parkway, Suite 200
The Tower Building
Rockville, MD 20852

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Buchanan, Lisa (HHS/OASH)
Sent: Monday, January 09, 2012 11:40 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Borror, Kristina C (HHS/OASH)
Subject: "SUPPORT Trial" (HHS Protocol 2U10HD034216)

Good morning Dr. Higgins,

I am reviewing responses' to allegations of noncompliance with Department of Health and Human Services (HHS) regulations for the protection of human research subjects (45 CFR Part 46) involving the above-referenced research. OHRP has only opened its investigation with the University of Alabama. However, we would like to review the informed consent documents for all of the sites (~20). The data coordinating center, RTI, recommended that we contact you for this information. (See email below.) Would it be possible for you to provide copies of all the most recent IRB-approved informed consent documents from the different sites in the SUPPORT study?

Please feel free to contact me if you have any questions regarding this request.

Thanks,
Lisa

Lisa Buchanan, MAOM
Public Health Analyst, Division of Compliance Oversight
Office for Human Research Protections
Department of Health and Human Services
1101 Wootton Parkway, Suite 200
Rockville, MD 20852
Ph: 240-453-8298
Fax: 240-453-6909

From: Borasky, David [mailto:dborasky@rti.org]
Sent: Thursday, August 04, 2011 12:19 PM
To: Borror, Kristina C (HHS/OASH)
Cc: Caddell, Juesta M.
Subject: RE: clarification requested

Hi Kristina –

We had a chance to discuss your request with the RTI DCC folks this morning and how RTI may be able to help facilitate this for OHRP.

As I mentioned this morning, the RTI IRB does not require the DCC to provide RTI IRB with copies of the approved informed consent documents for each site. I did confirm that the DCC requires sites to submit copies of study approval notices to the DCC, but they do not require submission of copies of site-level informed consent documents to the DCC. Some site do include them with the approval notices, but this is not done consistently and may not be done every time a consent document is amended at the site level. Therefore, the DCC's records for site-level consent documents are incomplete.

The RTI IRB and the Neonatal Research Network DCC appreciate your desire to expeditiously obtain site-level informed consent documents for the SUPPORT Trial. We believe that the best way to facilitate this is to have OHRP submit a formal request to the Neonatal Research Network steering committee via the NICHD project officer Rosemary

Higgins (contact information below) to have the RTI Data Coordinating Center collect copies of the final approved consent forms (as well as whether or not this is the initially approved documents or all versions that were used with participants for the duration of the study) for each of the SUPPORT Trial sites for transmittal to OHRP.

I hope this is a suitable approach.

Best,

Dave

Dr. Higgins contact information:

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

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David Borasky, MPH, CIP
Office of Research Protection
RTI International
3040 Cornwallis Rd
RTP, NC 27709
USA

Phone: 919-316-3903
Fax: 919-316-3897
E-mail: dborasky@rti.org

From: Borror, Kristina C (HHS/OASH) [mailto:Kristina.Borror@hhs.gov]
Sent: Friday, July 29, 2011 4:23 PM
To: Borasky, David
Cc: Caddell, Juesta M.
Subject: RE: clarification requested

Dave,
We were wondering if you would be able to get us copies of all the most recent IRB-approved informed consent documents from the different sites in the SUPPRT study. Is that possible?
Thanks for your assistance.
Kristina

From: Borasky, David [mailto:dborasky@rti.org]
Sent: Monday, July 25, 2011 1:13 PM
To: Borror, Kristina C (HHS/OASH)
Cc: Caddell, Juesta M.
Subject: RE: clarification requested

Thank you for the quick response Kristina.

RTI was not engaged in the conduct of the SUPPORT clinical protocol nor would have been considered the IRB of record. RTI serves as the network data coordinating center for all sites, and in this role received coded data for analysis.

Therefore, as per your email, we will not submit a response to the letter dated July 18, 2011.

Regards,

Dave

****
David Borasky, MPH, CIP
Office of Research Protection
RTI International
3040 Cornwallis Rd
RTP, NC 27709
USA

Phone: 919-316-3903
Fax: 919-316-3897
E-mail: dborasky@rti.org

From: Borror, Kristina C (HHS/OASH) [mailto:Kristina.Borror@hhs.gov]
Sent: Monday, July 25, 2011 1:00 PM
To: Borasky, David
Cc: Caddell, Juesta M.
Subject: RE: clarification requested

Dave,
If RTI is not engaged in the research, we do not require any additional information at this time. We'll let you know if we need anything else.

Kristina C. Borror, Ph.D.
Director
Division of Compliance Oversight
Office for Human Research Protections
1101 Wootton Parkway, Suite 200
The Tower Building
Rockville, MD 20852
email: kristina.borror@hhs.gov
Phone: (240) 453-8132
Fax: (240) 453-6909

From: Borasky, David [mailto:dborasky@rti.org]
Sent: Monday, July 25, 2011 11:10 AM
To: Borror, Kristina C (HHS/OASH)
Cc: Caddell, Juesta M.
Subject: clarification requested

Good morning Kristina,

On Friday we (RTI) received a letter from you that was addressed to both our signatory official (Ward Sax) and the SO of UAB (Dr. Marchase) related to the SUPPORT trial. However, we noticed that the letter's salutation was only addressed to Dr. Marchase.

For the SUPPORT Trial (and for the entire Neonatal Research Network) RTI serves as the data coordinating center and we have no oversight of the clinical research. We receive and analyze coded data, and do not have access to the code linking subjects to identifiers.

Given our role and that we are not in the salutation, we assume that OHRP does not expect a formal response from RTI. Would you please confirm if our assumption is correct, and if not, provide guidance on what OHRP would want RTI to provide given our role with the SUPPORT Trial? I leave on vacation tomorrow, so if you could reply to all I would appreciate it. Juesta Caddell is the Director of our IRB office and is the HPA on our FWA.

Thank you.

Dave

****

David Borasky, MPH, CIP
Office of Research Protection
RTI International
3040 Cornwallis Rd
RTP, NC 27709
USA

Phone: 919-316-3903
Fax: 919-316-3897
E-mail: dborasky@rti.org

From: Duara, Shahnaz
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: Research Subject Information and Consent Form
Date: Thursday, January 26, 2012 5:41:43 PM
Attachments: Research Subject Information and Consent Form.pdf

Here you are. These docs were stored away and took some finding. Hope this is all you needed.
Shahnaz

From: Garcia, Andrea V.
Sent: Thursday, January 26, 2012 3:43 PM
To: Duara, Shahnaz
Subject: Research Subject Information and Consent Form

Dr. Duara,

Attached please find the Research Subject Information and Consent Form.

Andrea V. Garcia
Administrative Assistant
University of Miami, Miller School of Medicine
Pediatrics Department - Neonatology Division
P.O. Box 016960
Miami, FL 33101
Office: (305) 585.6408
Facsimile: (305) 545.6581
E-mail: AGarcia9@med.miami.edu

UHealth
UNIVERSITY OF MIAMI HEALTH SYSTEM

UNIVERSITY OF MIAMI
MILLER SCHOOL
of MEDICINE

APPROVED
AS CORRECTED
Apr 14, 2006
WIRB®
Olympia, WA

RESEARCH SUBJECT INFORMATION AND CONSENT FORM

TITLE: The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

PROTOCOL NO.: None
WIRB® Protocol #20050156

SPONSOR: National Institute of Child Health and Human Development (NICHD)
Bethesda, Maryland
United States

INVESTIGATOR: Shahnaz Duara, M.D.
Holtz Center (ET5005)
1611 NW 12th Avenue
Miami, Florida 33136
United States

SITE(S): University of Miami
Holtz Center (ET5005)
1611 NW 12th Avenue
Miami, Florida 33136
United States

STUDY-RELATED PHONE NUMBER(S): Shahnaz Duara, M.D.
305-585-6408
305-585-5140 (24 Hours)

PURPOSE

You are being asked to allow your baby to participate in a clinical research study at the University of Miami/Jackson Medical Center, sponsored by the National Institute of Child Health and Human Development (NICHD).

SUBJECT IMPRINT

APPROVED
AS CORRECTED
Apr 14, 2005
WIRB®
Olympia, WA

Please read this consent form and ask your study doctor or study staff as many questions as you need to about the study before you decide to be part of the study or not. If there is any word or information that you don't understand, your study doctor or study staff will explain them to you. If after reading this consent form you agree to allow your baby to participate in the study you will be asked to sign this consent form. You may keep an unsigned copy of this consent form to think about or discuss with family or friends before making your decision.

If your baby is born prematurely, he/she will need some assistance breathing and will need to be given supplemental oxygen because his/her lungs may not be mature enough. All babies born at 27 weeks gestational age (3 months before due date) will need some help when they are born. A team of nurses, doctors, and respiratory therapists will evaluate and assist your baby within the first minutes of life. If your baby continues to need support for breathing for more than the first few moments of life, he/she may need to be intubated. This involves having a tube placed through the mouth and wind-pipe (trachea) to better deliver oxygen to the lungs. The mechanical ventilation machine will better deliver extra (supplemental) oxygen to the baby and if needed deliver surfactant (the substance that is lacking in these babies lungs because of their immaturity). All babies born prematurely at extremely low birth weights will need supplemental oxygen. However, too much or too little oxygen may be dangerous to immature organs, causing unwanted illnesses that may have life-long effects during the developmental stages of life.

This study has two aims:

AIM 1:
We want to find out if using Continuous Positive Airway Pressure (CPAP) / Positive End Expiratory Pressure (PEEP) (air pressure given to your baby to keep your baby's lung open) will reduce the need for intubation, the need for surfactant and/or the need for mechanical ventilation (the use of a machine to breathe for your baby) during the first 14 days of life.

AIM 2:
We want to determine what is the best level of oxygen saturation (SpO2) (the amount of oxygen that the blood carries to the organs of the body) required for these very small babies. The current normal levels range from 85% to 95% and this study will allow the comparison of a lower oxygen saturation range (85 to 89%) with a higher 02 saturation range (91% to 95%) until your infant no longer requires oxygen and has matured to within 4 weeks of his/her due date.

Your baby will be one of 1320 babies participating in this study at different hospitals within the United States, and one of 150 babies at the University of Miami/Jackson Children's Hospital.

SUBJECT IMPRINT

PROCEDURES

If your baby is born prematurely and you allow your child to participate in this study, immediately after birth the resuscitation will follow usual guidelines. Once your baby is stabilized, your baby will be randomly (by chance, like the flip of a coin) assigned to one of two study groups. Your baby has an equal chance of being in either of the study groups.

TO EVALUATE AIM 1: YOUR BABY WILL BE ASSIGNED A TREATMENT GROUP (CPAP GROUP) OR A CONTROL GROUP (EARLY SURFACTANT GROUP):

A. Treatment Group: (CPAP Group)

These infants will be managed as follow:

Delivery Room Management

If your baby requires positive pressure during resuscitation, CPAP or ventilation with (PEEP) will be used. CPAP will be continued until admission to the Neonatal Intensive Care Unit (NICU). Intubation will be done if your baby requires it.

If your baby requires intubation for resuscitation, he/she will receive surfactant within 60 minutes of birth. The other aspects of the resuscitation will be managed according to the Neonatal Resuscitation Program (NRP) guidelines and follow current practice.

NICU Management

If your baby is in the treatment group, while in the NICU, your baby will be managed on nasal CPAP. If your baby needs intubation, specific requirements for intubation (tube insertion), extubation (tube removal) and reintubation (reinsertion of the tube) have been developed and will continue in effect for a minimum of 14 days of life.

If your baby is intubated in the first 48 hours for respiratory distress, he/she will be given a minimum of one dose of surfactant. Up to 4 doses of surfactant may be given if needed.

B. Control Group: (Early surfactant and ventilation)

If your baby is in the control group, he/she will be treated using an approach considered similar to current standards of care. It is anticipated that a majority of these infants will be intubated and receive surfactant in the delivery room.

Infants in this group will be managed as follows:

Delivery Room Management

Infants will be intubated in the delivery room and given surfactant or receive surfactant within 60 minutes of birth. The other aspects of the resuscitation will be managed according to the NRP guidelines and follow current practice for the NICU.

NICU Management

Infants will continue to receive mechanical ventilation until it is no longer needed. These requirements will continue in effect for a minimum of 14 days for all infants.

TO EVALUATE AIM 2: (LOW VERSUS HIGH SPO2 RANGE)

In addition, once your baby is in the NICU, he/she will be randomly assigned to have the high level of oxygenation (91 to 95%) or the low level of oxygenation (85 to 89%). Your baby has an equal chance of being assigned to either study group. Both groups are within the range of usual standard of care for the NICU. Your baby will remain in the group he/she is assigned to as long as he/she requires oxygen.

The study pulse oximeter (a device used to measure your baby's oxygen level) will be applied to your baby within two hours after going to the NICU. The assigned pulse oximeter will remain on your baby and will be removed once your baby has been in room air and off ventilatory support or CPAP for 72 hours. If oxygen is required later on, the same oxygen levels will be used until 36 weeks gestational age.

The assigned oximeter will be used as long as the baby is receiving ventilator support. The oximeters will alarm if they are too low (84%) or too high (96%).

Once your baby is admitted to the NICU, he/she will receive the standard care according to the policies and procedures set by the NICU.

An ultrasound of your baby's head will be done between days 4 and 21, if one has not already been done. All babies will be seen at about 2 years of age for developmental assessment.

SUBJECT IMPRINT

RISKS

The major risk of this study is that your baby may not receive surfactant as early. Early surfactant is known to reduce disease severity and the chance of death. It also reduces lung damage.

Potential risks to the use of CPAP and/or PEEP include collapsed lung, decreased heart rate, blood pressure problems, and distention of the stomach. The risks of ventilation include damage to the airways or lungs, damage from the tube moving or becoming plugged. There may also be heart rate and blood pressure problems.

Prolonged exposure to very high levels of oxygen may cause complications to your baby such as damage to the eyes which can result in blindness. Complications of too little oxygen may include problems with childhood development.

There may be risks or side effects which are unknown at this time.

Your baby's condition may not get better or may become worse while he/she is in this study.

NEW FINDINGS

You will be told about any new information that might change your decision to allow your child to be in this study.

BENEFITS

The consequences of your baby's breathing problems may be improved because of participating in this study, however, this cannot be guaranteed. It is possible that there may be no direct medical benefit to your baby for participating. The information learned in this study may benefit other babies having similar problems in the future.

COST TO YOU

There is no cost to you for participating in this study.

SUBJECT IMPRINT

ALTERNATIVES

You have the alternative not to participate in this study and have your baby receive standard care after delivery. If you choose not to allow your baby to participate in the study, he or she will receive the standard care used at this institution. Ask the study doctor to discuss this with you.

CONFIDENTIALITY

Information from this study will be given to the sponsor. "Sponsor" includes any persons or companies which are contracted by the sponsor to have access to the research information during and after the study.

The information will also be given to the U.S. Food and Drug Administration (FDA). It may be given to governmental agencies in other countries where the study drug may be considered for approval. Medical records which identify your baby and the consent form signed by you will be looked at and/or copied for research or regulatory purposes by:

- the sponsor;
- Research Triangle Institute, an agent for the sponsor;

and may be looked at and/or copied for research or regulatory purposes by:

- the FDA;
- Department of Health and Human Services (DHHS) agencies;
- governmental agencies in other countries;
- the University of Miami; and
- the Western Institutional Review Board® (WIRB®).

Absolute confidentiality cannot be guaranteed because of the need to give information to these parties. The results of this research study may be presented at meetings or in publications. Your baby's identity will not be disclosed in those presentations.

Finally, if you should seek treatment at Jackson Health System, information from this study may be given to the treating physicians and other medical staff at Jackson Health System. In turn, the treating physicians and other medical staff at Jackson Health Systems may provide information about your baby's treatment and care to the study doctor and/or agents for the study doctor.

SUBJECT IMPRINT

COMPENSATION FOR INJURY

Your baby may be exposed to risk of injury from participation in this study. If injury occurs, treatment will in most cases be available. If you have insurance, your insurance company may or may not pay these costs. If you do not have insurance, or if your insurance company refuses to pay, you will be billed for these costs. Funds to compensate for pain, expenses, and other damages caused by injury are not routinely available.

SOURCE OF FUNDING

Funding for this research study will be provided by National Institute of Child Health and Human Development (NICHD).

VOLUNTARY PARTICIPATION/WITHDRAW

Your agreement to have your infant participate in this study is voluntary. You have the right to withdraw your consent or take your baby out of the study at any time. If you do decide to take your baby out of the study, he/she will continue to receive the same level of care that the hospital and the doctors provide. If you decide not to allow your baby to participate, or if you decide to stop participating at any time, there will be no penalty, nor loss of benefits, nor loss of medical care to which you or your baby are otherwise entitled.

The study doctor, Dr. Shahnaz Duara, or the sponsor of this study may decide to remove your baby from the study at any time without your consent if it is felt to be in the best interest of your baby.

QUESTIONS

You may ask questions, and request information about this research study at any time during the study. Dr. Shahnaz Duara or her study assistants will be available to answer any questions you may have at 305-585-6408 between 8:00am to 5:00pm or the physician on call in the NICU at 305-585-5140 (24 Hours).

SUBJECT IMPRINT

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AS CORRECTED
Apr 14, 2005
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Olympia, WA

If you have any questions about your rights, or the rights of your infants, as a research subject you may contact:

Western Institutional Review Board® (WIRB®)
3535 Seventh Avenue, SW
Olympia, Washington 98502
Telephone: 1-800-562-4789.

WIRB is a group of people who perform independent review of research.

Do not sign this consent form unless you have had a chance to ask questions and have received satisfactory answers to all of your questions.

If you agree to allow your baby to participate in this study, you will receive a signed and dated copy of this consent form for your records.

CONSENT

I have read the information in this consent form (or it has been read to me). I have discussed this study and the information provided with the study doctor. All my questions about the study and my baby's participation in it have been answered. I freely consent to allow my baby to participate in this research study.

I authorize the release of my baby's medical records for research or regulatory purposes to the sponsor, Research Triangle Institute, the FDA, DHHS agencies, governmental agencies in other countries, the University of Miami, and WIRB®.

SUBJECT IMPRINT

JACKSON MEMORIAL HOSPITAL
Miami, FLORIDA

JMHP 01-0305-1
3-1-79
C-640 CLINICAL RESEARCH CONSENT FORM

APPROVED
AS CORRECTED
Apr 14, 2005
WIRB®
Olympia, WA

By signing this consent form, I have not waived any of the legal rights which I or my child otherwise would have as a subject in a research study.

Printed Name of Subject

Signature of Mother — Date

Signature of Father (if available) — Date

OR

Signature of Legally Authorized Representative — Date

Authority of Subject's Legally Authorized Representative or Relationship to Subject

Signature of Witness — Date

Signature of Person Conducting Informed Consent Discussion — Date

Print name

SUBJECT IMPRINT

JACKSON MEMORIAL HOSPITAL
Miami, FLORIDA

JMHP 01-0305-1
3-1-79
C-640 CLINICAL RESEARCH CONSENT FORM

4-12357

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AS CORRECTED
Apr 14, 2005
WIRB®
Olympia, WA

---------- **Use the following only if applicable** ----------

If this consent form is read to the subject because the legally authorized representative is unable to read the form, an impartial witness not affiliated with the research or investigator must be present for the consent and sign the following statement:

I confirm that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject's legally authorized representative. The subject's legally authorized representative freely consented to participate in the research study.

Signature of Impartial Witness _____ Date _____

Note: This signature block cannot be used for translations into another language. A translated consent form is necessary for enrolling subjects who do not speak English.

Study Doctor: Shahnaz Duara, M.D.
Telephone: 305-585-6408 (office)
305-585-5140 (nights and weekends)

SUBJECT IMPRINT

JACKSON MEMORIAL HOSPITAL
Miami, FLORIDA

JMHP 01-0305-1
3-1-79
C-640 CLINICAL RESEARCH CONSENT FORM

IRB Protocol Number: 200050156 **Principal Investigator:** Shahnaz Duara, MD

Study Title ("the Research"): The Surfactant Positive Airway Pressure and pulse oximetry in extremely low birth weight infants

HIPAA Research Authorization Template – Form B
AUTHORIZATION TO USE AND DISCLOSE HEALTH INFORMATION

I agree to permit the ☐ *University of Miami* ☐ *Jackson Health System* ☒ *both*, and any of my doctors or other health care providers (together "Providers"), Principal Investigator and [*his /her/their/its*] collaborators and staff (together "Researchers"), to obtain, use and disclose health information about me as described below.

1. **The health information that may be used and disclosed includes:** all information collected during the research and procedures described in the Informed Consent Form for
   - ("the Research"); and
   - health information in my medical records that is relevant to the Research, includes my past medical history including medical information from my primary care physician and other medical information relating to my participation in the study.

2. **The Providers may disclose health information in my medical records to:**
   - the Researchers;
   - representatives of government agencies, review boards, and other persons who watch over the safety, effectiveness, and conduct of research; and
   - the sponsor of the Research, , National Institutes for Child Health Devel and (Print Sponsor Name) its agents and contractors (together "Sponsor").

3. **The Researchers may use and share my health information:**
   - among themselves, with the Sponsor, and with other participating Researchers to conduct the Research; and
   - as permitted by the Informed Consent Form.

4. **The Sponsor may use and share my health information** for purposes of the Research and as permitted by the consent form.

5. **Once my health information has been disclosed to a third party,** federal privacy laws may no longer protect it from further disclosure.

6. **Please note that:**
   You do not have to sign this Authorization, but if you do not, you may not participate in the Research. If you do not sign this authorization, your right to other medical treatment will not be affected.

University of Miami - Office of HIPAA Privacy and Security
PO BOX 019132 (M879)
Miami, FL 33101
hipaaprivacy@med.miami.edu
(305) 243-5000

AUTHORIZATION TO USE AND DISCLOSE HEALTH INFORMATION

Form D3901001E

Revised 01/09/06

Required Information: *Please Complete.*

NAME: _____

MRN: _____ ☐ IDX ☐ SMS

☐ SS # ☐ DL # ☐ PASSPORT # ☐ OTHER _____

ID#: _____

AGE: _____ DOB: ___/___/___

DATE OF SERVICE: ___/___/___

4-12359

You may change your mind and revoke (take back) this Authorization at any time and for any reason. To revoke this Authorization, you must write to either of the following:

*Research Study Personnel Name: Shahnaz Duara, MD or Ruth Everett, RN

Address: Department of Pediatrics/Neonatology (R-131) P.O. Box016960

Tel. No.: 305 585-6408

Human Subjects Research Office

Address: 1500 NW 12th AVE, Suite 1002 Miami, FL 33136

Tel. No.: (305) 243-3195

However, if you revoke this Authorization, you will not be allowed to continue taking part in the Research. Also, even if you revoke this Authorization, the Providers, Researchers and the Sponsor may continue to use and disclose the information they have already collected to protect the integrity of the research or as permitted by the Informed Consent Form.

While the Research is in progress, you may not be allowed to see your health information that is created or collected by the ☐ *University of Miami* ☐ *Jackson Health System* ☒ *both*, in the course of the Research. After the Research is finished, however, you may see this information as described in the ☐ *University of Miami* ☐ *Jackson Health System* ☒ *both*, Notice of Privacy Practices.

*Study personnel must send copies of participant revocations to:
Office of HIPAA Privacy and Security AND the Human Subjects Research Office.

7. **This Authorization does not have an expiration (ending) date.**

8. **You will be given a copy of this Authorization after you have signed it.**

Signature of participant or participant's legal representative _____ Date _____

Printed name of participant _____ Printed name of legal representative (if applicable) _____

Representative's relationship to participant _____

Study personnel must send copy with signature to the Office of HIPAA Privacy and Security
For questions, contact the Human Subjects Research Office at 305-243-3195.

University of Miami - Office of HIPAA Privacy and Security
PO BOX 019132 (M879) hipaaprivacy@med.miami.edu
Miami, FL 33101 (305) 243-5000

AUTHORIZATION TO USE AND DISCLOSE HEALTH INFORMATION

Form D3901001E

Revised 01/09/06

Required Information: **Swipe Keyplate if available and leave the box blank.**

WIRB®
(360) 252-2500
FAX: (360) 252-2498
1-800-562-4789

Western Institutional Review Board ®
Western International Review Board®
3535 SEVENTH AVENUE, SW, OLYMPIA, WA 98502-5010
P.O. BOX 12029, OLYMPIA, WA 98508-2029

Certificate of Approval

THE FOLLOWING WERE APPROVED:

INVESTIGATOR: Shahnaz Duara M.D.
Holtz Center (ET5005)
1611 NW 12th Avenue
Miami, Florida 33136

BOARD ACTION DATED: 04/14/2005
PANEL: 6
STUDY APPROVAL EXPIRES: 03/25/2006
STUDY NUM: 1065012
WIRB PRO NUM: 20050156
INVEST NUM: 112349
WO NUM: 1-312412-1

SPONSOR: National Institute of Child Health and Human Development (NICHD)
PROTOCOL NUM: None
AMD. PRO. NUM:
TITLE:
The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

APPROVAL INCLUDES:

Consent Form [IN0]

WIRB APPROVAL IS GRANTED SUBJECT TO:

All subjects who will be enrolled in the future for this study must sign the most current WIRB-approved consent form(s).

IF YOU HAVE ANY QUESTIONS, CONTACT WIRB AT 1-800-562-4789

This is to certify that the information contained herein is true and correct as reflected in the records of the Western Institutional Review Board (WIRB). WE CERTIFY THAT WIRB IS IN FULL COMPLIANCE WITH GOOD CLINICAL PRACTICES AS DEFINED UNDER THE U.S. FOOD AND DRUG ADMINISTRATION (FDA) REGULATIONS AND THE INTERNATIONAL CONFERENCE ON HARMONISATION (ICH) GUIDELINES.

Theodore D. Schultz, J.D., Chairman

4/15/2005
(Date)

This document electronically reviewed and approved by Orive, Otto on 4/15/2005 7:07:38AM PST. For more information call Client Services at 1-360-252-2500

ALL WIRB APPROVED INVESTIGATORS MUST COMPLY WITH THE FOLLOWING:

1. Conduct the research in accordance with the protocol, applicable laws and regulations, and the principles of research ethics as set forth in the Belmont Report.

2. Unless consent has been waived, conduct the informed consent process without coercion or undue influence, and provide the potential subject sufficient opportunity to consider whether or not to participate.

    a. Use only the most current consent form bearing the WIRB "APPROVED" stamp.

    b. Provide non-English speaking subjects with a certified translation of the approved consent form in the subject's first language. The translation must be approved by WIRB.

    c. Obtain pre-approval from WIRB for use of recruitment materials and other materials provided to subjects.

3. Obtain pre-approval from WIRB for any planned deviations and any changes in the research activity. The only exception is when changes are necessary to eliminate apparent immediate hazards to subjects. Immediately report to WIRB any such emergency changes implemented.

4. Promptly report to WIRB any new information that may adversely affect the safety of the subjects or the conduct of the trial.

    a. Report to WIRB all adverse events that are serious, unexpected and related, within 10 days of the investigator becoming aware of them. Other unexpected adverse events that involve risks to study subjects or others are to be submitted with continuing review reports.

    b. Promptly report to WIRB other unanticipated problems involving risks to human subjects or others. These events do not readily fit the formal definition of Adverse Event, but could impact human subject safety and/or rights. Examples include theft of a computer containing private identifiable subject information, or study staff getting ill from inhaling a study agent.

    c. Provide reports to WIRB concerning the progress of the research, when requested.

5. Report to WIRB any unplanned protocol variance that could adversely affect the safety or welfare of subjects, or the integrity of the research data, within 10 days of becoming aware of the variance. Other unplanned variances may be recorded on a log and submitted with continuing review reports.

Federal regulations require that WIRB conduct continuing review of approved research. You will receive Continuing Review Report forms from WIRB. These reports must be returned even though your study may not have started.

DISTRIBUTION OF COPIES:

Contact	Company Name
Translations Department, WIRB	WIRB USA
Jorge, Josie	University of Miami
Duara, Shahnaz M.D.	University of Miami
Everett, Ruth R.N.	University of Miami
Poole, Kenneth Ph.D.	Research Triangle Institute

SITES:

Address

Holtz Center (ET5005), 1611 NW 12th Avenue, Miami, Florida 33136

WIRB®
WESTERN INSTITUTIONAL REVIEW BOARD®
WESTERN INTERNATIONAL REVIEW BOARD®
3535 SEVENTH AVENUE, SW • OLYMPIA, WA 98502-5010
P.O. BOX 12029 • OLYMPIA, WA 98508-2029
(360) 252-2500 • 1-800-562-4789 • FAX (360) 252-2498

NOTICE: CONSENT FORM CORRECTION

Enclosed is a corrected version of your consent form and a new Certificate of Approval. Also enclosed is a "redlined" copy of the consent form, provided for your reference, which indicates the changes made by the Board. Items shown with a line through them have been deleted; items shown with a double underline have been added by WIRB.

The "clean" copy with the latest WIRB stamp is the official approved version. **ONLY THE CONSENT FORM VERSION WITH THE MOST RECENT APPROVAL STAMP MAY BE USED TO CONSENT YOUR SUBJECTS.**

We apologize for the inconvenience. If you have any questions, please contact us.

APPROVED
AS CORRECTED
Apr 14, 2005
WIRB®
Olympia, WA

RESEARCH SUBJECT INFORMATION AND CONSENT FORM

TITLE: The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

PROTOCOL NO.: None
WIRB® Protocol #20050156

SPONSOR: National Institute of Child Health and Human Development (NICHD)
Bethesda, Maryland
United States

INVESTIGATOR: Shahnaz Duara, M.D.
Holtz Center (ET5005)
1611 NW 12th Avenue
Miami, Florida 33136
United States

SITE(S): University of Miami
Holtz Center (ET5005)
1611 NW 12th Avenue
Miami, Florida 33136
United States

STUDY-RELATED PHONE NUMBER(S): Shahnaz Duara, M.D.
305-585-6408
305-585-5140 (24 Hours)

PURPOSE

You are being asked to allow your baby to participate in a clinical research study at the University of Miami/Jackson Medical Center, sponsored by the National Institute of Child Health and Human Development (NICHD).

SUBJECT IMPRINT

APPROVED
AS CORRECTED
Apr 14, 2005
WIRB®
Olympia, WA

Please read this consent form and ask your study doctor or study staff as many questions as you need to about the study before you decide to be part of the study or not. If there is any word or information that you don't understand, your study doctor or study staff will explain them to you. If after reading this consent form you agree to allow your baby to participate in the study you will be asked to sign this consent form. You may keep an unsigned copy of this consent form to think about or discuss with family or friends before making your decision.

If your baby is born prematurely, he/she will need some assistance breathing and will need to be given supplemental oxygen because his/her lungs may not be mature enough. All babies born at 27 weeks gestational age (3 months before due date) will need some help when they are born. A team of nurses, doctors, and respiratory therapists will evaluate and assist your baby within the first minutes of life. If your baby continues to need support for breathing for more than the first few moments of life, he/she may need to be intubated. This involves having a tube placed through the mouth and wind-pipe (trachea) to better deliver oxygen to the lungs. The mechanical ventilation machine will better deliver extra (supplemental) oxygen to the baby and if needed deliver surfactant (the substance that is lacking in these babies lungs because of their immaturity). All babies born prematurely at extremely low birth weights will need supplemental oxygen. However, too much or too little oxygen may be dangerous to immature organs, causing unwanted illnesses that may have life-long effects during the developmental stages of life.

This study has two aims:

AIM 1:
We want to find out if using Continuous Positive Airway Pressure (CPAP) / Positive End Expiratory Pressure (PEEP) (air pressure given to your baby to keep your baby's lung open) will reduce the need for intubation, the need for surfactant and/or the need for mechanical ventilation (the use of a machine to breathe for your baby) during the first 14 days of life.

AIM 2:
We want to determine what is the best level of oxygen saturation (SpO2) (the amount of oxygen that the blood carries to the organs of the body) required for these very small babies. The current normal levels range from 85% to 95% and this study will allow the comparison of a lower oxygen saturation range (85 to 89%) with a higher 02 saturation range (91% to 95%) until your infant no longer requires oxygen and has matured to within 4 weeks of his/her due date.

Your baby will be one of 1320 babies participating in this study at different hospitals within the United States, and one of 150 babies at the University of Miami/Jackson Children's Hospital.

SUBJECT IMPRINT

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If your baby is born prematurely and you allow your child to participate in this study, immediately after birth the resuscitation will follow usual guidelines. Once your baby is stabilized, your baby will be randomly (by chance, like the flip of a coin) assigned to one of two study groups. Your baby has an equal chance of being in either of the study groups.

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If your baby requires intubation for resuscitation, he/she will receive surfactant within 60 minutes of birth. The other aspects of the resuscitation will be managed according to the Neonatal Resuscitation Program (NRP) guidelines and follow current practice.

NICU Management

If your baby is in the treatment group, while in the NICU, your baby will be managed on nasal CPAP. If your baby needs intubation, specific requirements for intubation (tube insertion), extubation (tube removal) and reintubation (reinsertion of the tube) have been developed and will continue in effect for a minimum of 14 days of life.

If your baby is intubated in the first 48 hours for respiratory distress, he/she will be given a minimum of one dose of surfactant. Up to 4 doses of surfactant may be given if needed.

B. Control Group: (Early surfactant and ventilation)

If your baby is in the control group, he/she will be treated using an approach considered similar to current standards of care. It is anticipated that a majority of these infants will be intubated and receive surfactant in the delivery room.

SUBJECT IMPRINT

Infants in this group will be managed as follows:

Delivery Room Management

Infants will be intubated in the delivery room and given surfactant or receive surfactant within 60 minutes of birth. The other aspects of the resuscitation will be managed according to the NRP guidelines and follow current practice for the NICU.

NICU Management

Infants will continue to receive mechanical ventilation until it is no longer needed. These requirements will continue in effect for a minimum of 14 days for all infants.

TO EVALUATE AIM 2: (LOW VERSUS HIGH SPO2 RANGE)

In addition, once your baby is in the NICU, he/she will be randomly assigned to have the high level of oxygenation (91 to 95%) or the low level of oxygenation (85 to 89%). Your baby has an equal chance of being assigned to either study group. Both groups are within the range of usual standard of care for the NICU. Your baby will remain in the group he/she is assigned to as long as he/she requires oxygen.

The study pulse oximeter (a device used to measure your baby's oxygen level) will be applied to your baby within two hours after going to the NICU. The assigned pulse oximeter will remain on your baby and will be removed once your baby has been in room air and off ventilatory support or CPAP for 72 hours. If oxygen is required later on, the same oxygen levels will be used until 36 weeks gestational age.

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Once your baby is admitted to the NICU, he/she will receive the standard care according to the policies and procedures set by the NICU.

An ultrasound of your baby's head will be done between days 4 and 21, if one has not already been done. All babies will be seen at about 2 years of age for developmental assessment.

SUBJECT IMPRINT

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The major risk of this study is that your baby may not receive surfactant as early. Early surfactant is known to reduce disease severity and the chance of death. It also reduces lung damage.

Potential risks to the use of CPAP and/or PEEP include collapsed lung, decreased heart rate, blood pressure problems, and distention of the stomach. The risks of ventilation include damage to the airways or lungs, damage from the tube moving or becoming plugged. There may also be heart rate and blood pressure problems.

Prolonged exposure to very high levels of oxygen may cause complications to your baby such as damage to the eyes which can result in blindness. Complications of too little oxygen may include problems with childhood development.

There may be risks or side effects which are unknown at this time.

Your baby's condition may not get better or may become worse while he/she is in this study.

NEW FINDINGS

You will be told about any new information that might change your decision to allow your child to be in this study.

BENEFITS

The consequences of your baby's breathing problems may be improved because of participating in this study, however, this cannot be guaranteed. It is possible that there may be no direct medical benefit to your baby for participating. The information learned in this study may benefit other babies having similar problems in the future.

COST TO YOU

There is no cost to you for participating in this study.

SUBJECT IMPRINT

ALTERNATIVES

You have the alternative not to participate in this study and have your baby receive standard care after delivery. If you choose not to allow your baby to participate in the study, he or she will receive the standard care used at this institution. Ask the study doctor to discuss this with you.

CONFIDENTIALITY

Information from this study will be given to the sponsor. "Sponsor" includes any persons or companies which are contracted by the sponsor to have access to the research information during and after the study.

The information will also be given to the U.S. Food and Drug Administration (FDA). It may be given to governmental agencies in other countries where the study drug may be considered for approval. Medical records which identify your baby and the consent form signed by you will be looked at and/or copied for research or regulatory purposes by:

- the sponsor;
- Research Triangle Institute, an agent for the sponsor;

and may be looked at and/or copied for research or regulatory purposes by:

- the FDA;
- Department of Health and Human Services (DHHS) agencies;
- governmental agencies in other countries;
- the University of Miami; and
- the Western Institutional Review Board® (WIRB®).

Absolute confidentiality cannot be guaranteed because of the need to give information to these parties. The results of this research study may be presented at meetings or in publications. Your baby's identity will not be disclosed in those presentations.

Finally, if you should seek treatment at Jackson Health System, information from this study may be given to the treating physicians and other medical staff at Jackson Health System. In turn, the treating physicians and other medical staff at Jackson Health Systems may provide information about your baby's treatment and care to the study doctor and/or agents for the study doctor.

SUBJECT IMPRINT

COMPENSATION FOR INJURY

Your baby may be exposed to risk of injury from participation in this study. If injury occurs, treatment will in most cases be available. If you have insurance, your insurance company may or may not pay these costs. If you do not have insurance, or if your insurance company refuses to pay, you will be billed for these costs. Funds to compensate for pain, expenses, and other damages caused by injury are not routinely available.

SOURCE OF FUNDING

Funding for this research study will be provided by National Institute of Child Health and Human Development (NICHD).

VOLUNTARY PARTICIPATION/WITHDRAW

Your agreement to have your infant participate in this study is voluntary. You have the right to withdraw your consent or take your baby out of the study at any time. If you do decide to take your baby out of the study, he/she will continue to receive the same level of care that the hospital and the doctors provide. If you decide not to allow your baby to participate, or if you decide to stop participating at any time, there will be no penalty, nor loss of benefits, nor loss of medical care to which you or your baby are otherwise entitled.

The study doctor, Dr. Shahnaz Duara, or the sponsor of this study may decide to remove your baby from the study at any time without your consent if it is felt to be in the best interest of your baby.

QUESTIONS

You may ask questions, and request information about this research study at any time during the study. Dr. Shahnaz Duara or her study assistants will be available to answer any questions you may have at 305-585-6408 between 8:00am to 5:00pm or the physician on call in the NICU at 305-585-5140 (24 Hours).

SUBJECT IMPRINT

APPROVED
AS CORRECTED
Apr 14, 2005
WIRB®
Olympia, WA

If you have any questions about your rights, or the rights of your infants, as a research subject you may contact:

Western Institutional Review Board® (WIRB®)
3535 Seventh Avenue, SW
Olympia, Washington 98502
Telephone: 1-800-562-4789.

WIRB is a group of people who perform independent review of research.

Do not sign this consent form unless you have had a chance to ask questions and have received satisfactory answers to all of your questions.

If you agree to allow your baby to participate in this study, you will receive a signed and dated copy of this consent form for your records.

CONSENT

I have read the information in this consent form (or it has been read to me). I have discussed this study and the information provided with the study doctor. All my questions about the study and my baby's participation in it have been answered. I freely consent to allow my baby to participate in this research study.

I authorize the release of my baby's medical records for research or regulatory purposes to the sponsor, Research Triangle Institute, the FDA, DHHS agencies, governmental agencies in other countries, the University of Miami, and WIRB®.

SUBJECT IMPRINT

JACKSON MEMORIAL HOSPITAL
Miami, FLORIDA

JMHP 01-0305-1
3-1-79
C-640 CLINICAL RESEARCH CONSENT FORM

APPROVED
AS CORRECTED
Apr 14, 2005
WIRB®
Olympia, WA

By signing this consent form, I have not waived any of the legal rights which I or my child otherwise would have as a subject in a research study.

Printed Name of Subject

Signature of Mother — Date

Signature of Father (if available) — Date

OR

Signature of Legally Authorized Representative — Date

Authority of Subject's Legally Authorized Representative or Relationship to Subject

Signature of Witness — Date

Signature of Person Conducting Informed Consent Discussion — Date

Print name

SUBJECT IMPRINT

JACKSON MEMORIAL HOSPITAL
Miami, FLORIDA

JMHP 01-0305-1
3-1-79
C-640 CLINICAL RESEARCH CONSENT FORM

APPROVED
AS CORRECTED
Apr 14, 2005
WIRB®
Olympia, WA

---------- **Use the following only if applicable** ----------

If this consent form is read to the subject because the legally authorized representative is unable to read the form, an impartial witness not affiliated with the research or investigator must be present for the consent and sign the following statement:

I confirm that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject's legally authorized representative. The subject's legally authorized representative freely consented to participate in the research study.

Signature of Impartial Witness _____ Date _____

Note: This signature block cannot be used for translations into another language. A translated consent form is necessary for enrolling subjects who do not speak English.

Study Doctor: Shahnaz Duara, M.D.
Telephone: 305-585-6408 (office)
305-585-5140 (nights and weekends)

SUBJECT IMPRINT

JACKSON MEMORIAL HOSPITAL
Miami, FLORIDA

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: support consent
Date: Thursday, January 26, 2012 3:59:00 PM
Attachments: Support.consent.2.10.09.doc

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Ronald Goldberg, M.D. [mailto:ronald.goldberg@duke.edu]
Sent: Thursday, January 26, 2012 3:58 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Fw: support consent

Here you go.
Ron and Mike

From: Michael Cotten, M.D.
Sent: Thursday, January 26, 2012 03:54 PM
To: "Higgins, Rosemary \(NIH/NICHD\) [E]" <higginsr@mail.nih.gov> <higginsr@mail.nih.gov>
Cc: Ronald Goldberg, M.D.; Joanne Finkle, J.D.
Subject: support consent

Hi. here's the last approved version. for Duke

mc

C. Michael Cotten MD MHS
Associate Professor of Pediatrics
Medical Director Neonatology Clinical Research
Duke University Medical Center
Box 2739 DUMC
Durham, NC 27710
2424 Erwin Road Suite 504
Durham, NC 27705
ph: 919-681-4844
fax: 919-681-6065
email: michael.cotten@duke.edu

DUKE UNIVERSITY HEALTH SYSTEM

Consent To Participate In A Research Study

The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants: The SUPPORT Trial

Introduction:

You are being asked to allow your child to be in this study because there is a possibility he/she will be born between 12 and 16 weeks early (24-28 weeks gestational age). Dr. Michael Cotten and the Neonatology clinical research group at Duke Medical Center and colleagues at the 16 centers in the National Institutes for Child Health and Human Development (NICHD) Neonatal Research Network are conducting a research study to determine the best way to help extremely premature babies breathe better after they are born. This study will compare the effectiveness, risks and benefits of two different types of treatment for premature lung disease. The two methods being compared are CPAP (positive pressure applied with a face mask or nasal prongs to help keep the lungs inflated) in the delivery room and reduced use of a breathing machine to assist the baby's breathing *versus* intubation (using a breathing tube placed in the trachea or windpipe) in the delivery room and more aggressive use of mechanical ventilation (breathing for the baby using a machine). This study is also being done to learn the appropriate levels of oxygen saturation (oxygen levels in the blood) that should be maintained in extremely premature babies while they are being treated in the hospital. Dr Cotten and the Neonatology clinical research group are receiving salary support from the NICHD to conduct this study.

Purpose of the Study:

1) To compare the outcome of infants who receive delivery room CPAP and who have restrictive guidelines for having a breathing tube placed for mechanical ventilation with infants who have the tube placed and surfactant (a liquid which helps babies with immature lungs breath easier by helping keep their lungs from collapsing) given in the delivery room and have less strict guidelines for maintaining a breathing tube and mechanical ventilation.

2) To compare low range (85-89%) oxygen saturation levels with high range (91-95%) levels to determine if a lower range results in decreased ROP (Retinopathy of Prematurity, an eye disease that may result in impairment of vision or even blindness) which may be caused by excessive levels of oxygen.)

Duration of the Study: We expect to include about 1300 babies in the study from the 16 NICHD Neonatal Research Network hospitals around the country over a two year period. 60 babies will take part at Duke.

Background:

CPAP vs. Intubation/Surfactant. Research studies of surfactant treatment along with intubation and mechanical ventilation reduced mortality versus intubation and mechanical ventilation with no surfactant treatment. Other studies have suggested that many extremely premature babies may not need intubation or treatment with surfactant if they are treated with CPAP in the delivery room. Research studies suggest that avoiding intubation may help babies avoid lung damage associated with premature birth and subsequent mechanical ventilation, even if surfactant is used. Delivery room intubation and surfactant treatment has never been compared to CPAP treatment started in the delivery room.

DUKE UNIVERSITY HEALTH SYSTEM

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Some hospitals in the United States that provide care for extremely preterm infants like yours use CPAP in the delivery room, while other similar hospitals intubate every baby in the first hour of life and give all the infants between 24 and 28 weeks gestation surfactant. The decision as to which to use is currently made by the physician attending the delivery. This study will help doctors find out if it is better to intubate in the delivery room and treat infants like yours with surfactant in the first hour of life, or to start them on CPAP in the delivery room and try to limit the chance that they will need intubation.

Oxygen Level Study. The current alarm limits for oxygen saturation monitors in many neonatal intensive care units (NICU's) in the United States are set at 85% and 95%. The aim in many units is to keep oxygen saturations between 88 and 92%. This goal is based on research suggesting high levels of oxygen (> 95% saturation) in the first weeks of life are related to later development of ROP and damage to the lungs. We are not sure how much lower we should set the goal for oxygen saturation in extremely preterm infants and still avoid increasing the risk of developmental delay. Previous studies have suggested that risk of ROP decreases when oxygen saturation goals were set with a lower limit of 80% without any increase in risk in neurodevelopmental impairment in the first year after discharge. Currently in the United States, some hospital NICU's target oxygen levels in the lower end of the 85 – 95% range, while others target the higher range. Both treatment groups in this study (85-89% and 91-95%) fall within the alarm range currently used at Duke. The study will attempt to keep babies in one of these two ranges.

Each of the 4 possible combinations of treatments is considered standard care by some units in the United States.

Study Procedures:
Prior to delivery, and after your permission is given, your baby will be randomized (chosen by chance like the flip of a coin) to one of two lung treatment strategies. The treatments are as follows:

1) *CPAP* in the delivery room immediately after birth and continuing in the NICU, *or*

2) *Intubation* (placement of a tube in his/her trachea or windpipe) in the delivery room followed by surfactant administration and mechanical ventilation.

In addition to being randomly assigned to one of the two groups described above, your baby will be randomized to a High reading or Low reading oxygen saturation monitor, also known as an "oximeter" (a monitor that displays how much oxygen is in the blood). The oximeters used in this study are FDA approved, and they have been modified for research purposes. This modification makes the monitors show a value which is either slightly higher or slightly lower than the true oxygen level when values are between 85 and 95%. Outside those ranges, the oximeter works the same as the standard of care oximeter.

DUKE UNIVERSITY HEALTH SYSTEM

Consent To Participate In A Research Study
The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants: The SUPPORT Trial

Only the study coordinator will know which oxygen group your baby is in. Neither you nor the doctors, nurses, and respiratory therapists taking care of your baby will know which oximeter group your baby is in. Within the alarm range of the usual oxygen saturation monitors which we normally use, your baby will either be on the high end of normal or the low end. He/she will remain on this device until he/she reaches 36 weeks adjusted age (for example, 24 wks gestation plus 12 weeks of age = 36 weeks adjusted age). In the case of an emergency, the study doctor can quickly find out which oxygen saturation group your baby is in.

We will also collect information on how well your baby gains weight and grows. Other care will be conducted as normal during his/her participation in the study. Your baby will be followed periodically in our Special Infant Care Clinic (SICC) during the first 2 to 3 years of life. At these visits we check your baby's health and development. For this study, we will ask you to allow us to report the results of your baby's neurologic evaluation and developmental testing at the 18-22 months corrected age follow-up clinic visit.

Your baby will have routine ultrasounds of his/her head during his/her stay in the NICU. A copy of the head ultrasounds conducted between 4-14 days of life and at the time of the original expected due date will be collected for this study. If your baby's head ultrasound at the time of the expected due date occurs before 35 weeks post-menstrual age, your baby will receive another head ultrasounds for the purpose of this study between 35-42 weeks post-menstrual age. In addition, your baby will have a MRI (Magnetic Resonance Imaging) for the purpose of this research study between 35-42 weeks post-menstrual age. Neither the head ultrasound nor the MRI is experimental and both are currently used on infants at Duke University Medical Center. The MRI is a specialized brain scan that takes detailed pictures of the brain structure and can detect normal and abnormal brain tissue. If conducted for the purpose of this study, the head ultrasound and /or MRI will be paid for by the grant. If your baby is still in the NICU, your baby will need to be transported to the MRI suite in order to have the procedure. Only those patients considered stable for transport will undergo an MRI. If your baby is discharged home prior to 35-42 weeks PMA, you maybe asked to return to Duke University Medical Center for the head ultrasound and MRI procedures. The MRI will be conducted after your baby is swaddled while sleeping following a feeding and with the use of a jacket-like device that allows the baby to lie still without using sedation. A physician at the hospital in which you receive the head ultrasound and MRI will provide you with an interpretation of the results of the tests. Neither the ultrasound nor the MRI involves exposure to radiation. Please initial your choice below.

( ) **Yes, I agree to allow my baby to receive an MRI.**

( ) **No, I do not agree to allow my baby to receive an MRI.**

DUKE UNIVERSITY HEALTH SYSTEM

Consent To Participate In A Research Study
The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants: The SUPPORT Trial

We know that many babies born as early as your baby are at risk for breathing problems, especially wheezing and coughing during early childhood, after discharge from the NICU. The purpose of Breathing Outcomes Study described here is to determine the effect of the SUPPORT Study treatment on your baby's respiratory health in early childhood, during the first 18-22 months after his/her expected due date if he or she was to have been born at full term.

You and your infant's participation will begin with an interview at the time of your baby's first regular follow-up visit with the Special Infant Care Clinic (SICC). At this interview Dr. Goldstein or one of her research associates will ask you questions about your family, including questions about family history of breathing problems, and questions about your home, including things that may increase your child's risk of breathing problems. You do not need to answer any questions that make you uncomfortable. The interview will take about 15 minutes.

We will continue to stay in touch with you and your infant by telephone or in person at one of your subsequent SICC visits The main study center at the University of Rochester has trained interviewers who will call you by telephone every 6 months over the next 18-22 months, a total of three times. At these times, they will ask questions about your child's breathing (especially wheezing and coughing), medication use, and visits to a doctor, emergency room, or hospital visits for treatment of breathing problems. They will also ask you several questions about your family and yourself. The entire call should take about 15 minutes of your time, less if your baby has had no breathing problems.

They will schedule the telephone calls at a time that is convenient for you. The telephone calls will occur when your infant is 6, 12, and 18 months after his/her expected delivery at full term.

The results from your baby's questionnaire will be combined with other infants from around the country. However, your baby's name will never be included in any information that leaves Duke. Please initial your choice below.

(____) **Yes, I agree to be contacted.**

(____) **No, I do not agree to be contacted**

Risks :

Participation in this study may involve some added risks or discomforts. All of the treatments (CPAP in the delivery room, delivery room intubation plus surfactant, lower oxygen range, and higher oxygen range) proposed in this study are standard of care at various hospitals like Duke in the United States, so there are no predictable increases in risk for your baby.

Infants randomized to the CPAP group may, at some point in their care, require intubation and assisted ventilation (use of a breathing machine). The study provides guidelines for this, but if the attending physician deems this necessary at any time, participation in the study will not affect this decision

regardless of the study guideline. With CPAP, there is a small risk of skin damage to the nose. Your baby's nurses and doctors will closely monitor your baby's nose while he/she is on CPAP. Risks of surfactant therapy include slowing of the heart and a decrease in oxygen saturation during dosing as the surfactant liquid passes through the breathing tube into the lungs. Surfactant treatment may cause a rapid increase in how much the lungs expand with each breath. Trained respiratory therapists, nurses and physicians will monitor your baby for these effects during and after surfactant dosing.

The risks of higher versus lower oxygen saturation levels in the two ranges to be used in this study are unknown. Lower oxygen range may help infants avoid ROP and chronic lung disease (need for supplemental oxygen at 36 weeks post-conception or discharge) which has been associated with neurodevelopmental delay and higher oxygen levels may or may not have an effect on the risk of neurodevelopmental delay. It is unclear which oxygen level, if any, will help babies grow better. Both ranges are within the alarm limits set in infants like yours in the Duke NICU. Some unknown risks may be learned during the study. If these occur, you will be informed by the study personnel.

There are no known effects from exposure to magnetic fields (MRI). Temporary minor skin irritation from tape used to apply MRI-compatible monitoring electrodes may occur, but this risk is unlikely.

The only other risk of this study is the risk to confidentiality. Every effort will be made to keep your child's medical record confidential. There will be no name or other patient identification in any study report that may be published after the study is completed. Measures taken to protect you and your baby's identity are described in the confidentiality section of this document.

Benefits:

There may be benefits to your child directly from participation in this study. The knowledge gained from this study may help us improve treatment of babies in the future.

Data Handling and Confidentiality:

Clinical information will be collected from your baby's chart by Duke Neonatology Clinical Research study personnel. Information will be labeled with a code number. Coded information will be sent to the NICHD Neonatal Network's Data Collection Center at Research Triangle Institute (RTI) in Research Triangle Park, North Carolina. The study log linking the code number with your baby's identity will be kept under lock and key at Duke. Information directly identifying your baby will not leave Duke. Research records will be kept confidential to the extent provided by law, and will be maintained in the study record until your child reaches the age of 21 years or six years after the study is complete, whichever is longest. Your baby's study record may be reviewed in order to meet federal or state regulations. Reviewers of your child's study record may include representatives from the Food and Drug Administration, representatives of the National Institutes of Health (NIH) and the Duke Institutional Review Board (IRB, the hospital committee that supervises research in human beings). When research results from this study are reported in a professional setting, such as in a medical journal or at a scientific meeting, the identity of research subjects taking part in the study is withheld. If disclosed by the sponsor, the information is no longer covered by the federal privacy regulations.

DUKE UNIVERSITY HEALTH SYSTEM

Consent To Participate In A Research Study
The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants: The SUPPORT Trial

Costs and Compensation:
There is no charge to you or your child for participating in this research. You or your child's insurance will be responsible for paying the cost of routine medical care for your child's condition. The costs for your child's routine care will appear on his/her hospital bill. Although there is no compensation for allowing your child to participate in this project, we will give you $25 and a parking pass to help with travel expenses to the clinic for the 18 – 22 month visit.

Injuries:
Immediate necessary medical care is available at Duke University Medical Center in the event that your child is injured as a result of participation in this research study. However, there is no commitment by Duke University, Duke University Health System, Inc., or your child's Duke physicians to provide monetary compensation or free medical care to your child in the event of a study-related injury. For questions about the study or a research –related injury, contact Dr. Mike Cotten at 919-681-0630 during regular business hours and at 919-970-4381 after hours and on weekends and holidays.

Alternatives to Participation:
As an alternative to participation in this study, you may decide to have your baby's doctor decide which treatment your baby will receive. If you decide not to include your child in this study, none of his/her medical information will be included in the study data. Participation in research is entirely voluntary.

Right not to Participate or to Withdraw:
You may choose for your child not to be in the study, or, if you agree for your child to be in the study, you may withdraw him/her from the study at any time. If you withdraw him/her from the study, no new data will be collected for study purposes unless the data concern an adverse event (bad effect) related to the study. If such an adverse event occurs, we may need to review your child's entire medical record. All data that have already been collected for study purposes, and any new information about an adverse event related to the study, will be sent to the sponsor.

Your decision for your child not to participate or to withdraw from the study will not involve any penalty or loss of benefits to which you or your child are entitled, and will not affect your access to health care at Duke. If you do decide for your child to withdraw, we ask that you contact Dr. Cotten in writing and let him know that you are withdrawing from the study. His mailing address is: DUMC Box 3179, Durham, North Carolina, 27710. If you withdraw your child from the study, the attending physician will decide whether to maintain current treatment or change it, based on your child's needs at the time of the decision.

In addition, your child's doctor may decide to take him/her off this study if her/his condition gets worse, he/she has serious side effects, or the study doctor determines that it is no longer in your child's best interest to continue. The sponsor or regulatory agencies may stop this study at anytime without your consent. If this occurs, you will be notified and your child's study doctor will discuss other options with you. We will tell you about new information that may affect your child's health, welfare, or willingness to stay in this study.

DUKE UNIVERSITY HEALTH SYSTEM

Consent To Participate In A Research Study
The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants: The SUPPORT Trial

Whom to Call with Questions or Problems:

For questions about the study or a research-related injury, contact Dr. Cotten at 919-681-6025 during regular business hours and at 919-970-4381 (pager) or the Duke paging operator, 919-684-8111 after hours and on weekends and holidays. During regular business hours, you may also call the clinical research pager at 919-970-1425 and speak to a member of the Neonatology Clinical Research team. For questions about your child's rights as a research participant, contact the Duke University Health System Institutional Review Board (IRB) Office at (919) 668-5111.

Statement of Consent:

"The purpose of this study, procedures to be followed, risks and benefits have been explained to me. I have been allowed to ask questions, and my questions have been answered to my satisfaction. I have been told whom to contact if I have additional questions. I have read this consent form and agree for my child to be in this study, with the understanding that I may withdraw him/her at any time. I have been told that I will be given a signed copy of this consent form."

Signature of Parent/Guardian **Date**

Signature of Person Obtaining Consent **Date**

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: SUPPORT consent
Date: Thursday, January 26, 2012 3:58:00 PM
Attachments: Support.consent.2.10.09.doc

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Joanne Finkle, J.D. [mailto:j.finkle@duke.edu]
Sent: Thursday, January 26, 2012 3:55 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: SUPPORT consent

Please find SUPPORT consent attached.

Thanks, Joanne

Joanne Finkle, RN, JD
Clinical Research Associate II
Neonatal/Perinatal Research Unit
2424 Erwin Road suite 504
DUMC 2739
Durham, NC 27705
Work: 919-681-4911
Fax: 919-681-6065
Pager: (b)(6)

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Estelle Fischer"
Cc: "Kurt Schibler"
Subject: RE: FW: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)
Date: Thursday, January 26, 2012 3:24:00 PM

Estelle –

Nice to hear from you – hope you are doing well and THANKS!!

Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Estelle Fischer [mailto:Estelle.Fischer@cchmc.org]
Sent: Thursday, January 26, 2012 3:21 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Kurt Schibler
Subject: Re: FW: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)

Hi Rose:

Please see attached most recent version of the SUPPORT Trial informed consent document.

Thanks,

Estelle E. Fischer, MHSA, MBA
Clinical Research Manager
Division of Neonatology
Children's Hospital Medical Center (MLC 7009)
3333 Burnet Avenue
Cincinnati, OH 45229-3039
Phone: 513.803.0949 Fax: 513.803.0969

communication in error, please notify us immediately by telephone and destroy the message and its attachments.

>>> "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> 1/26/2012 2:54 PM >>>
Kurt –
Please send me your most recent SUPPORT Trial consent form today.

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, January 20, 2012 2:39 PM
To: 'Kurt Schibler'
Cc: Maddox, Yvonne (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Hirschfeld, Steven (NIH/NICHD) [E]
Subject: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)

Kurt-
As you are aware the Neonatal Research Network (NRN) continues to support studies under common protocols, but which require individual institutional IRB review prior to the conduct of these studies at each of the NRN sites. This is to inform you that The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), which provided the Federal support to the NRN, has been requested by the Office of Human Subjects Protection, to provide to the Office the most current consent form approved by your IRB and the corresponding IRB approval for the main SUPPORT Study, including any revisions, as soon as possible. As the NICHD Program Director of the NRN, I am requesting that the most recent consent form with IRB approval for your site for SUPPORT be submitted to me as soon as possible, but no later than January 26, 2012. Thank you for your cooperation.

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
6100 Executive Blvd., Room 4B03
MSC 7510

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For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: FW: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)
Date: Thursday, January 26, 2012 3:24:00 PM
Attachments: SUPPORT Trial-CCHMC ICS-04-28-09.doc

I am still waiting for Miami and Duke – I sent reminders earlier today –If I don't have them in the am, I will call both.

Thanks

Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Estelle Fischer [mailto:Estelle.Fischer@cchmc.org]
Sent: Thursday, January 26, 2012 3:21 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Kurt Schibler
Subject: Re: FW: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)

Hi Rose:

Please see attached most recent version of the SUPPORT Trial informed consent document.

Thanks,

Estelle E. Fischer, MHSA, MBA
Clinical Research Manager
Division of Neonatology
Children's Hospital Medical Center (MLC 7009)
3333 Burnet Avenue
Cincinnati, OH 45229-3039
Phone: 513.803.0949 Fax: 513.803.0969

the intended recipient, you are hereby notified that any disclosure, dissemination, distribution, copying, or action taken in reliance on the contents of this communication is strictly prohibited. If you have received this communication in error, please notify us immediately by telephone and destroy the message and its attachments.

>>> "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> 1/26/2012 2:54 PM >>>
Kurt –

Please send me your most recent SUPPORT Trial consent form today.

Thanks

Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
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Bethesda, MD 20892
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301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, January 20, 2012 2:39 PM
To: 'Kurt Schibler'
Cc: Maddox, Yvonne (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Hirschfeld, Steven (NIH/NICHD) [E]
Subject: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)

Kurt-

As you are aware the Neonatal Research Network (NRN) continues to support studies under common protocols, but which require individual institutional IRB review prior to the conduct of these studies at each of the NRN sites. This is to inform you that The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), which provided the Federal support to the NRN, has been requested by the Office of Human Subjects Protection, to provide to the Office the most current consent form approved by your IRB and the corresponding IRB approval for the main SUPPORT Study, including any revisions, as soon as possible. As the NICHD Program Director of the NRN, I am requesting that the most recent consent form with IRB approval for your site for SUPPORT be submitted to me as soon as possible, but no later than January 26, 2012. Thank you for your cooperation.

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH

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higginsr@mail.nih.gov

CINCINNATI CHILDREN'S HOSPITAL MEDICAL CENTER CONSENT TO PARTICIPATE IN A RESEARCH STUDY

STUDY TITLE: THE SURFACTANT POSITIVE AIRWAY PRESSURE AND PULSE OXIMETRY TRIAL IN EXTREMELY LOW BIRTH WEIGHT INFANTS (THE SUPPORT TRIAL)

SPONSOR NAME:
National Institutes of Health (NIH) /National Institute of Child Health and Human Development (NICHD)

INVESTIGATOR INFORMATION:

Vivek Narendran, MD	(513)-803-0961	(513) 820-3879
Principal Investigator Name	**Telephone Number**	**24 hr Emergency Contact**

Subject Name: _____ **Date of Birth:** ____/____/____

Throughout this document, references to "You" may stand for either the research study subject or for the parents or legal guardians of the research study subject if the subject is under 18 years of age or otherwise unable to legally give informed consent to participate in the research study. The signature(s) at the end will clarify whether the research study subject is signing this consent form on their own behalf or via a legal guardian or legal personal representative.

INTRODUCTION:

You have been asked to participate in a research study. Before agreeing to participate in this study, it is important that you read and understand the following explanation. It describes, in words that can be understood by a lay person, the purpose, procedures, benefits, risks and discomforts of the study and the precautions that will be taken. It also describes the alternatives available and the right to withdraw from the study at any time. No guarantee or assurance can be made as to the results of the study. Also, participation in the research study is completely voluntary. Refusal to participate will

involve no penalty or loss of benefits to which you are otherwise entitled. You may withdraw from the study at any time without penalty.

WHY IS THIS RESEARCH BEING DONE?

The purpose of this research study is to determine the best way to care for very premature infants to reduce the risk for lung disease and eye disease, and to see whether the treatment your infant receives, as part of this study, will improve breathing during the 6-22 months after his/her expected due date.

Very premature infants less than 28 weeks gestational age often develop lung disease and eye disease which may lead to long term disability or death. This lung disease and eye disease may be caused by the kind of treatment that is used normally in the delivery room and in the nursery. This current treatment can cause either collapse of the lungs or too much expansion of the lungs. This may cause injury to the lung leading to long term lung disease or possibly death.

Too much oxygen in the beginning days of life can cause the blood vessels in the eye to grow abnormally. At the same time, not enough oxygen can adversely affect an infant's growth and brain development. Your infant's oxygen is monitored by a machine called a pulse oximeter. This machine tells ~~us~~ how much oxygen is in the blood stream. The study doctors are trying to find the best oxygen level to prevent these lung and eye diseases.

WHY HAVE YOU BEEN ASKED TO TAKE PART IN THIS RESEARCH STUDY?

You are being asked to take part in this research study because you may deliver your infant early. Infants that are delivered early, or premature, are at a higher risk of developing lung disease and eye disease.

WHO SHOULD NOT BE IN THE RESEARCH STUDY?

- Anyone who delivers outside the hospital center
- Anyone who delivers before 24 weeks gestation or after 28 weeks gestation
- If your infant has a known birth defect

HOW LONG WILL YOUR INFANT BE IN THE RESEARCH STUDY?

Your infant's participation in this research study will last until the age of 22 months. The doctor who is caring for your infant may decide to take your infant off this research study at any time if he/she feels it is necessary.

During that time, we will gather information from your infant's medical record, including results of routine NICU assessments, such as head ultrasounds and ophthalmologic exams.

All infants with a birth weight of ≤ 1500 grams have an eye exam at 32 weeks post menstrual age or 5-6 weeks of age, whichever comes last. For purposes of the SUPPORT Trial, the results of these exams will be recorded until the infant's eyes reach final status. This may include exams after discharge home or transfer to another hospital.

The majority of this study will take place while your infant is in the hospital. Once he/she has been discharged, there will be one more assessment done at a routine 18 - 22 month follow-up visit at the High Risk clinic.

At the follow-up visit, your child will have a basic health check, as well as a neurological examination. After being weighed and measured, your child will meet with the developmental psychometrist, and the Bayley Scales of Infant Development will be administered. All tests are standard tests frequently used in the assessment of child development, child behavior, and neurological function.

The following questionnaires will be completed by the psychometrist through an interview with the caregiver:

1) Socio-Economic Status (SES) at nursery discharge.
2) Socio-Economic Status (SES) at 18 + 4 months of age.
3) Medical History
4) Family Resource Scale - measures the adequacy of different resources in the household.
5) The Brief Infant-Toddler Social and Emotional Assessment (BITSEA).
6) SUPPORT Trial Breathing Outcomes Study: 6 - 12 Month Interview (SUPF02 Rel 1.0)
7) SUPPORT Trial Breathing Outcomes Study: 8 - 22 Month Interview (SUPF03 Rel 1.0)

A more complete description of all these tests is available as an appendix to this consent form if requested. All these tests will be administered by a single developmental psychometrist. All children will be examined in the study program.

WHO IS CONDUCTING THE RESEARCH STUDY?

This study is sponsored by National Institutes of Health (NIH)/National Institutes of Child Health & Human Development (NICHD).

The study is directed by Vivek Narendran, MD, the researcher at Cincinnati Children's Hospital Medical Center.

HOW MANY PEOPLE WILL TAKE PART IN THE RESEARCH STUDY?

Approximately 1345 infants will be asked to take part in this study.

The NICHD Neonatal Research Network has 16 sites taking part in this study. The University Hospital, the Good Samaritan Hospital, and the Cincinnati Children's Hospital comprise the Cincinnati site within the Neonatal Research Network.

WHAT IS INVOLVED IN THE RESEARCH STUDY?

Neither you, nor the researcher conducting this study will know what group your infant will be assigned. Your infant will have a one in four chance of being placed in any group. However, in the event of an emergency, your study doctor will be able to find out which treatment you are receiving.

In the hospital:

If you agree to have your infant participate in this study, he/she will be assigned to one of the four study groups described below. A flip-of-the-coin method will be used to assign infants to a group.

The four study groups are as follow:

- Strong efforts will be made in this group to keep infants off the ventilator (breathing machine) and the infants will be assigned to a lower blood oxygen range of 85% to 89%.
- Strong efforts will be made in this group to keep infants off the ventilator (breathing machine) and the infants will be assigned to a slightly higher blood oxygen range of 91% to 95%.
- Routine standard care will be practiced in this group and infants will be assigned to a lower blood oxygen level of 85%-89%.
- Routine standard care will be practiced in this group and infants will be assigned to a higher blood oxygen level of 91%-95%.

Strong efforts to keep infants off the ventilator include the use of continuous positive airway pressure or CPAP. This provides some pressure to keep the lungs expanded, but allows the infant to breathe on his/her own. Routine standard care will include the use of a ventilator (breathing machine) and a medicine called surfactant. This medicine is put directly in the lungs through the breathing tube in your infant's throat and helps your infant to breathe easier.

Because oxygen affects how well infants grow, measurements of your infant's weight, length and head circumference will be taken from birth until hospital discharge. Nutrition information will also be collected.

Optional:

It is not known whether breathing extra oxygen as treatment for lung problems causes a depletion of anti-oxidants or a build up of oxidants. These substances may alter lung growth and development and make premature babies more likely to wheeze in early childhood. Anti-oxidant levels can be detected in the blood. One milliliter of blood from the placenta will be collected and analyzed for anti-oxidant levels. Two thirds of one milliliter of blood (0.67cc or 13 drops) will also be collected from your infant when he or she is 14 days and 28 days old. The total amount of blood is 1.3 milliliters (1.3 milliliters is equal to 24 drops or approximately one - fifth of a teaspoon) over a 1 month time period. This amount of blood is considered safe for purposes of research by the Federal Government's National Institute of Health. Every attempt will be made to draw these blood samples at the same time as blood testing that is done as part of routine care in the NICU. You may accept or decline this extra blood collection.

☐ Accept ☐ Decline

After discharge:

Once your infant is discharged, we will continue to stay in touch with you and your infant, by telephone, or in person, at one of your routine visits at the High Risk Infant Follow-Up Clinic at Children's Hospital, every six months over the next 6-22 months.

During this routine medical check-up, trained staff will meet with you and your child to ask you some questions, check your child's growth measurements, and check your child's level of development by interacting with him/ her.

There will be a total of 3 study visits or calls during this time. During these clinic visits and/ or telephone calls, we will ask questions about your child's breathing (especially wheezing and coughing), medication use, and visits to a doctor, emergency room, or hospital for treatment of breathing problems. We will also ask you several questions about your family and yourself. Answering the study questions should take about 15 minutes of your time, less if your baby has had no breathing problems.

The telephone calls will be scheduled when your infant is 6, 12, and 18 months after his/her expected delivery at full term. We will schedule the calls at a time that is convenient to you.

The results from your infant's questionnaire will be combined with the results of other infants from around the country; however, your infant's name will not be used.

WHAT ARE THE RISKS AND DISCOMFORTS OF THE RESEARCH STUDY?

Trying to keep infants off the breathing machine, and on CPAP, may lead to: a) an increased respiratory effort, b) brief periods of a pause in their breathing (apnea), ~~and~~ c) higher carbon dioxide in their blood, and d) nasal septum breakdown. Safeguards are in place to monitor these side effects. This may include the use of a ventilator (breathing machine) when appropriate.

Trying to leave infants on the ventilator (breathing machine) may lead to: a) worsening lung injury due to the pressures used by the machine, b) mechanical complications such as obstruction or loss of airway, and c) prolonged hospital stay. Safeguards are in place to monitor these side effects. The doctor will make changes as needed.

For the optional portion of this study, every attempt will be made to draw the blood samples at the same time as blood testing for routine care. In the event that it is necessary to draw blood by venipuncture -- clinical personnel will take the small amount of blood from a vein in your baby's arm or leg by needle stick, or by heelstick. Risks associated with drawing blood from your baby's arm or leg include momentary discomfort and/or bruising. Infection, excess bleeding, clotting, and/or fainting are also possible, although unlikely.

There may be unknown or unforeseen risks associated with study participation.

One of the risks of participating in research is the loss of confidentiality. Please see confidentiality section.

ARE THERE DIRECT BENEFITS TO TAKING PART IN THE RESEARCH STUDY?

There may be a direct benefit to your child participating in this study, in that information about his/ her development may be learned during the 6 -22 month follow-up study period, following discharge from the hospital. This information will be gathered from the assessments and your child's interaction with study personnel during this period.

WHAT OTHER CHOICES ARE THERE?

You may decide to **not** allow your infant to take part in this research. You may choose to have your infant treated with the usual standard medical care as determined by the doctor. If you refuse participation in this study, it will not change your infant's care in the nursery.

If you decide to allow your infant to take part in this research, you will receive any new information during the course of the study concerning significant treatment findings. This may affect your willingness to continue your infant's participation and you may withdraw your infant from the study at any time.

HOW WILL INFORMATION ABOUT YOU BE KEPT PRIVATE AND CONFIDENTIAL?

Every effort will be made to maintain the confidentiality of your medical information and your infant's medical or research information. Medical record information and potentially identifying information such as your infant's name and birth date are classified as "Protected Health Information" or "PHI".

Protected Health Information is defined as health information, whether verbal or recorded in any form (such as on a piece of paper or entered into a computer), that identifies you, or your infant, as an individual, or offers a reasonable basis to believe that the information could be used to identify you or your infant.

Study records that identify your child will be kept confidential as required by law. Federal Privacy Regulations provide safeguards for privacy, security and authorized access. Except when required by law, your child will not be identified by name, social security number, address, telephone number, or any other direct personal identifier in study records disclosed outside of Cincinnati Children's Hospital Medical Center.

By signing this consent form you are giving permission for representatives of the Cincinnati Children's Hospital Medical Center ("CCHMC"), the investigator and CCHMC employees involved with the research study, including the Institutional Review Board and the Office for Research Compliance, and/ or their appointed agent, as well as the National Institutes of Health, to inspect sections of your medical records and your infant's medical and research records related to this study.

When a study is submitted to the FDA, the clinical investigator agrees to allow the FDA access to the study records. The FDA will treat the information as confidential, but on rare occasions disclosure to third parties may be required by law. Therefore, absolute protection of confidentiality cannot be promised or implied.

A Data and Safety Monitoring Board, an independent group of experts, will be reviewing the data from this research throughout the study. The investigator will tell you about new information from this or other studies that may affect your health, welfare, or willingness to stay in this study.

The information from the research study may be published; however, you will not be identified in such a publication. The publication will not contain information about you that would enable someone to determine your identity as a research participant without

your authorization.

Cincinnati Children's Hospital Medical Center and/or the Investigator will take the following precautionary measures to protect your privacy and confidentiality of your research and/or medical records: and those of your infant.

No information such as name, address, telephone number, etc. that could be used to easily identify your infant will be kept as part of the research records.

A copy of this consent form will be included in your infant's medical research record.

Your infant will be registered in the Cincinnati Children's Hospital Medical Center's computer system as a research subject which may be beneficial for future clinical care.

USE AND DISCLOSURE OF YOUR PROTECTED HEALTH INFORMATION

The Protected Health Information described in the section above will be used /disclosed for the purpose of research by CCHMC to the other persons or entities identified above.

"Use" of an individual's health information is defined as the sharing, examination or analysis (break down) of the information that is collected and maintained for the length of the research study.

"Disclosure" of an individual's health information is defined as the release, transfer, providing access to, or to reveal in any other manner, the information outside the persons or entity holding the information as described in the section "How Will Information About You Be Kept Private And Confidential" in this consent form.

Once your Protected Health Information is disclosed, the information may be subject to re-disclosure and may no longer be protected by the federal privacy regulations.

AVAILABILITY OF INFORMATION?

As indicated above, you will receive any new information during the course of the study concerning significant treatment findings.

WHAT ARE YOUR COSTS TO BE IN THIS STUDY?

The procedures of this study are standard methods of caring for premature infants and will be billed to your infant's hospital account. There will be no additional studies or assessments, including head ultrasounds, performed for study purposes only; all studies are clinically indicated.

Funds are not available to cover the costs of any ongoing medical care and you remain responsible for the cost of non-research care.

If you have questions about your medical bill relative to research participation, you may contact Dr. Vivek Narendran by calling (513) 558-0557.

WILL YOU BE PAID TO PARTICIPATE IN THIS RESEARCH STUDY?

There is no payment or reimbursement for participation in this research study.

WHAT COMPENSATION IS AVAILABLE IN CASE OF INJURY?

If you believe that you have been injured as a result of participation in biomedical or behavioral research you are to contact Dr. Vivek Narendran by calling (513) 558-0557 or the Director of Social Services (513-636-4711) to discuss your concerns. Cincinnati Children's Hospital Medical Center follows a policy of making all decisions concerning compensation and/or medical treatment for physical injuries occurring during or caused by participation in biomedical or behavioral research on an individual basis.

WHAT ARE YOUR RIGHTS AS A PARTICIPANT?

Your participation in this study is completely **voluntary**. You may choose either to take part or not to take part in this research study. Your decision whether or not to participate will not result in any penalty or loss of benefits to you and the standard medical care for your condition will remain available to you.

If you decide to take part in the research study, you are **free to withdraw** your consent and discontinue participation in this research study at any time. Leaving the study will not result in any penalty or loss of benefits to you.

You may revoke (choose to withdraw) this Authorization as provided under the Health Insurance Portability and Accountability Act of 1996 (HIPAA") at any time after you have signed it by providing Dr. Vivek Narendran with a written statement that you wish to withdraw this Authorization. Your withdrawal of this Authorization will be effective immediately and your Protected Health Information can no longer be used/disclosed for research purposes by CCHMC and the other persons or entities that are identified in the "Use or Disclosure of Your Protected Health Information" section of this consent, except to the extent that CCHMC and/or the other persons or entities identified above have already taken action in reliance upon your consent. In addition, your Protected Health Information may continue to be used / disclosed to preserve the integrity of this research study.

The investigators will tell you about significant new findings developed during the course of the research and new information that may affect your health, welfare, or willingness to stay in this study.

If you have questions about the study, you will have a chance to talk to one of the study staff or your regular doctor. Do not sign this form unless you have had the chance to ask questions and have received satisfactory answers.

Nothing in this consent form waives any legal rights you may have nor does it release the investigator, the sponsor, the institution, or its agents from liability for negligence.

For further information about your rights, please see CCHMC Notice of Privacy Practices. A copy of the CCHMC Notice of Privacy Practices may be obtained from any patient registration area or online at www.cincinnatichildrens.org (From the internet page select in the following order: About Us, Corporate Information, HIPAA). You may also contact our Privacy Officer at 513-636-4707 to obtain a copy.

ABILITY TO CONDITION TREATMENT ON PARTICIPATION IN THIS STUDY

You have a right to refuse to sign this consent to use/disclose your Protected Health Information for research purposes.

If you refuse to sign this consent, you may not be able to receive research-related treatment.
If you refuse to sign this consent, your rights concerning treatment, payment for services, and enrollment in a health plan or eligibility for benefits will not be affected.

WHOM DO YOU CALL IF YOU HAVE QUESTIONS OR PROBLEMS?

For questions about this research study or to report a research-related injury, you can contact the researcher Dr. Vivek Narendran at (513) 558-0557. Researchers are available to answer any questions you may have about the research at any time.

If you have general questions about your rights as a research participant in this research study, you may call the Cincinnati Children's Hospital Medical Center Institutional Review Board at (513) 636-8039.

Cincinnati Children's

CINCINNATI CHILDREN'S HOSPITAL MEDICAL CENTER CONSENT TO PARTICIPATE IN A RESEARCH STUDY

STUDY TITLE: THE SURFACTANT POSITIVE AIRWAY PRESSURE AND PULSE OXIMETRY TRIAL IN EXTREMELY LOW BIRTH WEIGHT INFANTS (THE SUPPORT TRIAL)

INVESTIGATOR INFORMATION:

Vivek Narendran, MD	(513) 558-0557	(513) 820-3879
Principal Investigator Name	Telephone Number	24 hr Emergency Contact

SIGNATURES:

I have read the information given above. The investigator or his/her designee have personally discussed with me the research study and have answered my questions. I am aware that, like in any research, the investigators cannot always predict what may happen or possibly go wrong. I have been given sufficient time to consider if I (or my child) should participate in this study. I hereby consent for myself (or my child) to take part in this study as a research study subject.

_____ Date:_____
Parent/Legal Guardian (Signature)

_____ Date:_____
Parent/Legal Guardian (Signature)

_____ Date:_____
Investigator or specific individual who has been designated to obtain consent (Signature)

_____ Date:_____
Investigator (Signature)

This research study and consent form have been reviewed and approved by the Cincinnati Children's Hospital Medical Center Institutional Review Board (telephone number 513-636-8039).

From: Luc Brion
To: Kristi Watterberg; Carl D'Angio; Martin Keszler
Cc: Higgins, Rosemary (NIH/NICHD) [E]; dwallace@rti.org; Pablo Sanchez
Subject: RE: revised protocol
Date: Friday, January 27, 2012 3:13:58 PM

I suspect that the hypothesis would have to be changed from that proposed by Brenda Poindexter "SBT will be more useful than clinical information alone" into something like "babies who pass the SBT are more likely to remain extubated than those who fail the SBT."
Luc

Luc P. Brion, MD
Professor of Pediatrics
Director, Fellowship Training Program in Neonatal-Perinatal Medicine
University of Texas Southwestern Medical School Program
The University of Texas Southwestern Medical Center at Dallas
5323 Harry Hines Boulevard, STOP 9063
Dallas, TX 75390-9063
Office: (214) 648-3903
Fax: (214) 648-2481
luc.brion@utsouthwestern.edu

From: Kristi Watterberg [mailto:kwatterberg@salud.unm.edu]
Sent: Friday, January 27, 2012 1:45 PM
To: Carl D'Angio; Luc Brion; Martin Keszler
Cc: Rose (higginsr@mail.nih.gov); dwallace@rti.org; Pablo Sanchez
Subject: RE: revised protocol

Agree - and will test the hypothesis that the SBT is a better predictor than clinical criteria - Kristi

>>> "D'Angio, Carl" <Carl_Dangio@URMC.Rochester.edu> 1/27/2012 8:14 AM >>>
Luc,

I looked this over. You did a good job in addressing the comments. Specifically, I think you struck a reasonable balance for when to notify the clinical team.

I still have one area of confusion that I hope you and Dennis can clarify: I would think that the primary objective of this sort of study would be to establish the sensitivity, specificity, etc. of this test in this population. That is, to take all infants who qualify clinically for extubation, apply the test, and develop a 2 x 2 table. The comparison would thus not be those with a positive test to the whole group of babies studied, but rather:

	Test positive	Test negative
Successfully extubated	a	b
Not successfully extubated	c	d

One could evaluate outcome by chi-square and develop sensitivity, specificity, PPA, NPV, and likelihood ratios.

I don't know whether the statistics change or not for this. I hope I am making myself clear.

Good luck with this.

Carl

Carl T. D'Angio, MD
Associate Professor of Pediatrics and Medical Humanities
Director, Neonatal Clinical Research
Director, Pediatric Clinical Research Office
Division of Neonatology
Golisano Children's Hospital
University of RochesterMedicalCenter
601 Elmwood Avenue, Box 651
Rochester, NY14642
Phone (585) 273-4911, Fax (585) 461-3614
carl_dangio@urmc.rochester.edu

From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
Sent: Monday, January 23, 2012 7:25 PM
To: Keszler, Martin; Kristi Watterberg
Cc: D'Angio, Carl; dwallace@rti.org; Rose (higginsr@mail.nih.gov); Pablo Sanchez
Subject: RE: revised protocol

Thanks, Martin.

All:
I attach the revised version, in which I eliminated several manuscripts, which are not needed anymore. I also eliminated Martin's comments except the one for Dennis
Please let me know if you have any additional suggestions by January 27th so I can I send the protocol to the review committee at least one week before the next protocol review standing committee call (February 7th).

Dennis:
Please could you extract the data from SUPPORT as indicated in my previous email sent Fri 1/20/2012 8:58 AM. This information is for the bottom of page 7 of the version without the Word tracking [Results pending from Dennis].
Please let us know if we are planning too many secondary analyses.

Thanks for your help,

Luc

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Director, Fellowship Training Program in Neonatal-Perinatal Medicine
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Office: (214) 648-3903
Fax: (214) 648-2481
luc.brion@utsouthwestern.edu

From: Keszler, Martin [mailto:MKeszler@Wihri.org]
Sent: Monday, January 23, 2012 5:37 PM
To: Luc Brion; Kristi Watterberg
Cc: Carl_Dangio@URMC.Rochester.edu; dwallace@rti.org; Rose (higginsr@mail.nih.gov); Pablo Sanchez
Subject: RE: revised protocol

Luc, here are my edits and comments. Sorry I could not get this back to you sooner.
Keep up the good work. We're almost there!
Cheers,
M.

Martin Keszler MD
Mkeszler@WIHRI.org
(401) 274-1122, x7490

From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
Sent: Monday, January 23, 2012 5:14 PM
To: Kristi Watterberg
Cc: Carl_Dangio@URMC.Rochester.edu; Keszler, Martin; dwallace@rti.org; Rose (higginsr@mail.nih.gov); Pablo Sanchez
Subject: RE: revised protocol

Kristi:

Oops! I missed a few more mistakes! Thanks a lot for taking the time to read the documents and thanks your comments.

Kristi, Carl, Martin, Dennis, Rose:

I looked carefully at the printout and edited the text further; corrections should come in blue this time; this will allow you to detect changes I made today.

Best regards,

Luc

Luc P. Brion, MD
Professor of Pediatrics
Director, Fellowship Training Program in Neonatal-Perinatal Medicine
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Office: (214) 648-3903
Fax: (214) 648-2481
luc.brion@utsouthwestern.edu

From: Kristi Watterberg [mailto:KWatterberg@salud.unm.edu]
Sent: Monday, January 23, 2012 2:42 PM
To: Luc Brion
Cc: Carl_Dangio@URMC.Rochester.edu; MKeszler@Wihri.org
Subject: Re: revised protocol

A lot of work in a short time, Luc! A couple of minor points:
Background: this must be a typo: "extubation predicted by a positive SBT was 3/43 (93%), compared with a success rate of 39/50 (78%) in the"

The two statements below seem to conflict - in each, you are looking at the SBT vs. clinical factors to predict successful extubation, even though they're stated a little differently.
The null hypothesis is that the percentage of successful extubation among patients with positive SBT is not different from that in those extubated based on criteria established for extubation in the main hydrocortisone study.
The primary question is not to determine whether SBT is better predictive than clinical information; this would be best studied by a randomized trial.

There seems to be a missing clause in the following sentence: "If an occasional infant requires more than this, e.g., bag and mask ventilation or additional resuscitation."
Kristi

>>> Luc Brion <Luc.Brion@UTSouthwestern.edu> 1/21/2012 4:59 PM >>>
Martin, Carl, Kristi, Dennis, Rose:

Thanks a lot for all the feedback at the meeting.

Here is the updated protocol, taking into account all the suggestions from the protocol review committee and a first draft of the revised sample size analysis (not seen by Dennis yet).
Please let me know your suggestions (if possible by January 27th) so I can I send the protocol to the review committee at least one week before the next protocol review standing committee call (February 7th).
Thanks and best regards,
Luc

Luc P. Brion, MD
Professor of Pediatrics
Director, Fellowship Training Program in Neonatal-Perinatal Medicine The University of Texas Southwestern MedicalCenter at Dallas
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UT Southwestern MedicalCenter
The future of medicine, today.

From: Luc Brion
To: Wallace, Dennis; Keszler, Martin; Kristi Watterberg
Cc: Carl_Dangio@URMC.Rochester.edu; Higgins, Rosemary (NIH/NICHD) [E]; Pablo Sanchez
Subject: RE: revised protocol
Date: Friday, January 27, 2012 11:51:35 AM

Dennis, Carl, Martin:

The proposal will not pass the protocol review committee unless we build a primary hypothesis as indicated by the chair of the protocol review committee: "The authors state that because this is an observational study, there is no primary hypothesis. This needs to be revised to reflect the analyses that will be done (hypothesis could be that the SBT will be more useful than clinical information alone)."

I revised the protocol along this recommendation.

I agree with Dennis and Carl that the statistical comparison should be between those with a positive SBT and those with a negative SBT so that the 2 groups are independent.

I think that the power should be calculated based on assumptions that we cannot verify yet until we have the data from SUPPORT.

Dennis: were you able to extract the data from the SUPPORT trial?

Luc

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luc.brion@utsouthwestern.edu

From: Wallace, Dennis [mailto:dwallace@rti.org]
Sent: Friday, January 27, 2012 10:48 AM
To: Keszler, Martin; Luc Brion; Kristi Watterberg
Cc: Carl_Dangio@URMC.Rochester.edu; higginsr@mail.nih.gov; Pablo Sanchez
Subject: RE: revised protocol

Martin,

I'm fine with that also. The only caveat is that we now have a primary hypothesis that has more than 98% power, so we could probably cut sample size substantially and still be well-powered for the primary analysis, but really lack the sample size needed to characterize the operating characteristics well. I just wanted to make sure that we didn't get asked to reduce sample size to

reduce costs since we have excess power for the primary.

Dennis

From: Keszler, Martin [mailto:MKeszler@Wihri.org]
Sent: Friday, January 27, 2012 11:23 AM
To: Wallace, Dennis; Luc Brion; Kristi Watterberg
Cc: Carl_Dangio@URMC.Rochester.edu; higginsr@mail.nih.gov; Pablo Sanchez
Subject: RE: revised protocol

My initial quick response:
We agree with your stated preference, but the Protocols Review is pushing us to do the SBT positive vs. SBT negative as a primary outcome. The two are not mutually exclusive and I am glad we have more than adequate power to look at it this way. Seems prudent to take the path of least resistance and go along with the Protocols Review recommendation.
Luc, others, do you see it the same way?
Have a good w/e
M

Martin Keszler MD
Mkeszler@WIHRI.org
(401) 274-1122, x7490

From: Wallace, Dennis [mailto:dwallace@rti.org]
Sent: Friday, January 27, 2012 10:56 AM
To: Luc Brion; Keszler, Martin; Kristi Watterberg
Cc: Carl_Dangio@URMC.Rochester.edu; higginsr@mail.nih.gov; Pablo Sanchez
Subject: RE: revised protocol

Luc,

Sorry that I've taken a while to respond, but I believe that the hypothesis test problem is a bit more complicated than suggested by the current version of the protocol (which is why we decided not to move in that direction originally), and I'm trying to determine how one could actually do the tests that you are wanting and then do the power calculations that are needed for that hypothesis test.

As the proposal is currently written, you've described an analysis and a set of power calculations for a study set up as follows. You have two independent cohorts of individuals, one of which has extubated participants based on the results of a positive clinical test and one of which has extubated participants based on the result of a positive SBT. However, that study is not the one that we're doing. In our study, we have a single cohort of individuals, specifically a cohort of individuals that is "positive" on some set of clinical criteria. Within that cohort, we are dividing the cohort into two sub-cohorts, those that are positive for SBT and those that are negative for SBT. As such, the only hypotheses that I know how to test are those associated with the different sub-cohorts, not those comparing a sub-cohort to the total cohort being tested. I think that's why we didn't try to do a hypothesis test initially, as we thought that the operating characteristics of the SBT were a more interesting question than testing hypotheses about individuals who were positive on the SBT and those who were negative on the SBT.

Given the concerns outlined in the paragraph above, my preference would be to maintain the

original focus on the characterization of the operating characteristics of the SBT. However, if you think that we are going to have to do hypothesis testing to move this forward, we'll need to frame the hypothesis tests in terms of the two sub-cohorts (at least that's the only way that I see to do it easily without having all sorts of complications). In doing so, testing whether the probability of successful extubation is higher in individuals with a positive SBT than in individuals with a "positive" clinical test, with the data that we have is equivalent to testing whether the probability of a successful extubation is higher in individuals with a positive SBT than in individuals with a negative SBT. I did some quick calculations based on the information that I saw in the latest version of the proposal. If I understand that proposal correctly, you think we will have approximately 370 subjects available for this cohort study. Under the assumption that 70% or 80% of those individuals will have a positive SBT, the sample sizes for the two sub-cohorts (positive, negative) would be (259, 111) and (296, 74). Under these assumptions and taking the numbers in the table in the latest proposal if you assume that the success among those with positive SBT is 10% greater than success in the total cohort (with total cohort success in the range of 60% to 75 %) then success in those with a negative SBT will only be in the range of 20% to 50%. Thus the difference in success between those with positive SBT and those with negative SBT is generally in the range of 30% to 50%. With the sample sizes shown, you have a very large power (always greater than 95%) to show that difference. Again, I don't find that these hypothesis tests are nearly as interesting as the operating characteristics of the screening tool, but if the group thinks that the primary aim should be to test successful extubation in those who have a positive test to those who have a negative test, then you have an excess of power to do that.

I need to spend this afternoon getting ready for another Steering Committee meeting that starts at 8 tomorrow morning, but if you want me to write this up formally, I'm happy to do some other analyses this weekend and try to get that to you next week, but I don't think that the power calculations in the current version reflect that study that you are actually doing.

Dennis

From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
Sent: Thursday, January 26, 2012 4:24 PM
To: Keszler, Martin; Kristi Watterberg; Wallace, Dennis
Cc: Carl_Dangio@URMC.Rochester.edu; Rose (higginsr@mail.nih.gov); Pablo Sanchez
Subject: RE: revised protocol

Thanks, I am waiting for Dennis.

Dennis:
Will you have the time to look at the protocol by tomorrow?
Luc

Luc P. Brion, MD
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Fax: (214) 648-2481
luc.brion@utsouthwestern.edu

From: Keszler, Martin [mailto:MKeszler@Wihri.org]
Sent: Thursday, January 26, 2012 3:22 PM
To: Luc Brion; Kristi Watterberg
Cc: Carl_Dangio@URMC.Rochester.edu; dwallace@rti.org; Rose (higginsr@mail.nih.gov); Pablo Sanchez
Subject: RE: revised protocol

Looks good, as best as I can sort it out ☺.
Go for it!
Cheers,
M

Martin Keszler MD
Mkeszler@WIHRI.org
(401) 274-1122, x7490

From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
Sent: Monday, January 23, 2012 7:25 PM
To: Keszler, Martin; Kristi Watterberg
Cc: Carl_Dangio@URMC.Rochester.edu; dwallace@rti.org; Rose (higginsr@mail.nih.gov); Pablo Sanchez
Subject: RE: revised protocol

Thanks, Martin.

All:
I attach the revised version, in which I eliminated several manuscripts, which are not needed anymore. I also eliminated Martin's comments except the one for Dennis
Please let me know if you have any additional suggestions by January 27th so I can I send the protocol to the review committee at least one week before the next protocol review standing committee call (February 7th).

Dennis:
Please could you extract the data from SUPPORT as indicated in my previous email sent Fri 1/20/2012 8:58 AM. This information is for the bottom of page 7 of the version without the Word tracking [Results pending from Dennis].
Please let us know if we are planning too many secondary analyses.

Thanks for your help,

Luc

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luc.brion@utsouthwestern.edu

From: Keszler, Martin [mailto:MKeszler@Wihri.org]
Sent: Monday, January 23, 2012 5:37 PM
To: Luc Brion; Kristi Watterberg
Cc: Carl_Dangio@URMC.Rochester.edu; dwallace@rti.org; Rose (higginsr@mail.nih.gov); Pablo Sanchez
Subject: RE: revised protocol

Luc, here are my edits and comments. Sorry I could not get this back to you sooner.
Keep up the good work. We're almost there!
Cheers,
M.

Martin Keszler MD
Mkeszler@WIHRI.org
(401) 274-1122, x7490

From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
Sent: Monday, January 23, 2012 5:14 PM
To: Kristi Watterberg
Cc: Carl_Dangio@URMC.Rochester.edu; Keszler, Martin; dwallace@rti.org; Rose (higginsr@mail.nih.gov); Pablo Sanchez
Subject: RE: revised protocol

Kristi:

Oops! I missed a few more mistakes! Thanks a lot for taking the time to read the documents and thanks your comments.

Kristi: Carl, Martin, Dennis, Rose:

I looked carefully at the printout and edited the text further; corrections should come in blue this

time; this will allow you to detect changes I made today.

Best regards,

Luc

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Fax: (214) 648-2481
luc.brion@utsouthwestern.edu

From: Kristi Watterberg [mailto:KWatterberg@salud.unm.edu]
Sent: Monday, January 23, 2012 2:42 PM
To: Luc Brion
Cc: Carl_Dangio@URMC.Rochester.edu; MKeszler@Wihri.org
Subject: Re: revised protocol

A lot of work in a short time, Luc! A couple of minor points:

Background: this must be a typo: "extubation predicted by a positive SBT was 3/43 (93%), compared with a success rate of 39/50 (78%) in the"

The two statements below seem to conflict - in each, you are looking at the SBT vs. clinical factors to predict successful extubation, even though they're stated a little differently.

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Martin, Carl, Kristi, Dennis, Rose:

Thanks a lot for all the feedback at the meeting.

Here is the updated protocol, taking into account all the suggestions from the protocol review committee and a first draft of the revised sample size analysis (not seen by Dennis yet).

Please let me know your suggestions (if possible by January 27th) so I can I send the protocol to the review committee at least one week before the next protocol review standing committee call (February 7th).

Thanks and best regards,
Luc

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Office: (214) 648-2835
Fax: (214) 648-2481
luc.brion@utsouthwestern.edu

From: Estelle Fischer
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Kurt Schibler
Subject: RE: FW: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)
Date: Thursday, January 26, 2012 4:02:37 PM

Yes..thanks...Hope you as well..e

>>> "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> 1/26/2012 3:24 PM >>>
Estelle –
Nice to hear from you – hope you are doing well and THANKS!!
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Estelle Fischer [mailto:Estelle.Fischer@cchmc.org]
Sent: Thursday, January 26, 2012 3:21 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Kurt Schibler
Subject: Re: FW: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)

Hi Rose:

Please see attached most recent version of the SUPPORT Trial informed consent document.

Thanks,

Estelle E. Fischer, MHSA, MBA
Clinical Research Manager
Division of Neonatology
Children's Hospital Medical Center (MLC 7009)
3333 Burnet Avenue
Cincinnati, OH 45229-3039
Phone: 513.803.0949 Fax: 513.803.0969

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>>> "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> 1/26/2012 2:54 PM >>>
Kurt –

Please send me your most recent SUPPORT Trial consent form today.

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, January 20, 2012 2:39 PM
To: 'Kurt Schibler'
Cc: Maddox, Yvonne (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Hirschfeld, Steven (NIH/NICHD) [E]
Subject: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)

Kurt-
As you are aware the Neonatal Research Network (NRN) continues to support studies under common protocols, but which require individual institutional IRB review prior to the conduct of these studies at each of the NRN sites. This is to inform you that The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), which provided the Federal support to the NRN, has been requested by the Office of Human Subjects Protection, to provide to the Office the most current consent form approved by your IRB and the corresponding IRB approval for the main SUPPORT Study, including any revisions, as soon as possible. As the NICHD Program Director of the NRN, I am requesting that the most recent consent form with IRB approval for your site for SUPPORT be submitted to me as soon as possible, but no later than January 26, 2012. Thank you for your cooperation.

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch

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higginsr@mail.nih.gov

From: Estelle Fischer
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Kurt Schibler
Subject: Re: FW: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)
Date: Thursday, January 26, 2012 3:21:30 PM
Attachments: SUPPORT Trial-CCHMC ICS-04-28-09.doc

Hi Rose:

Please see attached most recent version of the SUPPORT Trial informed consent document.

Thanks,

Estelle E. Fischer, MHSA, MBA
Clinical Research Manager
Division of Neonatology
Children's Hospital Medical Center (MLC 7009)
3333 Burnet Avenue
Cincinnati, OH 45229-3039
Phone: 513.803.0949 Fax: 513.803.0969

>>> "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> 1/26/2012 2:54 PM >>>
Kurt –
Please send me your most recent SUPPORT Trial consent form today.

Thanks
Rose

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From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, January 20, 2012 2:39 PM
To: 'Kurt Schibler'
Cc: Maddox, Yvonne (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Hirschfeld, Steven (NIH/NICHD) [E]
Subject: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)

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Cincinnati Children's

CINCINNATI CHILDREN'S HOSPITAL MEDICAL CENTER CONSENT TO PARTICIPATE IN A RESEARCH STUDY

STUDY TITLE: THE SURFACTANT POSITIVE AIRWAY PRESSURE AND PULSE OXIMETRY TRIAL IN EXTREMELY LOW BIRTH WEIGHT INFANTS (THE SUPPORT TRIAL)

SPONSOR NAME:
National Institutes of Health (NIH) /National Institute of Child Health and Human Development (NICHD)

INVESTIGATOR INFORMATION:

Vivek Narendran, MD	(513)-803-0961	(513) 820-3879
Principal Investigator Name	**Telephone Number**	**24 hr Emergency Contact**

Subject Name: _____ **Date of Birth:** ____/____/____

Throughout this document, references to "You" may stand for either the research study subject or for the parents or legal guardians of the research study subject if the subject is under 18 years of age or otherwise unable to legally give informed consent to participate in the research study. The signature(s) at the end will clarify whether the research study subject is signing this consent form on their own behalf or via a legal guardian or legal personal representative.

INTRODUCTION:

You have been asked to participate in a research study. Before agreeing to participate in this study, it is important that you read and understand the following explanation. It describes, in words that can be understood by a lay person, the purpose, procedures, benefits, risks and discomforts of the study and the precautions that will be taken. It also describes the alternatives available and the right to withdraw from the study at any time. No guarantee or assurance can be made as to the results of the study. Also, participation in the research study is completely voluntary. Refusal to participate will

involve no penalty or loss of benefits to which you are otherwise entitled. You may withdraw from the study at any time without penalty.

WHY IS THIS RESEARCH BEING DONE?

The purpose of this research study is to determine the best way to care for very premature infants to reduce the risk for lung disease and eye disease, and to see whether the treatment your infant receives, as part of this study, will improve breathing during the 6-22 months after his/her expected due date.

Very premature infants less than 28 weeks gestational age often develop lung disease and eye disease which may lead to long term disability or death. This lung disease and eye disease may be caused by the kind of treatment that is used normally in the delivery room and in the nursery. This current treatment can cause either collapse of the lungs or too much expansion of the lungs. This may cause injury to the lung leading to long term lung disease or possibly death.

Too much oxygen in the beginning days of life can cause the blood vessels in the eye to grow abnormally. At the same time, not enough oxygen can adversely affect an infant's growth and brain development. Your infant's oxygen is monitored by a machine called a pulse oximeter. This machine tells ~~us~~ how much oxygen is in the blood stream. The study doctors are trying to find the best oxygen level to prevent these lung and eye diseases.

WHY HAVE YOU BEEN ASKED TO TAKE PART IN THIS RESEARCH STUDY?

You are being asked to take part in this research study because you may deliver your infant early. Infants that are delivered early, or premature, are at a higher risk of developing lung disease and eye disease.

WHO SHOULD NOT BE IN THE RESEARCH STUDY?

- Anyone who delivers outside the hospital center
- Anyone who delivers before 24 weeks gestation or after 28 weeks gestation
- If your infant has a known birth defect

HOW LONG WILL YOUR INFANT BE IN THE RESEARCH STUDY?

Your infant's participation in this research study will last until the age of 22 months. The doctor who is caring for your infant may decide to take your infant off this research study at any time if he/she feels it is necessary.

During that time, we will gather information from your infant's medical record, including results of routine NICU assessments, such as head ultrasounds and ophthalmologic exams.

All infants with a birth weight of ≤ 1500 grams have an eye exam at 32 weeks post menstrual age or 5-6 weeks of age, whichever comes last. For purposes of the SUPPORT Trial, the results of these exams will be recorded until the infant's eyes reach final status. This may include exams after discharge home or transfer to another hospital.

The majority of this study will take place while your infant is in the hospital. Once he/she has been discharged, there will be one more assessment done at a routine 18 - 22 month follow-up visit at the High Risk clinic.

At the follow-up visit, your child will have a basic health check, as well as a neurological examination. After being weighed and measured, your child will meet with the developmental psychometrist, and the Bayley Scales of Infant Development will be administered. All tests are standard tests frequently used in the assessment of child development, child behavior, and neurological function.

The following questionnaires will be completed by the psychometrist through an interview with the caregiver:

1) Socio-Economic Status (SES) at nursery discharge.
2) Socio-Economic Status (SES) at 18 + 4 months of age.
3) Medical History
4) Family Resource Scale - measures the adequacy of different resources in the household.
5) The Brief Infant-Toddler Social and Emotional Assessment (BITSEA).
6) SUPPORT Trial Breathing Outcomes Study: 6 - 12 Month Interview (SUPF02 Rel 1.0)
7) SUPPORT Trial Breathing Outcomes Study: 8 - 22 Month Interview (SUPF03 Rel 1.0)

A more complete description of all these tests is available as an appendix to this consent form if requested. All these tests will be administered by a single developmental psychometrist. All children will be examined in the study program.

WHO IS CONDUCTING THE RESEARCH STUDY?

This study is sponsored by National Institutes of Health (NIH)/National Institutes of Child Health & Human Development (NICHD).

The study is directed by Vivek Narendran, MD, the researcher at Cincinnati Children's Hospital Medical Center.

HOW MANY PEOPLE WILL TAKE PART IN THE RESEARCH STUDY?

Approximately 1345 infants will be asked to take part in this study.

The NICHD Neonatal Research Network has 16 sites taking part in this study. The University Hospital, the Good Samaritan Hospital, and the Cincinnati Children's Hospital comprise the Cincinnati site within the Neonatal Research Network.

WHAT IS INVOLVED IN THE RESEARCH STUDY?

Neither you, nor the researcher conducting this study will know what group your infant will be assigned. Your infant will have a one in four chance of being placed in any group. However, in the event of an emergency, your study doctor will be able to find out which treatment you are receiving.

In the hospital:

If you agree to have your infant participate in this study, he/she will be assigned to one of the four study groups described below. A flip-of-the-coin method will be used to assign infants to a group.

The four study groups are as follow:

- Strong efforts will be made in this group to keep infants off the ventilator (breathing machine) and the infants will be assigned to a lower blood oxygen range of 85% to 89%.
- Strong efforts will be made in this group to keep infants off the ventilator (breathing machine) and the infants will be assigned to a slightly higher blood oxygen range of 91% to 95%.
- Routine standard care will be practiced in this group and infants will be assigned to a lower blood oxygen level of 85%-89%.
- Routine standard care will be practiced in this group and infants will be assigned to a higher blood oxygen level of 91%-95%.

Strong efforts to keep infants off the ventilator include the use of continuous positive airway pressure or CPAP. This provides some pressure to keep the lungs expanded, but allows the infant to breathe on his/her own. Routine standard care will include the use of a ventilator (breathing machine) and a medicine called surfactant. This medicine is put directly in the lungs through the breathing tube in your infant's throat and helps your infant to breathe easier.

Because oxygen affects how well infants grow, measurements of your infant's weight, length and head circumference will be taken from birth until hospital discharge. Nutrition information will also be collected.

Optional:

It is not known whether breathing extra oxygen as treatment for lung problems causes a depletion of anti-oxidants or a build up of oxidants. These substances may alter lung growth and development and make premature babies more likely to wheeze in early childhood. Anti-oxidant levels can be detected in the blood. One milliliter of blood from the placenta will be collected and analyzed for anti-oxidant levels. Two thirds of one milliliter of blood (0.67cc or 13 drops) will also be collected from your infant when he or she is 14 days and 28 days old. The total amount of blood is 1.3 milliliters (1.3 milliliters is equal to 24 drops or approximately one - fifth of a teaspoon) over a 1 month time period. This amount of blood is considered safe for purposes of research by the Federal Government's National Institute of Health. Every attempt will be made to draw these blood samples at the same time as blood testing that is done as part of routine care in the NICU. You may accept or decline this extra blood collection.

☐ Accept ☐ Decline

After discharge:

Once your infant is discharged, we will continue to stay in touch with you and your infant, by telephone, or in person, at one of your routine visits at the High Risk Infant Follow-Up Clinic at Children's Hospital, every six months over the next 6-22 months.

During this routine medical check-up, trained staff will meet with you and your child to ask you some questions, check your child's growth measurements, and check your child's level of development by interacting with him/ her.

There will be a total of 3 study visits or calls during this time. During these clinic visits and/ or telephone calls, we will ask questions about your child's breathing (especially wheezing and coughing), medication use, and visits to a doctor, emergency room, or hospital for treatment of breathing problems. We will also ask you several questions about your family and yourself. Answering the study questions should take about 15 minutes of your time, less if your baby has had no breathing problems.

The telephone calls will be scheduled when your infant is 6, 12, and 18 months after his/her expected delivery at full term. We will schedule the calls at a time that is convenient to you.

The results from your infant's questionnaire will be combined with the results of other infants from around the country; however, your infant's name will not be used.

WHAT ARE THE RISKS AND DISCOMFORTS OF THE RESEARCH STUDY?

Trying to keep infants off the breathing machine, and on CPAP, may lead to: a) an increased respiratory effort, b) brief periods of a pause in their breathing (apnea), and c) higher carbon dioxide in their blood, and d) nasal septum breakdown. Safeguards are in place to monitor these side effects. This may include the use of a ventilator (breathing machine) when appropriate.

Trying to leave infants on the ventilator (breathing machine) may lead to: a) worsening lung injury due to the pressures used by the machine, b) mechanical complications such as obstruction or loss of airway, and c) prolonged hospital stay. Safeguards are in place to monitor these side effects. The doctor will make changes as needed.

For the optional portion of this study, every attempt will be made to draw the blood samples at the same time as blood testing for routine care. In the event that it is necessary to draw blood by venipuncture -- clinical personnel will take the small amount of blood from a vein in your baby's arm or leg by needle stick, or by heelstick. Risks associated with drawing blood from your baby's arm or leg include momentary discomfort and/or bruising. Infection, excess bleeding, clotting, and/or fainting are also possible, although unlikely.

There may be unknown or unforeseen risks associated with study participation.

One of the risks of participating in research is the loss of confidentiality. Please see confidentiality section.

ARE THERE DIRECT BENEFITS TO TAKING PART IN THE RESEARCH STUDY?

There may be a direct benefit to your child participating in this study, in that information about his/ her development may be learned during the 6 -22 month follow-up study period, following discharge from the hospital. This information will be gathered from the assessments and your child's interaction with study personnel during this period.

WHAT OTHER CHOICES ARE THERE?

You may decide to **not** allow your infant to take part in this research. You may choose to have your infant treated with the usual standard medical care as determined by the doctor. If you refuse participation in this study, it will not change your infant's care in the nursery.

If you decide to allow your infant to take part in this research, you will receive any new information during the course of the study concerning significant treatment findings. This may affect your willingness to continue your infant's participation and you may withdraw your infant from the study at any time.

HOW WILL INFORMATION ABOUT YOU BE KEPT PRIVATE AND CONFIDENTIAL?

Every effort will be made to maintain the confidentiality of your medical information and your infant's medical or research information. Medical record information and potentially identifying information such as your infant's name and birth date are classified as "Protected Health Information" or "PHI".

Protected Health Information is defined as health information, whether verbal or recorded in any form (such as on a piece of paper or entered into a computer), that identifies you, or your infant, as an individual, or offers a reasonable basis to believe that the information could be used to identify you or your infant.

Study records that identify your child will be kept confidential as required by law. Federal Privacy Regulations provide safeguards for privacy, security and authorized access. Except when required by law, your child will not be identified by name, social security number, address, telephone number, or any other direct personal identifier in study records disclosed outside of Cincinnati Children's Hospital Medical Center.

By signing this consent form you are giving permission for representatives of the Cincinnati Children's Hospital Medical Center ("CCHMC"), the investigator and CCHMC employees involved with the research study, including the Institutional Review Board and the Office for Research Compliance, and/ or their appointed agent, as well as the National Institutes of Health, to inspect sections of your medical records and your infant's medical and research records related to this study.

When a study is submitted to the FDA, the clinical investigator agrees to allow the FDA access to the study records. The FDA will treat the information as confidential, but on rare occasions disclosure to third parties may be required by law. Therefore, absolute protection of confidentiality cannot be promised or implied.

A Data and Safety Monitoring Board, an independent group of experts, will be reviewing the data from this research throughout the study. The investigator will tell you about new information from this or other studies that may affect your health, welfare, or willingness to stay in this study.

The information from the research study may be published; however, you will not be identified in such a publication. The publication will not contain information about you that would enable someone to determine your identity as a research participant without

your authorization.

Cincinnati Children's Hospital Medical Center and/or the Investigator will take the following precautionary measures to protect your privacy and confidentiality of your research and/or medical records: and those of your infant.

No information such as name, address, telephone number, etc. that could be used to easily identify your infant will be kept as part of the research records.

A copy of this consent form will be included in your infant's medical research record.

Your infant will be registered in the Cincinnati Children's Hospital Medical Center's computer system as a research subject which may be beneficial for future clinical care.

USE AND DISCLOSURE OF YOUR PROTECTED HEALTH INFORMATION

The Protected Health Information described in the section above will be used /disclosed for the purpose of research by CCHMC to the other persons or entities identified above.

"Use" of an individual's health information is defined as the sharing, examination or analysis (break down) of the information that is collected and maintained for the length of the research study.

"Disclosure" of an individual's health information is defined as the release, transfer, providing access to, or to reveal in any other manner, the information outside the persons or entity holding the information as described in the section "How Will Information About You Be Kept Private And Confidential" in this consent form.

Once your Protected Health Information is disclosed, the information may be subject to re-disclosure and may no longer be protected by the federal privacy regulations.

AVAILABILITY OF INFORMATION?

As indicated above, you will receive any new information during the course of the study concerning significant treatment findings.

WHAT ARE YOUR COSTS TO BE IN THIS STUDY?

The procedures of this study are standard methods of caring for premature infants and will be billed to your infant's hospital account. There will be no additional studies or assessments, including head ultrasounds, performed for study purposes only; all studies are clinically indicated.

Funds are not available to cover the costs of any ongoing medical care and you remain responsible for the cost of non-research care.

If you have questions about your medical bill relative to research participation, you may contact Dr. Vivek Narendran by calling (513) 558-0557.

WILL YOU BE PAID TO PARTICIPATE IN THIS RESEARCH STUDY?

There is no payment or reimbursement for participation in this research study.

WHAT COMPENSATION IS AVAILABLE IN CASE OF INJURY?

If you believe that you have been injured as a result of participation in biomedical or behavioral research you are to contact Dr. Vivek Narendran by calling (513) 558-0557 or the Director of Social Services (513-636-4711) to discuss your concerns. Cincinnati Children's Hospital Medical Center follows a policy of making all decisions concerning compensation and/or medical treatment for physical injuries occurring during or caused by participation in biomedical or behavioral research on an individual basis.

WHAT ARE YOUR RIGHTS AS A PARTICIPANT?

Your participation in this study is completely **voluntary**. You may choose either to take part or not to take part in this research study. Your decision whether or not to participate will not result in any penalty or loss of benefits to you and the standard medical care for your condition will remain available to you.

If you decide to take part in the research study, you are **free to withdraw** your consent and discontinue participation in this research study at any time. Leaving the study will not result in any penalty or loss of benefits to you.

You may revoke (choose to withdraw) this Authorization as provided under the Health Insurance Portability and Accountability Act of 1996 (HIPAA") at any time after you have signed it by providing Dr. Vivek Narendran with a written statement that you wish to withdraw this Authorization. Your withdrawal of this Authorization will be effective immediately and your Protected Health Information can no longer be used/disclosed for research purposes by CCHMC and the other persons or entities that are identified in the "Use or Disclosure of Your Protected Health Information" section of this consent, except to the extent that CCHMC and/or the other persons or entities identified above have already taken action in reliance upon your consent. In addition, your Protected Health Information may continue to be used / disclosed to preserve the integrity of this research study.

The investigators will tell you about significant new findings developed during the course of the research and new information that may affect your health, welfare, or willingness to stay in this study.

If you have questions about the study, you will have a chance to talk to one of the study staff or your regular doctor. Do not sign this form unless you have had the chance to ask questions and have received satisfactory answers.

Nothing in this consent form waives any legal rights you may have nor does it release the investigator, the sponsor, the institution, or its agents from liability for negligence.

For further information about your rights, please see CCHMC Notice of Privacy Practices. A copy of the CCHMC Notice of Privacy Practices may be obtained from any patient registration area or online at www.cincinnatichildrens.org (From the internet page select in the following order: About Us, Corporate Information, HIPAA). You may also contact our Privacy Officer at 513-636-4707 to obtain a copy.

ABILITY TO CONDITION TREATMENT ON PARTICIPATION IN THIS STUDY

You have a right to refuse to sign this consent to use/disclose your Protected Health Information for research purposes.

If you refuse to sign this consent, you may not be able to receive research-related treatment.
If you refuse to sign this consent, your rights concerning treatment, payment for services, and enrollment in a health plan or eligibility for benefits will not be affected.

WHOM DO YOU CALL IF YOU HAVE QUESTIONS OR PROBLEMS?

For questions about this research study or to report a research-related injury, you can contact the researcher Dr. Vivek Narendran at (513) 558-0557. Researchers are available to answer any questions you may have about the research at any time.

If you have general questions about your rights as a research participant in this research study, you may call the Cincinnati Children's Hospital Medical Center Institutional Review Board at (513) 636-8039.

CINCINNATI CHILDREN'S HOSPITAL MEDICAL CENTER CONSENT TO PARTICIPATE IN A RESEARCH STUDY

STUDY TITLE: THE SURFACTANT POSITIVE AIRWAY PRESSURE AND PULSE OXIMETRY TRIAL IN EXTREMELY LOW BIRTH WEIGHT INFANTS (THE SUPPORT TRIAL)

INVESTIGATOR INFORMATION:

Vivek Narendran, MD	(513) 558-0557	(513) 820-3879
Principal Investigator Name	Telephone Number	24 hr Emergency Contact

SIGNATURES:

I have read the information given above. The investigator or his/her designee have personally discussed with me the research study and have answered my questions. I am aware that, like in any research, the investigators cannot always predict what may happen or possibly go wrong. I have been given sufficient time to consider if I (or my child) should participate in this study. I hereby consent for myself (or my child) to take part in this study as a research study subject.

_____ Date:_____
Parent/Legal Guardian (Signature)

_____ Date:_____
Parent/Legal Guardian (Signature)

_____ Date:_____
Investigator or specific individual who has been designated to obtain consent (Signature)

_____ Date:_____
Investigator (Signature)

This research study and consent form have been reviewed and approved by the Cincinnati Children's Hospital Medical Center Institutional Review Board (telephone number 513-636-8039).

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "GOLDB008@MC.DUKE.EDU"
Subject: FW: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)
Date: Thursday, January 26, 2012 2:56:00 PM
Importance: High

Ron –

Please send me your most recent SUPPORT Main Trial consent form today.

Thanks

Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, January 20, 2012 2:48 PM
To: 'GOLDB008@MC.DUKE.EDU'
Cc: Maddox, Yvonne (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Hirschfeld, Steven (NIH/NICHD) [E]
Subject: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)

Ron

As you are aware the Neonatal Research Network (NRN) continues to support studies under common protocols, but which require individual institutional IRB review prior to the conduct of these studies at each of the NRN sites. This is to inform you that The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), which provided the Federal support to the NRN, has been requested by the Office of Human Subjects Protection, to provide to the Office the most current consent form approved by your IRB and the corresponding IRB approval for the main SUPPORT Study, including any revisions, as soon as possible. As the NICHD Program Director of the NRN, I am requesting that the most recent consent form with IRB approval for your site for SUPPORT be submitted to me as soon as possible, but no later than January 26, 2012. Thank you for your cooperation.

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch

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301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Duara, Shahnaz"
Subject: FW: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)
Date: Thursday, January 26, 2012 2:53:00 PM
Importance: High

Shahnaz –

Please send me your most recent SUPPORT main trail consent form today.

Thanks

Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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301-435-7909
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301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, January 20, 2012 2:40 PM
To: 'Duara, Shahnaz'
Cc: Maddox, Yvonne (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Hirschfeld, Steven (NIH/NICHD) [E]
Subject: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)

Shahnaz-

As you are aware the Neonatal Research Network (NRN) continues to support studies under common protocols, but which require individual institutional IRB review prior to the conduct of these studies at each of the NRN sites. This is to inform you that The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), which provided the Federal support to the NRN, has been requested by the Office of Human Subjects Protection, to provide to the Office the most current consent form approved by your IRB and the corresponding IRB approval for the main SUPPORT Study, including any revisions, as soon as possible. As the NICHD Program Director of the NRN, I am requesting that the most recent consent form with IRB approval for your site for SUPPORT be submitted to me as soon as possible, but no later than January 26, 2012. Thank you for your cooperation.

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higginsr@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Ehrenkranz, Richard"
Subject: FW: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)
Date: Thursday, January 26, 2012 2:52:00 PM
Importance: High

Richard – Can you send me your latest SUPPORT main Trial consent today? Thanks
Rose

Rosemary D. Higgins, MD
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301-496-5575
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higginsr@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, January 20, 2012 2:38 PM
To: 'Ehrenkranz, Richard'
Cc: Maddox, Yvonne (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Hirschfeld, Steven (NIH/NICHD) [E]
Subject: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)

Richard-
As you are aware the Neonatal Research Network (NRN) continues to support studies under common protocols, but which require individual institutional IRB review prior to the conduct of these studies at each of the NRN sites. This is to inform you that The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), which provided the Federal support to the NRN, has been requested by the Office of Human Subjects Protection, to provide to the Office the most current consent form approved by your IRB and the corresponding IRB approval for the main SUPPORT Study, including any revisions, as soon as possible. As the NICHD Program Director of the NRN, I am requesting that the most recent consent form with IRB approval for your site for SUPPORT be submitted to me as soon as possible, but no later than January 26, 2012. Thank you for your cooperation.

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301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Zaterka-Baxter, Kristin"
Subject: RE: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)
Date: Thursday, January 26, 2012 11:46:00 AM

She had included me on the email – I have asked Ben to send me the pdf
Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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higginsr@mail.nih.gov

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Thursday, January 26, 2012 11:46 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)

Just FYI

Kris Zaterka-Baxter, RN, BSN, CCRP
RTI International
Res Clinical Study Specialist

3340 Cornwallis Rd
Research Triangle Park, NC 27709
Phone: 919-485-7750
Fax: 919-485-7762

From: Abramczyk, Kathleen [mailto:kabramc@med.wayne.edu]
Sent: Thursday, January 26, 2012 11:29 AM
To: Shankaran, Seetha; :; Zaterka-Baxter, Kristin
Cc: Bara, Rebecca
Subject: RE: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)

The most recent consent(3/25/2009) and IRB approval(expires6/6/2012) for SUPPORT have been faxed to Dr. Higgins and K. Zaterka-Baxter.
KathyA

From: Shankaran, Seetha
Sent: Thursday, January 26, 2012 10:50 AM

To: Abramczyk, Kathleen
Subject: FW: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)

Kathy
Can you pl do today
Seetha

Seetha Shankaran, MD
Professor of Pediatrics
Wayne State University School of Medicine
Director, Division of Neonatal/Perinatal Medicine
Children's Hospital of Michigan and
Hutzel Women's Hospital
313-745-1436 (o)
313-745-5867 (f)
sshankar@med.wayne.edu

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, January 20, 2012 2:40 PM
To: Shankaran, Seetha
Cc: Maddox, Yvonne (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Hirschfeld, Steven (NIH/NICHD) [E]
Subject: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)

Seetha
As you are aware the Neonatal Research Network (NRN) continues to support studies under common protocols, but which require individual institutional IRB review prior to the conduct of these studies at each of the NRN sites. This is to inform you that The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), which provided the Federal support to the NRN, has been requested by the Office of Human Subjects Protection, to provide to the Office the most current consent form approved by your IRB and the corresponding IRB approval for the main SUPPORT Study, including any revisions, as soon as possible. As the NICHD Program Director of the NRN, I am requesting that the most recent consent form with IRB approval for your site for SUPPORT be submitted to me as soon as possible, but no later than January 26, 2012. Thank you for your cooperation.

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Hoult, Ben (NIH/OD) [E]
Subject: FW: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)
Date: Thursday, January 26, 2012 11:33:00 AM

Ben –
Can you scan and email me the FAX from Kathy from Wayne State??
thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Abramczyk, Kathleen [mailto:kabramc@med.wayne.edu]
Sent: Thursday, January 26, 2012 11:29 AM
To: Shankaran, Seetha; Higgins, Rosemary (NIH/NICHD) [E]; kzaterka@rti.org
Cc: Bara, Rebecca
Subject: RE: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)

The most recent consent(3/25/2009) and IRB approval(expires6/6/2012) for SUPPORT have been faxed to Dr. Higgins and K. Zaterka-Baxter.
KathyA

From: Shankaran, Seetha
Sent: Thursday, January 26, 2012 10:50 AM
To: Abramczyk, Kathleen
Subject: FW: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)

Kathy
Can you pl do today
Seetha

Seetha Shankaran, MD
Professor of Pediatrics
Wayne State University School of Medicine
Director, Division of Neonatal/Perinatal Medicine
Children's Hospital of Michigan and
Hutzel Women's Hospital
313-745-1436 (o)
313-745-5867 (f)

sshankar@med.wayne.edu

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: 20120125163811072.pdf - Adobe Acrobat Professional
Date: Thursday, January 26, 2012 7:47:00 AM
Attachments: 20120125163811072.pdf

Here is Brown's consent form

Rose

Project Title: The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

A: The nature, duration and purpose of study.

You are being asked to give permission for your baby to participate in a research study designed to determine the best way to decrease the severity of the lung disease and eye disease common in premature babies by comparing two methods of treatment currently used in hospitals in the U.S. 1) Continuous Positive Airway Pressure or CPAP (the pressure used to keep the lungs inflated between breaths) after birth or 2) Ventilation (breathing machine) and *surfactant* (a liquid medication placed into the breathing tube) after birth.

We will also be studying the ranges of oxygen saturation that are currently being used with these same babies. You and your baby were selected as possible participants because you are less than 28 weeks pregnant and your baby may be born prematurely. The doctors at Women & Infants' Hospital along with 15 other centers across the country, are participating in this project sponsored by the National Institute of Child Health and Development. The duration of the study is until the infant is discontinued from oxygen; however, your infant will be followed throughout his/her hospital stay. In order to see if your infant's breathing improves as a result of the treatment received in this study we will ask you a few questions prior to your infant's discharge from the hospital and also at 6, 12 and 18-22 months corrected age. These questions will take about 10-20 minutes to complete.

If your baby is born prematurely he/she will be at risk for a breathing problem called **Respiratory Distress Syndrome (RDS).** A baby's lungs are made up of tiny lung sacs; each one is supposed to open and close as the baby breathes in and out. Oxygen is supposed to go in and carbon dioxide is supposed to come out. This works well in full term babies and adults. However, in premature babies, the lungs do not always work this way. Some lung sacs open and close normally and others collapse and stick together when the baby breathes out making it harder for the baby to breathe. Doctors treat this problem with expanding breaths and pressure to keep the lungs slightly inflated between those breaths. Keeping a little air pressure after the baby breathes out (inflating pressure) makes it easier for the baby to take the next breath.

After your baby is born, if he/she needs help breathing, the doctor or respiratory therapist may place a breathing bag over the baby's nose and mouth to provide oxygen and manual breaths. Sometimes a device called a Neopuff is used to force air into the baby's lungs. This inflating pressure is called Continuous Positive Airway Pressure or CPAP. Some hospitals use CPAP at birth and others use ventilation and surfactant. If a baby needs to be ventilated (placed on a breathing machine) *surfactant* is usually given through a breathing tube into the baby's windpipe to try to help keep the lung sacs expanded.

Another part of the study will be looking at the ranges of oxygen saturation that are currently being used with premature infants and how it affects their eyes. Doctors, nurses and others taking care of your baby use a machine called a pulse oximeter in routine daily care to help them adjust the oxygen to meet the baby's needs. Sometimes higher ranges are used and sometimes lower ranges are used. All of them are acceptable ranges used in different institutions. In this part of the study we would like to pinpoint the exact range that should be used to help prevent some of the problems that occur with premature babies such as Retinopathy of Prematurity (ROP). This is when there is abnormal blood vessel growth in the eye. It causes scar tissue to build up around the retina and if it pulls on the retina hard enough it can cause blindness. It is known that ROP is increased by prolonged use of supplemental oxygen. At the same time, not enough oxygen can affect growth and development. The study doctors are trying to find the best oxygen level to prevent lung and eye disease.

B: The means by which it is conducted.

If your baby is born before a gestational age of 28 weeks, he/she will be randomly (like the toss of a coin) assigned to one of 4 groups:- 1) Early CPAP/Low oxygen saturation ranges, 2) Early CPAP/High oxygen saturation ranges, 3) Early Ventilation and surfactant /Low oxygen saturation ranges and 4) Early Ventilation and surfactant/High oxygen saturation ranges.

If your baby is assigned to early CPAP he/she will be treated with CPAP in the delivery room and will remain on it upon admission to the nursery. If, at any time your baby shows signs of needing intubation (a breathing tube in the windpipe) for breathing purposes, then he/she will be intubated. If this happens within the first 48 hours he/she will also be given surfactant.

If your baby is assigned to early Ventilation and surfactant he/she will be placed on a ventilator (breathing machine) in the delivery room and will be given surfactant into the lung within the first hour of birth.

For the first 14 days of life, there will be guidelines for the doctors in the nursery to follow. These guidelines help them decide when to place babies on the breathing machines and when to try and take them off the breathing machines. These guidelines will also help decide when to put them on and take them off of CPAP.

The babies in this study will also be randomly placed into a group monitored with lower oxygen saturations ranges or higher saturation ranges. Oxygen saturation is measured on a baby with a machine called a pulse oximeter. It uses a tiny sensor on the hand or foot of the baby and can give the doctors a measurement of how saturated the baby's blood is with oxygen. Oximeters are not painful and can provide oxygen saturation measurements 24 hours a day. The babies assigned to the lower oxygen saturation range will have a target saturation of 85%-89%, while the babies in the higher oxygen saturation range will have a target saturation of 91% to 95%. All of these saturations are considered normal ranges for premature infants.

The pulse oximeters used in this trial are FDA approved and have been modified for research purposes. This modification makes the monitors show a value which is either slightly higher or slightly lower than the true oxygen level when values are between 85% and 95%. Outside those ranges, the oximeter works the same as the standard of care device. If the saturation falls below 85% or goes higher than 95% then the pulse oximeter will alarm so that the doctors and nurses know when to turn your baby's oxygen up or down. This modification prevents the nursery staff from knowing which group your baby is in so that all infants are treated in an identical fashion.

If your baby is requiring oxygen therapy close to 36 weeks gestational age a test will be done to determine the severity of his or her lung disease. During this evaluation the oxygen given will be decreased gradually while continuously measuring the amount of oxygen in the blood using a standard pulse oximeter. If a saturation falls below an acceptable range, your child will be returned to the prior oxygen level.

You will also be contacted by a Follow –Up staff member at 6 and 12 months corrected age to ask you questions about your baby's breathing (especially coughing and wheezing), medication use, and visits to a doctor, Emergency Room, or Hospital for treatment of breathing problems. We will also ask you several questions about your family and yourself. As with all information we collect, the answers to these questions will be kept confidential and no names will be used.

Follow up at 18 months of age is essential for this study. The follow up visit will include a medical history, growth measurements, neurological exams including testing reflexes, developmental assessments and some questions about your baby's breathing and breathing symptoms similar to those asked at 6 and 12 months corrected age. This visit will take approximately 1.5 to 2 hours. Families who participate in this project are agreeing to remain in contact with the investigators and to return to the Neonatal Follow up Clinic with their child when he/she is 18 months of age. In order to successfully evaluate any eye disease your baby may develop the investigators will also want to follow up with your

baby's eye doctor after discharge and obtain the results of your baby's eye exams until the eye results are final.

C: The possible benefit

The investigators do not promise or guarantee that your baby will receive direct benefit from being in the study. There may be benefits to your baby directly, including a possible decrease in chronic lung disease (need for oxygen near discharge) and/or a decrease in the need for eye surgery as a result of exposure to oxygen. Because we do not know in advance which treatment strategies are most effective, it is also possible that your baby will receive no direct benefit. However, as noted above, each of the 4 possible combinations of treatments is considered by some units to represent their desired approach.

D: The potential risks, and discomforts.

Because all of the treatments proposed in this study are standards of care at different hospitals across the country there is no predictable increase in risk for your baby. Infants randomized to the Early CPAP group may, at some point in their care, require intubation and assisted ventilation (methods to help them breathe). Participation in this study will not affect this decision if the attending physician deems it necessary. Some unknown risks may be learned during the study. If this occurs, you will be informed by the study personnel.

E: Alternatives

If you do not want your baby to participate in this study, he/she will receive routine care given in the delivery room and nursery which may or may not include the use of CPAP and/or surfactant administration. He/she will most likely have oxygen saturation measured with a pulse oximeter as well.

Project Title: **The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants**

1. I have been told about this study. The experimental procedures have been discussed with me. I have had a chance to ask questions. My questions were answered to my satisfaction.

2. I authorize my confidential, protected health care information to be shared with individuals, persons and groups associated with this study. My confidential health care information will be used only as necessary to participate in this study. Except when required by law, I will not be identified in study records disclosed outside of Women & Infants' Hospital by name, social security number, address, telephone number, or any other direct personal identifier. For records disclosed outside of Women & Infants' Hospital the investigator or his staff will assign me a unique identifying code. The key to the code will be kept in a locked file in Dr. Laptook's research office.

3. I authorize as part of the study that Dr. Abbott Laptook and his study team) report the results of study related laboratory tests and x-rays to the study sponsor the National Institute of Child Health and Development(NICHD) and the Data Coordinating Center (Research Triangle Institute) . These would include laboratory tests such my baby's blood counts and tests to measure e.g; liver and kidney function and all x-rays or ultrasound, CT or MRI scans and the results of all my baby's eye exams. Information may have to be released when required by law when reasonable cause is shown under government regulations, or proper judicial orders. It may also be released to an official of the United States Food and Drug Administration, the United States Department of Health and Human Services, the United States Inspector General, the United States Office of Civil Rights, representatives of the NICHD and the Research Triangle Institute and the Women & Infants Hospital and its Institutional Review Board. If my research record is reviewed by any of these groups, they may also need to review my entire medical record. If disclosed by the sponsor, the information is no longer covered by the federal privacy regulations.

4. I authorize the retention of the study results in my child's research record (until the child reaches the age of 21). At the end of this retention period, either the research information not already in the child's record will be destroyed or information identifying the child will be removed from such study results. Any research information in the child's record will be kept indefinitely.

5. Any information from the study will be used for education or research purposes. My child's or my name will not be used.

6. I will be told of any changes to the risks or benefits of this study.

7. I do not have to take part in this study.
   I do not have to authorize use of my confidential, protected health information.
   My authorization to share my protected, personal health information expires after 21 years.

8. I am free to withdraw my consent at anytime. I am free to stop taking part in the study at any time. I will still receive the best care possible for me and/or my child. If I want to withdraw I should contact Dr. Abbott Laptook in writing and let him know I am withdrawing. His mailing address is Pediatric Suite, Women & Infants' Hospital, 101 Dudley Street, Providence, RI, 02905. If I withdraw my consent or permission the information which has already been collected about me or my child by the Hospital or the researchers will be kept by the researchers or hospital. This information may be needed to complete reports of this research.

Project Title: **The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants**

9. In the event that injury occurs as result of this research, I am requested to notify the Principal Investigator Dr. Abbott Laptook at 401-274-1122, extension 1221.
Should I be injured in a research project, treatment will be provided at Women & Infants Hospital, or at another appropriate health care institution, at no cost to me beyond that which third party payers will cover.
Further information in regard to this may be obtained from Barbara Riter, Manager, Research Administration, whose telephone number is (401)-453-7677.

10. If I have questions about this study, I may call Dr. Abbott Laptook at 401-274-1122, extension 1221.If I have questions about my rights as a research subject, I may call Barbara Riter, Manager, Research Administration, at (401) 453-7677.

11. I will be given a copy of this signed consent form.

Future Contact: I have initialed whether I authorize the researchers to contact me:

_____I authorize the researchers to contact me in the future for research purposes.

Signature: _____ Date: _____ Time: _____ AM / PM

Name (please print):_____

Name of Translator (if used): _____

Translator's signature: _____

If not for self: relationship to patient: _____

Person who explained study: _____ Date: _____

Hospital policy states that the signed original consent form is to be included in the subject's medical record. One copy of the original signed consent form is to be given to the subject. One copy of the signed original consent form should be retained in the investigator's files.

From: Rich, Wade
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: Pediatrics - 2011-2121.R1
Date: Wednesday, January 25, 2012 4:57:02 PM

FYI,
Wade

-----Original Message-----
From: onbehalfof+ksparks+aap.org@manuscriptcentral.com
[mailto:onbehalfof+ksparks+aap.org@manuscriptcentral.com] On Behalf Of ksparks@aap.org
Sent: Wednesday, January 25, 2012 1:44 PM
To: Rich, Wade
Subject: Pediatrics - 2011-2121.R1

25-Jan-2012

RE: 2011-2121.R1 - Enrollment of ELBW Infants in a Clinical Research Study May Not Be Representative

Dear Mr. Wade Rich:

Pediatrics is pleased to announce the early release of your article in eFirst pages on February 27, 2012. This will be your definitive publication date. The media embargo will lift at 12:01 a.m. ET on the day of publication.

Under the title of each online article, you will see a string like this: doi: 10.1542/peds.2008-1536 This is the Digital Object Identifier (DOI) number; the doi follows the life of an article.

Articles can be cited using the DOI. For more information on using DOIs to cite articles, visit www.doi.org.

To cite your online, published ahead of print article, use this format:

Author(s), Article Title, Pediatrics published online: date (doi: 10.1542/peds.year.4-digit number)

Congratulations on your forthcoming publication.

Sincerely,

Lewis R. First, MD
Editor-in-Chief
Pediatrics Editorial Office
University of Vermont College of Medicine
89 Beaumont Ave, Given D201
Burlington, VT 05405-0068
Telephone: 802.656.2505
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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: SUPPORT consent
Date: Wednesday, January 25, 2012 4:46:00 PM

- I think we need the following:

- Wayne State
- Miami
- Cincinnati
- Yale
- Duke

Is this right??

I will send reminders

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Archer, Stephanie (NIH/NICHD) [E]
Sent: Tuesday, January 24, 2012 11:36 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT consent

OK. Still missing:

- Wayne State
- Miami
- Emory
- Cincinnati
- Yale
- Brown
- Duke
- Rochester
- Tufts
- Iowa

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tuesday, January 24, 2012 11:06 AM
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: SUPPORT consent

We only need the most recent (2009)

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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CDBPM, NIH
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Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Archer, Stephanie (NIH/NICHD) [E]
Sent: Tuesday, January 24, 2012 10:55 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT consent

Do you only want the one from 2009 for Alabama, or all of the ones they sent?

Stephanie Wilson Archer
The Eunice Kennedy Shriver
National Institute of Child Health and Human Development
Pregnancy & Perinatology Branch
6100 Executive Boulevard, Room 4B03
Rockville, MD 20852

Tel. 301-496-0430
Fax 301-496-3790
archerst@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tuesday, January 24, 2012 9:58 AM
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: SUPPORT consent

here is what I have so far - can you save to the N drive and print a hard copy of each?
Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch

CDBPM, NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Buchanan, Lisa (HHS/OASH)
Cc: Borror, Kristina C (HHS/OASH)
Subject: RE: "SUPPORT Trial" (HHS Protocol 2U10HD034216)
Date: Wednesday, January 25, 2012 4:43:00 PM

Hi,

We have most of these and are going to send to you on Friday – can I use the address below for Fed EX?

Division of Compliance Oversight
Office for Human Research Protections
1101 Wootton Parkway, Suite 200
The Tower Building
Rockville, MD 20852

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Buchanan, Lisa (HHS/OASH)
Sent: Monday, January 09, 2012 11:40 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Borror, Kristina C (HHS/OASH)
Subject: "SUPPORT Trial" (HHS Protocol 2U10HD034216)

Good morning Dr. Higgins,

I am reviewing responses' to allegations of noncompliance with Department of Health and Human Services (HHS) regulations for the protection of human research subjects (45 CFR Part 46) involving the above-referenced research. OHRP has only opened its investigation with the University of Alabama. However, we would like to review the informed consent documents for all of the sites (~20). The data coordinating center, RTI, recommended that we contact you for this information. (See email below.) Would it be possible for you to provide copies of all the most recent IRB-approved informed consent documents from the different sites in the SUPPORT study?

Please feel free to contact me if you have any questions regarding this request.

Thanks,
Lisa

Lisa Buchanan, MAOM
Public Health Analyst, Division of Compliance Oversight
Office for Human Research Protections
Department of Health and Human Services
1101 Wootton Parkway, Suite 200
Rockville, MD 20852
Ph: 240-453-8298
Fax: 240-453-6909

From: Borasky, David [mailto:dborasky@rti.org]
Sent: Thursday, August 04, 2011 12:19 PM
To: Borror, Kristina C (HHS/OASH)
Cc: Caddell, Juesta M.
Subject: RE: clarification requested

Hi Kristina –

We had a chance to discuss your request with the RTI DCC folks this morning and how RTI may be able to help facilitate this for OHRP.

As I mentioned this morning, the RTI IRB does not require the DCC to provide RTI IRB with copies of the approved informed consent documents for each site. I did confirm that the DCC requires sites to submit copies of study approval notices to the DCC, but they do not require submission of copies of site-level informed consent documents to the DCC. Some site do include them with the approval notices, but this is not done consistently and may not be done every time a consent document is amended at the site level. Therefore, the DCC's records for site-level consent documents are incomplete.

The RTI IRB and the Neonatal Research Network DCC appreciate your desire to expeditiously obtain site-level informed consent documents for the SUPPORT Trial. We believe that the best way to facilitate this is to have OHRP submit a formal request to the Neonatal Research Network steering committee via the NICHD project officer Rosemary Higgins (contact information below) to have the RTI Data Coordinating Center collect copies of the final approved consent forms (as well as whether or not this is the initially approved documents or all versions that were used with participants for the duration of the study) for each of the SUPPORT Trial sites for transmittal to OHRP.

I hope this is a suitable approach.

Best,

Dave

Dr. Higgins contact information:

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
6100 Executive Blvd., Room 4B03
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Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

****

David Borasky, MPH, CIP
Office of Research Protection
RTI International
3040 Cornwallis Rd
RTP, NC 27709
USA

Phone: 919-316-3903
Fax: 919-316-3897
E-mail: dborasky@rti.org

From: Borror, Kristina C (HHS/OASH) [mailto:Kristina.Borror@hhs.gov]
Sent: Friday, July 29, 2011 4:23 PM
To: Borasky, David
Cc: Caddell, Juesta M.
Subject: RE: clarification requested

Dave,
We were wondering if you would be able to get us copies of all the most recent IRB-approved informed consent documents from the different sites in the SUPPRT study. Is that possible?
Thanks for your assistance.
Kristina

From: Borasky, David [mailto:dborasky@rti.org]
Sent: Monday, July 25, 2011 1:13 PM
To: Borror, Kristina C (HHS/OASH)
Cc: Caddell, Juesta M.
Subject: RE: clarification requested

Thank you for the quick response Kristina.

RTI was not engaged in the conduct of the SUPPORT clinical protocol nor would have been considered the IRB of record. RTI serves as the network data coordinating center for all sites, and in this role received coded data for analysis.

Therefore, as per your email, we will not submit a response to the letter dated July 18, 2011.

Regards,

Dave

****

David Borasky, MPH, CIP
Office of Research Protection
RTI International
3040 Cornwallis Rd
RTP, NC 27709
USA

Phone: 919-316-3903
Fax: 919-316-3897
E-mail: dborasky@rti.org

From: Borror, Kristina C (HHS/OASH) [mailto:Kristina.Borror@hhs.gov]
Sent: Monday, July 25, 2011 1:00 PM
To: Borasky, David
Cc: Caddell, Juesta M.
Subject: RE: clarification requested

Dave,
If RTI is not engaged in the research, we do not require any additional information at this time. We'll let you know if we need anything else.

Kristina C. Borror, Ph.D.
Director
Division of Compliance Oversight
Office for Human Research Protections
1101 Wootton Parkway, Suite 200
The Tower Building
Rockville, MD 20852
email: kristina.borror@hhs.gov
Phone: (240) 453-8132
Fax: (240) 453-6909

From: Borasky, David [mailto:dborasky@rti.org]
Sent: Monday, July 25, 2011 11:10 AM
To: Borror, Kristina C (HHS/OASH)
Cc: Caddell, Juesta M.
Subject: clarification requested

Good morning Kristina,

On Friday we (RTI) received a letter from you that was addressed to both our signatory official (Ward Sax) and the SO of UAB (Dr. Marchase) related to the SUPPORT trial. However, we noticed that the letter's salutation was only addressed to Dr. Marchase.

For the SUPPORT Trial (and for the entire Neonatal Research Network) RTI serves as the data coordinating center and we have no oversight of the clinical research. We receive and analyze coded data, and do not have access to the code linking subjects to identifiers.

Given our role and that we are not in the salutation, we assume that OHRP does not expect a formal response from RTI. Would you please confirm if our assumption is correct, and if not, provide guidance on what OHRP would want RTI to provide given our role with the SUPPORT Trial? I leave on vacation tomorrow, so if you could reply to all I would appreciate it. Juesta Caddell is the Director of our IRB office and is the HPA on our FWA.

Thank you.

Dave

****

David Borasky, MPH, CIP
Office of Research Protection
RTI International
3040 Cornwallis Rd
RTP, NC 27709
USA

Phone: 919-316-3903
Fax: 919-316-3897
E-mail: dborasky@rti.org

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: Bell_SUPPORT_consent 5-19-08
Date: Wednesday, January 25, 2012 2:02:00 PM
Attachments: Bell_SUPPORT_consent 5-19-08.rtf

INFORMED CONSENT DOCUMENT

Project Title: **The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants**

Research Team: **Edward Bell, MD**
Michael Acarregui, MD
Gretchen Cress, BSN, RN
Karen Johnson, BSN, RN
Laura Knosp, BSN, RN
Nancy Krutzfield, MSN
Ruthann Schrock, BSN
John Widness, MD
Sara Scott, BSN, RN

This consent form describes the research study to help you decide if you want to participate and allow your child to participate. This form provides important information about what you will be asked to do during the study, about the risks and benefits of the study, and about your rights as a research subject.

- If you have any questions about or do not understand something in this form, you should ask the research team for more information.
- You should discuss your participation with anyone you choose such as family or friends.
- Do not sign this form unless the study research team has answered your questions and you decide that you want to be part of this study.
- Your decision will not affect your infant's right to medical care that is not research-related.

WHAT IS THE PURPOSE OF THIS STUDY?

This is a research study. We are inviting you and your child to participate in this research study because there is a possibility that he/she will be born 12-16 weeks early (at 24 to 28 weeks of pregnancy).

There are 5 purposes of this research study:

- The first is to compare two ways of helping babies who were born prematurely and have difficulty breathing. One way is by using a mask or tube in the baby's nose, called CPAP (continuous positive airway pressure) to assist the baby with his/her breathing immediately after birth and continuing in the NICU. The second way is using a breathing tube in the baby's windpipe, mechanical ventilation and a drug called surfactant, which is given into the breathing tube. We will compare these two to see if there is a difference in the amount of breathing help the babies require and how long they will continue to need this help during the first two weeks of life.
- The second purpose is to compare babies who have oxygen saturations kept in the high end of the normal range with babies who have oxygen saturations kept in the low end of the normal range.
- The third purpose is to compare brain imaging by ultrasound and magnetic resonance imaging (MRI), done around the time when a baby would normally be born, to determine if one method of imaging gives more useful information than the other.

- The fourth purpose is to compare outcomes of babies in the two oxygen saturation ranges after they go home, particularly in regards to any wheezing or chronic coughing they might have.
- The fifth purpose is to compare outcomes of babies in the two oxygen saturation ranges after they go home, particularly in regards to their growth.

HOW MANY PEOPLE WILL PARTICIPATE?

Approximately 75 babies and their mothers will take part in this study at the University of Iowa. This study is being conducted at 15 other centers, and the total number of babies and mothers in all the centers combined will be approximately 1300.

HOW LONG WILL I BE IN THIS STUDY?

If you agree for yourself and your baby to take part in this study, your involvement will last until your baby is 18-22 months old.

WHAT WILL HAPPEN DURING THIS STUDY?

A few minutes before your baby is born, (s)he will be randomly assigned, like the flip of a coin, to either the "CPAP" group or "Intubation" group to manage his/her breathing immediately after birth.

The first assignment will determine his/her care in the delivery room as follows:
If your baby is randomized to the CPAP group, a mask or tube in the nose will be used immediately after birth to assist your baby with his/her breathing in the delivery room and continued when he/she is admitted to the NICU. If your baby requires more help with his/her breathing, a breathing tube will be placed in the windpipe and the ventilator used. Your baby will receive all routine care for premature babies with breathing problems. This may include giving a medication called surfactant into the lungs through the breathing tube.
If your baby is randomized to the Intubation group, your baby will have a breathing tube placed in the windpipe in the delivery room and will be admitted to the NICU. Your baby will receive all routine care for premature babies with breathing problems. This will include giving a medication called surfactant into the lungs through the breathing tube.

The second treatment assignment will determine which end of the normal oxygen saturation range (high or low end) will be used as follows:
When your baby is admitted to the NICU, he/she will be randomized (assigned by chance similar to the flip of a coin) to be kept in a certain oxygen saturation range. This will determine if your baby will have his/her oxygen saturation level kept in the high or low part of the normal oxygen saturation range. The study oximeter (blood oxygen monitor) will be used for as long as your baby is requiring oxygen and until he/she has been in room air (no extra oxygen) for at least 3 days. We don't know which level is best for premature infants and that is why we're doing the study.

Other aspects of your infant's care will be the standard treatments for premature babies in the UIHC

NICU.

All babies in the study will have the following:

We will measure your baby's weight (using the scale routinely used), length (using a special board to measure premature babies), and head circumference (using the paper measuring tape routinely used) when he/she is 7, 14, 21 and 28 days old, at the time your baby is 32 weeks gestation (about 8 weeks before his/her due date), at the time your baby is 36 weeks gestation (about 4 weeks before his/her due date) and right before he/she is discharged.
All babies born prematurely at UIHC routinely have ultrasounds of their heads. Your baby will have the routine ultrasounds of his/her head as well as a test called a MRI (Magnetic Resonance Imaging) study. The ultrasound is a painless procedure where a probe is placed on your baby's soft spot and a picture is made by sound waves. The MRI is a specialized brain scan that takes detailed pictures of the brain structure and can detect normal and abnormal brain tissue. It is very likely that we will need to sedate your baby (giving medication to help relax him/her) during the procedure. The MRI will be done around the time when your baby would normally have been born. Your baby will be swaddled and monitored throughout the procedure.

All babies who participate in the project will return to the UIHC High Risk Infant Follow-up Clinic at regular intervals during the first two years. When the children enrolled in this study return for their 18-22 month old assessments of growth and development, the study will collect information at that visit. The information collected will include who takes care of your baby, what their marital status is, what their income and medical insurance are, who lives in the household with the baby, the baby's medical history, and the results of the physical exam and developmental testing.

To learn about the breathing outcomes of babies in the study, we will interview you before your baby is discharged from the hospital. At this interview, we will ask you questions about your family, including questions about family history of breathing problems, and questions about your home, including things that may increase your child's risk of breathing problems. The interview will take about 15 minutes.

We will continue to stay in touch with you and your infant by telephone or in person at one of your visits every 6 months over the next 18-22 months, a total of three times. At these times, we will ask questions about your child's breathing (especially wheezing and coughing), medication use, and visits to a Doctor, Emergency Room, or Hospital visits for treatment of breathing problems. We will also ask you several questions about your family and yourself. You do not need to answer any questions that make you uncomfortable. The entire call should take about 15 minutes of your time, less if your baby has had no breathing problems.

We will schedule the telephone calls at a time that is convenient for you. The telephone calls will occur when your infant is 6, 12, and 18 months after his/her expected delivery at full term.

The following chart is a summary of what will happen and when:

At Delivery	Days of Life 7, 14, 21, 28, 32 weeks, 36 weeks
CPAP or Intubation with Surfactant Higher or lower oxygen saturation assignment Ends at 14 days of life	Measurements (weight, length, head)
35 to 42 weeks gestation (around "term")	**At discharge**
Head ultrasound and MRI	Measurements (weight, length, head)
6 months of age, 12 months of age	**18-22 months of age**
Interview (by phone or in person)	Interview (by phone or in person) High Risk Infant Follow-up Clinic visit

WHAT ARE THE RISKS OF THIS STUDY?

There may be some risks from being in this study. The use of CPAP and intubation in managing infants' breathing are within usual standard of care at UIHC NICU. CPAP and intubation with ventilation have the risk of trauma to the airway, abnormal lung damage by air getting into the tissues, and the possibility that the tube may cause air to get into the stomach.

During the brain MRI we will need to attach monitors to your infant to keep track of his or her heart rate and respiration. The tape we use to attach the electrodes may cause temporary minor skin irritation The MRI makes a loud, banging noise while it is taking pictures. A set of special earmuffs will be placed over your child's ears to help with the noise. There are no known harmful effects from exposure to magnetic fields (MRI). However, some patients undergoing this procedure become anxious. If sedation is necessary, risks from the medication used include decreased blood pressure and the possibility of breathing difficulty. Your baby's heart rate and respiration will be closely monitored.

Some of the interview questions may make you uncomfortable. You may choose not to answer any or all of the questions

Are there any Unforeseen Risks?

In addition to the risks described above, there may be unknown risks, or risks that we did not anticipate, associated with being in this study.

WHAT ARE THE BENEFITS OF THIS STUDY?

We don't know if you or your baby will benefit from being in this study.

However, we hope that, in the future, other people might benefit from this study because the knowledge learned may help in the understanding of the use of CPAP or a breathing tube to help premature babies with breathing immediately after birth and in the NICU. It may also help us to learn more about premature infants managed in the high and low ends of the normal range of oxygen saturation. We may also gain knowledge about using MRI to detect brain injuries. Finally, knowledge may be gained about the effects of CPAP and oxygen on breathing and growth outcomes of premature infants.

WHAT OTHER TREATMENT OPTIONS ARE THERE?

Before you decide whether or not you want your baby to be in this study, your doctor will discuss the other options that are available to you. Instead of being in this study, you could choose to have your baby treated in the routine way, which may include help with his/her breathing in the delivery room and NICU using the mask, tube in the nose or breathing tube in the windpipe with a ventilator, surfactant and an oximeter to monitor oxygen saturations.

WILL IT COST ME ANYTHING TO BE IN THIS STUDY?

You and your baby will not have any additional costs for being in this research study.

You and/or your medical/hospital insurance carrier will remain responsible for your and your baby's regular medical care expenses.

WILL I BE PAID FOR PARTICIPATING?

You and your baby will not be paid for being in this research study.

WHO IS FUNDING THIS STUDY?

The National Institute of Health, NICHD Neonatal Research Network is funding this research study. This means that the University of Iowa is receiving payments from The National Institute of Health, NICHD Neonatal Research Network to support the activities that are required to conduct the study. No one on the research team will receive a direct payment or increase in salary from The National Institute of Health, NICHD Neonatal Research Network for conducting this study.

WHAT IF I AM INJURED AS A RESULT OF THIS STUDY?

- If either you or your baby is injured or becomes ill from taking part in this study, medical treatment is available at the University of Iowa Hospitals and Clinics.

- No compensation for treatment of research-related illness or injury is available from the University of Iowa unless it is proven to be the direct result of negligence by a University employee.
- If either you or your baby experiences a research-related illness or injury, you and/or your medical or hospital insurance carrier will be responsible for the cost of treatment.

WHAT ABOUT CONFIDENTIALITY?

We will keep your and your baby's participation in this research study confidential to the extent permitted by law. However, it is possible that other people may become aware of your or your baby's participation in this study. For example, federal government regulatory agencies, The National Institute of Health, NICHD Neonatal Research Network, auditing departments of the University of Iowa and the University of Iowa Institutional Review Board (a committee that reviews and approves research studies) may inspect and copy records pertaining to this research. Some of these records could contain information that personally identifies you or your baby.

To help protect your and your baby's confidentiality, we will label information with a code number. The study logs linking the code number with your infant's identity will be kept in a locked office, in a locked file cabinet and password-protected computer files. If we write a report or article about this study or share the study data set with others, we will do so in such a way that you and your baby cannot be directly identified.

A copy of this Informed Consent Document will be placed in your and your baby's medical record.

WILL MY HEALTH INFORMATION BE USED DURING THIS STUDY?

The Federal Health Insurance Portability and Accountability Act (HIPAA) requires University of Iowa Health Care to obtain your permission for the research team to access or create "protected health information" about you for purposes of this research study. Protected health information is information that personally identifies you and your baby and relates to your and your baby's past, present, or future physical or mental health condition or care. We will access or create health information about you and your baby, as described in this document, for purposes of this research and for your baby's treatment. Once University of Iowa Health Care has disclosed your protected health information to us, it may no longer be protected by the Federal HIPAA privacy regulations, but we will continue to protect your and your baby's confidentiality as described under "Confidentiality."

We may share your health information related to this study with other parties including federal government regulatory agencies, the University of Iowa Institutional Review Boards and support staff, and The National Institute of Health, NICHD Neonatal Research Network.
You and your baby cannot participate in this study unless you permit us to use your and your baby's protected health information. If you choose *not* to allow us to use your protected health information, we will discuss any non-research alternatives available to you. Your decision will not affect your right to medical care that is not research-related. Your signature on this Consent Document authorizes University of Iowa Health Care to give us permission to use or create health information about you and your baby.

Although you may not be allowed to see study information until after this study is over, you may be given access to your and your baby's health care records by contacting your health care provider. Your permission for us to access or create protected health information about you and your baby for purposes of this study has no expiration date. You may withdraw your permission for us to use your and your baby's health information for this research study by sending a written notice to: Dr. Edward Bell

University of Iowa Hospitals & Clinics
200 Hawkins Drive
Dept. of Pediatrics, 8811 JPP
Iowa City, Iowa 52242

However, we may still use your and your baby's health information that was collected before withdrawing your permission. Also, if we have sent your and your baby's health information to a third party, such as the study sponsor, or we have removed your identifying information, it may not be possible to prevent its future use. You will receive a copy of this signed document.

IS BEING IN THIS STUDY VOLUNTARY?

Taking part in this research study is completely voluntary. You may choose for you and/or your baby not to take part at all. If you choose for your baby to be in this study, you may stop your and his/her participation at any time. If you decide not to have you and/or your child be in this study, or if you decide to stop you or your baby from participating at any time, you and your baby won't be penalized or lose any benefits for which you otherwise qualify.

Will I Receive New Information About the Study while Participating?

If we obtain any new information during this study that might affect your willingness to continue participating or to let your baby continue participating in the study, we'll promptly provide you with that information.

Can Someone Else End my Participation in this Study?

Under certain circumstances, the researchers or the study sponsor might decide to end your and your baby's participation in this research study earlier than planned. This might happen because your baby needs to be treated in a way outside the study protocol or because funding for the research study is ended.

WHAT IF I HAVE QUESTIONS?

We encourage you to ask questions. If you have any questions about the research study itself, please contact: Dr. Edward Bell at (319)356-4006 or Karen Johnson, R.N. at (319)356-2924.

If you have questions, concerns, or complaints about your rights as a research subject or about research related injury, please contact the Human Subjects Office, 340 College of Medicine Administration Building, The University of Iowa, Iowa City, Iowa, 52242, (319) 335-6564, or e-mail irb@uiowa.edu. General information about being a research subject can be found by clicking "Info for Public" on the Human Subjects Office web site, http://research.uiowa.edu/hso.

This Informed Consent Document is not a contract. It is a written explanation of what will happen during the study if you decide to participate. You are not waiving any legal rights by signing this Informed Consent Document. Your signature indicates that this research study has been explained to you, that your questions have been answered, and that you agree to take part in this study. You will receive a copy of this form.

Parent Subject's Name (printed): _____

_____ _____
(Signature of Parent Subject) (Date)

Parent/Guardian or Legally Authorized Representative's Name and Relationship to Subject:

Child Subject's Name (printed): _____

_____ _____
(Parent/Guardian Name - printed) (Relationship to Subject - printed)

_____ _____
(Signature of Parent/Guardian or Legally Authorized Representative) (Date)

Statement of Person Who Obtained Consent

I have discussed the above points with the subject or, where appropriate, with the subject's legally authorized representative. It is my opinion that the subject understands the risks, benefits, and procedures involved with participation in this research study.

_____ _____
(Signature of Person who Obtained Consent) (Date)

From: Bell, Edward (Pediatrics)
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Surfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)
Date: Wednesday, January 25, 2012 2:01:30 PM
Attachments: Bell SUPPORT consent 5-19-08.rtf

Rose,
Here is the last version of the consent that was used to enroll patients in the SUPPORT main trial at Iowa.
Ed

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, January 20, 2012 1:43 PM
To: Bell, Edward (Pediatrics)
Cc: Maddox, Yvonne (NIH/NICHD) [E]; Hirschfeld, Steven (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]
Subject: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)

Ed
As you are aware the Neonatal Research Network (NRN) continues to support studies under common protocols, but which require individual institutional IRB review prior to the conduct of these studies at each of the NRN sites. This is to inform you that The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), which provided the Federal support to the NRN, has been requested by the Office of Human Subjects Protection, to provide to the Office the most current consent form approved by your IRB and the corresponding IRB approval for the main SUPPORT Study, including any revisions, as soon as possible. As the NICHD Program Director of the NRN, I am requesting that the most recent consent form with IRB approval for your site for SUPPORT be submitted to me as soon as possible, but no later than January 26, 2012. Thank you for your cooperation.

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Myriam Peralta, M.D."; "yvaucher@ucsd.edu"
Cc: "Finer, Neil"; "Wally Carlo, M.D."
Subject: SUPPORT FU papers
Date: Tuesday, January 24, 2012 1:32:00 PM

Hi,

Can you let me know if you are ready to submit the SUPPORT Follow Up Papers?

Thanks for all the hard work

Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Wally Carlo, M.D."
Subject: RE: SUPPORT results
Date: Tuesday, January 24, 2012 1:22:00 PM

We can tell him that the manuscripts have not yet been published and so we are not yet able to share the results as we do not want to jeopardize our chances for publication

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
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6100 Executive Blvd., Room 4B03
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Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Tuesday, January 24, 2012 1:14 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: SUPPORT results

HI Rose:

Jack Sinclair wrote to me asking for the NID/death results presented at Hot Topics. What can we say or not say?

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
1700 6th Avenue South
176F Suite 9380R
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 (b)(6)

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: Tufts_SUPPORT Study ICF_2009.pdf - Adobe Acrobat Professional
Date: Tuesday, January 24, 2012 1:03:00 PM
Attachments: Tufts_SUPPORT Study ICF_2009.pdf

TUFTS MEDICAL CENTER
DEPARTMENT OF PEDIATRICS, DIVISION OF NEWBORN MEDICINE

INFORMED CONSENT FORM TO PARTICIPATE IN RESEARCH

The Surfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT) in Extremely Low Birth Weight Infants

Principal Investigator: Ivan D. Frantz III, MD
Co-investigator: John M. Fiascone, MD

INTRODUCTION

Your baby is invited to participate in a research study to compare two ways to assist premature babies to breathe and to compare two ranges of blood oxygen saturation levels by which premature babies are managed. You are being asked to allow your child to be in the study because (s)he might be born 12-16 weeks early (at 24 to 28 weeks of pregnancy). If your baby is born at or after 28 weeks of pregnancy, (s)he will not be enrolled in this study.

The study is being conducted by the National Institutes of Child Health and Human Development Neonatal Research Network, of which Tufts Medical Center is a member. Nationwide, a total of 1300 patients are expected to enroll in this study and we expect that about 30 of those infants will be from Tufts Medical Center. Children enrolled in the study will be involved for two years.

BACKGROUND

Babies born prematurely are at risk for breathing problems. A baby's lungs are made up of tiny air sacs. Each one is supposed to open and close as the baby breathes in and out. This works well in full term babies and adults; however, in premature babies the lung sacs don't always work this way. Some lung sacs open and close normally; others collapse and stick together when the baby breathes out making it harder to breathe.

Almost all babies born between 24-28 weeks of pregnancy require some treatment to help them breath. Doctors use one of two different treatment approaches. One approach is to give the baby a medication called surfactant shortly after delivery to try and keep the lung sacs expanded. Surfactant is given directly into the lungs via a breathing tube that is inserted into the airway (referred to as intubation). The baby is then maintained on a ventilator (breathing machine) until the baby may tolerate removal of the ventilator. A second treatment approach is to keep the lungs slightly inflated (or open) between breaths. This may be done by placing small tubes in the

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Approved 11 June 2008
Valid Until 12 May 2009

baby's nostrils to provide a small amount of continuous air pressure (CPAP) in the lungs to make it easier for the baby to take a breath. It is at present not clear if one of these approaches is better than the other.

Babies may also develop longer-term problems. The need for oxygen extending to four weeks prior to the baby's normal due date at full-term means your baby has a disease called Bronchopulmonary dysplasia (BPD), which is characterized by abnormal lung development. Premature babies are also at risk for an eye disease called Retinopathy of Prematurity (ROP). This problem affects the blood vessel growth in their eyes and may result in vision problems or even blindness. The amount of oxygen that a baby receives (oxygen saturation) may be a risk factor for ROP. The oxygen saturation is routinely monitored with a pulse oximeter. This oximeter uses a tiny probe, which is much like a band-aid applied to the foot or hand. There has not been consensus across the country about what is the best oxygen saturation range in which to keep premature babies, however the normal range of saturation is generally considered to fall between 85-95%.

Either treatment (CPAP or use of breathing tube, surfactant and breathing machine) is acceptable medical practice, with some hospitals favoring one or the other. One treatment has not been proven to be better than the other. Based on our interpretation of the medical literature, the standard medical treatment at Tufts Medical Center for babies born at less than 27 weeks gestational age is use of a breathing tube, breathing machine and administration of surfactant in the delivery room. Babies born 27-28 weeks gestational age receive surfactant if they are intubated for any reason in the delivery room. At Tufts Medical Center oxygen saturation is kept between 88-94%.

PURPOSE OF STUDY

The primary purpose of this study is to evaluate the effect of two respiratory treatments and two ranges of blood oxygen saturation levels on the incidence and/or severity of BPD and ROP. We hope to determine if providing CPAP instead of ventilator support may reduce the incidence and/or severity of BPD and if a lower oxygen saturation range results in decreased ROP. Additionally, we will study two methods to detect brain injury and will follow your baby's growth and development. Specifically, this study will:

1. Compare two ways of assisting premature infants to breathe. Infants who receive CPAP in the delivery room with specific guidelines for further breathing support will be compared to infants who have a breathing tube placed, surfactant given in the delivery room, followed by breathing support.
2. Find out the oxygen level that should be used to help prevent some of the eye injury that may occur in premature babies. Specifically, infants in lower range (85-89%) and higher range (91-95%) oxygen levels (saturation) will be compared.

Tufts Medical Center IRB # 7856
Approved 11 June 2008
Valid Until 12 May 2009

3. Compare brain imaging by ultrasound or magnetic resonance imaging (MRI), done around the time when a baby would normally be born, to determine if one method gives more useful information about brain injury than the other.
4. Determine any effect of the study treatments on premature babies' growth and respiratory, neurological and developmental health during the first 18-22 months after his/her expected delivery at full term.

STUDY PROCEDURES

If you decide to allow your child to be in this study, a few minutes before your child is born, (s)he will be randomly assigned, like the flip of a coin, to one of two lung treatment strategies and one of two oxygen treatment levels. Your infant will be assigned to one of the four groups shown below. Each of the 4 possible combinations of treatments is considered by some hospitals to represent their desired standard approach. No one approach is known to be better than the others.

CPAP Higher oxygen saturation	CPAP Lower oxygen saturation
Surfactant + breathing machine Higher oxygen saturation	Surfactant + breathing machine Lower oxygen saturation

The treatments are as follows: 1) CPAP in the delivery room immediately after birth and continuing in the intensive care nursery (NICU), or 2) placement of a breathing tube in the windpipe in the delivery room followed by surfactant administration and ventilation (breathing for the baby using a machine). Infants randomized to the CPAP group may, at some point in their care, require a breathing tube and a breathing machine. If the attending physician deems this necessary, participation in the study will not affect this decision. If intubation occurs within the first 48 hours of birth, the baby will receive surfactant. Study guidelines for lung treatments of infants in both groups will be followed for two weeks.

In addition to being randomly assigned to one of the two groups described above, your baby will be randomly assigned to having an oximeter (blood oxygen monitor) which reads slightly high or one that reads slightly low. The oximeters used in this study are devices approved by the U.S. Government's Food and Drug Administration which have been modified for research purposes. This modification makes the monitors show an oxygen saturation value that is either a little higher or a little lower than the true oxygen reading when values are in the normal range

Tufts Medical Center IRB # 7856
Approved 11 June 2008
Valid Until 12 May 2009

(between 85 and 95%). Outside those ranges, the oximeter works the same as a standard oximeter. This will allow us to keep the saturations at the high or low end of the normal range and still protect the study infants from undesirable oxygen levels. The doctors and nurses taking care of your infant will not know if (s)he is in the high or low saturation group. This is to help assure that all patients are cared for in the same way. Your child will be on a study oximeter until about four weeks before the original "due date" or until transfer to a hospital not participating in this study. At that time, the oximeter will be changed to a standard one for the remainder of his/her hospital stay.

Other aspects of your infant's care will be the standard treatments for premature babies in the Tufts Medical Center NICU. Information from your baby's medical record about medical care your baby received and results of tests and data that pertain to your baby will be documented in your baby's research study records. This information will include respiratory support; feeding and weekly growth measurements of body weight, length, and head circumference; and results of eye exams.

Your baby will have routine ultrasounds of his/her head during his/her stay in the NICU. A copy of the head ultrasounds conducted between 4-14 days of life and at the time of the original expected due date will be collected for this study. If your baby's head ultrasound at the time of the expected due date occurs before 35 weeks post-menstrual age, your baby will receive another head ultrasound for the purpose of this study between 35-42 weeks post-menstrual age. In addition, your baby will have a MRI (Magnetic Resonance Imaging) for the purpose of this research study between 35-42 weeks post-menstrual age. Neither the head ultrasound nor the MRI is experimental and both are currently used on infants at Tufts Medical Center. The ultrasound shows the structure of your baby's brain by bouncing sound waves off of it. You may have seen an ultrasound of your baby during your pregnancy. The MRI is a specialized brain scan that takes detailed pictures of the brain structure and can detect normal and abnormal brain tissue. If conducted for the purpose of this study, the head ultrasound and/or MRI will be paid for by The National Institutes of Child Health and Human Development at no cost to you. If your baby is still in the NICU, your baby will need to be transported to the MRI suite in order to have the procedure. Only those patients considered stable for transport will undergo an MRI. If your baby is discharged home prior to 35-42 weeks PMA, you will be asked to return to Tufts Medical Center for the head ultrasound and MRI procedures. If your baby is transferred to another hospital participating in this study, the head ultrasound and/or MRI may take place at that hospital. The MRI will be conducted after your baby is swaddled while sleeping following a feeding and with the use of a jacket-like device that allows the baby to lie still without using sedation. A physician at the hospital in which you receive the head ultrasound and MRI will provide you with an interpretation of the results of the tests. Neither the ultrasound nor the MRI involves exposure to radiation.

At the time your baby is discharged from the NICU, you will be asked questions about your socioeconomic status such as how much money your family earns, the level of education you have completed, and information about your household. You will also be asked questions about any family history of breathing problems or respiratory illness.

All children in the Tufts Medical Center NICU return to the NICU Follow-up Clinic at regular intervals during the first two years as part of their routine medical care. We will continue to stay in touch with you by telephone or in person at these visits over the next 18-23 months. At these times, we will ask questions about your child's breathing (especially wheezing and coughing), medication use, and visits to a doctor, emergency room, or hospital for treatment of breathing problems. We will also ask you several questions about your family and yourself. Each interview should take 15 minutes or less of your time. When your baby returns to the NICU follow-up clinic for his/her 18-month-old assessment of growth, development, and coordinated movement skills, the study will collect that outcome information. In order to successfully evaluate the approaches to lung treatment and oxygen used in this study, follow up at 18-22 months is essential for this study. Families who participate in this project are agreeing to remain in contact with the investigators and to return to the NICU Follow-up clinic with their child when (s)he is 18 months of age.

Research procedures for this study occur while your baby is in the hospital and if discharged home prior to 35 weeks post-menstrual age, when your baby returns to the hospital for a head ultrasound and/or MRI. Data will be collected for this study at the 18-month follow-up visit that your child attends as part of standard medical care. Subjects in this study must participate in all aspects of the study including the MRI and head ultrasounds and 18-month follow-up visit.

Doctors working on the SUPPORT study hope that it will be possible to follow the children who participated in SUPPORT for more than 18-22 months. If money for longer follow-up is obtained, we would like to follow your child for up to 6-7 years. If money for longer follow up is obtained we ask your permission for the study doctor and/or his designee to contact you about possible additional years of follow-up. Your child could only participate in SUPPORT follow-up beyond 18-22 months with your written consent, but you would not be under any obligation to continue.

RISKS AND DISCOMFORTS

This study does not pose significant risks beyond those inherent in a sick premature baby. For example, premature infants with respiratory distress syndrome are at increased risk of pneumothorax (collapse of lung) however there is no evidence supporting a difference in this risk between the respiratory treatments being studied (breathing tube and breathing machine v. CPAP

Tufts Medical Center IRB # 7856
Approved 11 June 2008
Valid Until 12 May 2009

in the delivery room). It is not known if the known reduction of death and disease severity as a result of surfactant in the delivery room and the reduction of BPD in babies that receive surfactant will be less than, offset, or increased by the early use of CPAP. Infants treated with CPAP often swallow air and have a tube placed into the stomach to remove it None of the aspects of the study are believed to be uncomfortable beyond the discomfort associated with routine medical care. All treatments are standard of care at some NICUs across the country.

There are no known effects from exposure to magnetic fields (MRI). Temporary minor skin irritation from tape used to apply MRI-compatible monitoring electrodes may occur, but this risk is unlikely.

Some unknown risks may be learned during the study. You will be told of any new information that is learned which may affect your child's condition or influence your willingness to have him/her continue participation in this study.

Another risk of this study is the risk to confidentiality. Every effort will be made to keep your child's medical record confidential. There will be no name or other patient identification in any study report that may be published after the study is completed. Measures taken to protect you and your baby's identity are described in the confidentiality section of this document.

BENEFITS

There may be benefits to your child directly, including a decrease in chronic lung disease and/or a decrease in the need for eye surgery as a result of exposure to oxygen. Because we do not know in advance the actual strategies chosen for your child, or which of study groups is the most effective, it is also possible that your baby will not receive these possible benefits. However, all babies in the study may benefit from the MRI that is conducted for purposes of this research. Babies may benefit from this procedures if they identify brain injury, which may allow for earlier treatment than would normally occur. If the doctor sees anything on the MRI that would help treat your infant, s/he will use that information.

ALTERNATIVES TO PARTICIPATION

The alternative to having your child participate in this project is not to participate. If you choose not to have your child participate, he/she will receive the standard care for premature infants.

CONTACT INFORMATION

If you have any questions about the study or concerns during the study, you may contact the investigator (Dr. Frantz) or his designees via the Tufts Medical Center Paging Operator: (617)

636-5114 or Tufts Medical Center (617) 636-5008. If you have question about your rights as a research study subject, call the Tufts Medical Center Institutional Review Board (IRB) at (617) 636-7512. The Institutional Review Board is a group of doctors, nurses, and non-medical people who review human research studies for safety and protection of people who take part in the studies. Federal law requires the Institutional Review Board to review and approve any research study involving humans. This must be done before the study can begin. The study is also reviewed on a regular basis while it is in progress. This research study has been reviewed and approved by the IRB of Tufts Medical Center.

RESEARCH RELATED INJURY

All forms of medical diagnosis and treatment, whether routine or experimental, involve some risk of injury. In spite of all precautions, your child might develop medical complications from participating in this study. If such complications arise, immediate necessary medical care is available at Tufts Medical Center. Either you or your health insurance will be responsible for the costs of medical care that is medically necessary or indicated for your infant.

COSTS

There is no extra cost to participate in this study beyond the costs of medical care that is medically necessary or indicated for your infant's care and which is the responsibility of you or your health insurance. The head ultrasound and MRI conducted for the sole purpose of research is paid for by the National Institutes of Child Health and Human Development, which is the sponsor of this study.

PAYMENT

If your baby is discharged home prior to the MRI and head ultrasound procedures at 35-42 weeks post-menstrual age, you will be reimbursed reasonable travel expenses to get to these appointments. A gift certificate to a local department store for $20.00 will be provided per child at the 18-month follow-up visit as an appreciation payment for your child's participation.

VOLUNTARY PARTICIPATION/WITHDRAWAL

Taking part in this research study is completely your choice and you are free to change your mind. You can decide to stop taking part in this study at any time for any reason and your child will receive standard medical care. If you want to stop participation in this study, we ask that you contact Dr. Ivan D. Frantz III by writing, telephone or in person and let him know that you are withdrawing your child from the study. Dr. Frantz can be reached via telephone through the Tufts Medical Center Paging Operator: (617) 636-5114 or Tufts Medical Center NICU (617)

Tufts Medical Center IRB # 7856
Approved 11 June 2008
Valid Until 12 May 2009

636-5008. His mailing address is 800 Washington Street, Tufts Medical Center #44, Boston, MA 02111. At that time we will ask your permission to continue using data that has already been collected as part of the study prior to your withdrawal. At the discretion of the Principal Investigator, subjects may be taken out of this study due to unanticipated circumstances. Examples of reasons for taking a participant out of the study include: the investigator deciding that continued participation could be harmful to your child, the study being canceled, or some other administrative reason.

CONFIDENTIALITY

Extensive efforts are made to protect all research subjects from the use of information that will adversely affect them. Specifically, access to information about you and your child is restricted to the Tufts Medical Center Division of Newborn Medicine clinical research staff that is involved in this study. Clinical and research information with respect to this study is maintained in a research file separate from hospital medical records and will not be placed in the official Tufts Medical Center medical record by research staff. Clinical information collected from your baby's chart for this study will be labeled with a coded study ID number. Coded information will be sent to the NICHD Neonatal Research Network's Data Coordinating Center at Research Triangle Institute (RTI) in Research Triangle Park, North Carolina. The key linking the code number with your baby's identity will be kept secure at the Tufts Medical Center Division of Newborn Medicine clinical research office. Your baby's head ultrasound and MRI images may be identified with a header listing you baby's name, hospital number and birth date since it is not always possible to remove your baby's identification from these scans. These scans will be sent to RTI so that study radiologists may read the image and ensure consistent interpretation across all of the babies around the country that are participating in this study. The study radiologists will not have any other information about your child. In no other instance, will information directly identifying your baby, such as name or medical record number, to study data collected leave Tufts Medical Center. Research data from which your child may be identified will not be disclosed to third parties except with your written permission or as required by law. If research results from this study are reported in a professional setting, such as in a medical journal or at a scientific meeting, the identity of research subjects taking part in the study is withheld.

Tufts Medical Center IRB # 7856
Approved 11 June 2008
Valid Until 12 May 2009

PARTICIPANT'S STATEMENT

I have read this consent form and have discussed with Dr. Frantz or his/her representative the procedures described above. I have been given the opportunity to ask questions, which have been answered to my satisfaction. I understand that any questions that I might have will be answered verbally or, if I prefer, with a written statement.

I understand that I will be informed of any new findings developed during the course of this research study that may affect my willingness to stay in this research study.

I understand that my participation is voluntary. I understand that I may refuse to participate in this study. I also understand that if, for any reason, I wish to discontinue participation in this study at any time, I will be free to do so, and this will have no effect on my future care or treatment by my physicians or this hospital.

I understand that in the event I become ill or am injured as a result of participating in this research study, medical care will be provided to me. However, such medical care will not be provided free of charge, even if the injury or illness is a direct result of this research study. I understand that no funds to provide financial compensation for research-related injury or illness are available.

If I have any questions concerning my rights as a research subject in this study, I may contact the Institutional Review Board at (617) 636-7512.

I have been fully informed of the above-described study with its risks and benefits, and I hereby consent to the procedures set forth above.

I understand that as a participant in this study my identity and my medical records and data relating to this research study will be kept confidential, except as required by law, and except for inspections by the U.S. Food and Drug Administration which regulates investigational drug studies, and the study sponsor.

_____ _____
Date One Parent/Legal Authorized Representative Signature

I have fully explained to _____ the nature and purpose of the above-described study and the risks that are involved in its performance. I have answered all questions to the best of my ability.

_____ _____
Date Principal Investigator or Representative's Signature

Tufts Medical Center IRB # 7856
Approved 11 June 2008
Valid Until 12 May 2009

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Testa, Veronika"; "McGowan, Elisabeth C"
Subject: RE: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)
Date: Tuesday, January 24, 2012 11:55:00 AM

Thanks
Please send me the most recent consent form for the main study trail recruitment from 2009.

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Testa, Veronika [mailto:vtesta@tuftsmedicalcenter.org]
Sent: Tuesday, January 24, 2012 11:52 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; McGowan, Elisabeth C
Subject: RE: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)

Hello Rose,

Attached, please find a pdf of our IRB approval for the SUPPORT study.

Best regards,
Veronika

Veronika Testa, BSN, RN, CCRC
Project Manager
Tufts Medical Center
800 Washington Street, Box 391
Boston, MA 02111
☎: 617.636.2379 | 🖷: 617.636.8329
✉: vtesta@tuftsmedicalcenter.org

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, January 23, 2012 9:54 AM
To: McGowan, Elisabeth C
Cc: Testa, Veronika
Subject: Re: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)

To me

Thanks
Rose

From: McGowan, Elisabeth C [mailto:emcgowan@tuftsmedicalcenter.org]
Sent: Monday, January 23, 2012 09:35 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Testa, Veronika <vtesta@tuftsmedicalcenter.org>
Subject: RE: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)

Hi Rose,

My administrative assistant will be in mid-week, and we will send the SUPPORT documentation as well as all other renewals. Everything has been completed.

Who should I send to ?

Liz

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, January 20, 2012 3:28 PM
To: McGowan, Elisabeth C
Subject: Fw: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)

Liz
Can you send?
Thanks
Rose

From: Frantz, Ivan [mailto:Ivan.Frantz@childrens.harvard.edu]
Sent: Friday, January 20, 2012 03:24 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: McGowan, Elisabeth C <emcgowan@tuftsmedicalcenter.org>
Subject: RE: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)

Rose: I no longer have access, but Liz should be able to get the items to you.

Ivan

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, January 20, 2012 2:43 PM
To: Frantz, Ivan
Cc: Maddox, Yvonne (NIH/NICHD) [E]; Hirschfeld, Steven (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]
Subject: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)

Ivan
As you are aware the Neonatal Research Network (NRN) continues to support studies under common protocols, but which require individual institutional IRB review prior to the conduct of these studies at each of the NRN sites. This is to inform you that The Eunice Kennedy Shriver National Institute of Child Health and Human

Development (NICHD), which provided the Federal support to the NRN, has been requested by the Office of Human Subjects Protection, to provide to the Office the most current consent form approved by your IRB and the corresponding IRB approval for the main SUPPORT Study, including any revisions, as soon as possible. As the NICHD Program Director of the NRN, I am requesting that the most recent consent form with IRB approval for your site for SUPPORT be submitted to me as soon as possible, but no later than January 26, 2012. Thank you for your cooperation.

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

The information in this e-mail is intended only for the person to whom it is addressed. If you believe this e-mail was sent to you in error and the e-mail contains patient information, please contact the Tufts Medical Center HIPAA Hotline at (617) 636-4422. If the e-mail was sent to you in error but does not contain patient information, please contact the sender and properly dispose of the e-mail.

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: SUPPORT consent
Date: Tuesday, January 24, 2012 11:54:00 AM

I gave them until Thursday

Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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CDBPM, NIH
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Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Archer, Stephanie (NIH/NICHD) [E]
Sent: Tuesday, January 24, 2012 11:36 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT consent

OK. Still missing:

- Wayne State
- Miami
- Emory
- Cincinnati
- Yale
- Brown
- Duke
- Rochester
- Tufts
- Iowa

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tuesday, January 24, 2012 11:06 AM
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: SUPPORT consent

We only need the most recent (2009)

Rosemary D. Higgins, MD

Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Archer, Stephanie (NIH/NICHD) [E]
Sent: Tuesday, January 24, 2012 10:55 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT consent

Do you only want the one from 2009 for Alabama, or all of the ones they sent?

Stephanie Wilson Archer
The Eunice Kennedy Shriver
National Institute of Child Health and Human Development
Pregnancy & Perinatology Branch
6100 Executive Boulevard, Room 4B03
Rockville, MD 20852

Tel. 301-496-0430
Fax 301-496-3790
archerst@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tuesday, January 24, 2012 9:58 AM
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: SUPPORT consent

here is what I have so far - can you save to the N drive and print a hard copy of each?
Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: SUPPORT consent
Date: Tuesday, January 24, 2012 11:09:00 AM

They only asked for the most recent and didn't specify Spanish – we are only sending the English versions

Rosemary D. Higgins, MD
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For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Archer, Stephanie (NIH/NICHD) [E]
Sent: Tuesday, January 24, 2012 11:08 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT consent

What about Spanish versions?

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tuesday, January 24, 2012 11:06 AM
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: SUPPORT consent

We only need the most recent (2009)

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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higginsr@mail.nih.gov

From: Archer, Stephanie (NIH/NICHD) [E]
Sent: Tuesday, January 24, 2012 10:55 AM

To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT consent

Do you only want the one from 2009 for Alabama, or all of the ones they sent?

Stephanie Wilson Archer
The Eunice Kennedy Shriver
National Institute of Child Health and Human Development
Pregnancy & Perinatology Branch
6100 Executive Boulevard, Room 4B03
Rockville, MD 20852

Tel. 301-496-0430
Fax 301-496-3790
archerst@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tuesday, January 24, 2012 9:58 AM
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: SUPPORT consent

here is what I have so far - can you save to the N drive and print a hard copy of each?
Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: SUPPORT consent
Date: Tuesday, January 24, 2012 9:57:00 AM
Attachments: CWRU.pdf
New Mexico.doc
Stanfrod.doc
UAB.pdf
UT Houston.pdf
UCSD.pdf
Utah - University Hospital.doc
Utah IHC.pdf
UTSW.docx
Wake Forest.doc

---

here is what I have so far - can you save to the N drive and print a hard copy of each?
Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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higginsr@mail.nih.gov

IRB NUMBER: 11-04-29
IRB APPROVAL DATE: 08/15/2011
IRB EXPIRATION DATE: 06/15/2012

UNIVERSITY HOSPITALS CASE MEDICAL CENTE
CONSENT FOR INVESTIGATIONAL STUDIES

Project Title: SURFACTANT POSITIVE AIRWAY PRESSURE AND PULSE OXIMETRY IN EXTREMELY LOW BIRTHWEIGHT (ELBW) INFANTS- The SUPPORT Trial

Principal Investigator M. Walsh

Introduction

You have been admitted to MacDonald Women's Hospital and you are at risk for delivering your baby prematurely. If your baby is born early he/she may need help with his/her breathing immediately after birth in the delivery room and in the Neonatal Intensive Care Unit (NICU). Premature babies who need help with their breathing may also require extra amounts of oxygen. Many babies born before 28 weeks' gestation require this care.

You are being asked to allow your child to be considered for a research study will compare several ways which are normally used to help support breathing problems in infants who have premature lungs to see which is most helpful and least harmful. 1310 infants will be enrolled in this study.

You will need to be able to read and understand this consent form in order to allow your baby to be enrolled in this study. If you do not feel you are able to read and understand this consent, you should not sign to give your permission for your child to be enrolled in this study.

There are two common ways to help premature babies with breathing after birth. One common way is **CPAP** which stands for continuous positive airway pressure. A mask over the nose and mouth or soft nasal prongs placed into the tip of the nose may be used to provide air flow to help open the baby's lungs and give extra oxygen. Another common way is **Intubation** which is the placement of a breathing tube which is passed through the mouth into the airway and connected to a breathing machine (ventilator) to assist with respirations, give extra amounts of oxygen and give surfactant (a medication given into the lungs to help with breathing problems). Both ways are routinely used in the delivery room and in the NICU. The pediatric doctors, nurses and respiratory therapists will evaluate your baby's breathing immediately after birth and during his/her time in the NICU.

If a baby requires extra amounts of oxygen it is important that the concentration of oxygen in the blood (oxygen saturation) be monitored. A pulse oximeter is used to monitor the oxygen saturation. A sensor (the instrument that reads the oxygen saturation) is placed on the baby's hand, wrist or foot and is attached to the oximeter which then gives a continuous reading of the oxygen saturation.

It is important to keep the oxygen saturation in a certain range (85%-95%). Some doctors will want to keep the oxygen saturation level close to the upper part of the range. Some doctors prefer to keep the oxygen saturation close to the lower part of the range. Keeping the level in either end of the normal range is routinely used in the NICU for premature babies. If your baby requires extra amounts of oxygen when admitted to the NICU, an oximeter will be used in order to keep the oxygen within the normal range.

Project Title: SURFACTANT POSITIVE AIRWAY PRESSURE AND PULSE OXIMETRY IN EXTREMELY LOW BIRTHWEIGHT (ELBW) INFANTS- The SUPPORT Trial

Principal Investigator M. Walsh

Purpose

There are two purposes for this research study:

The first purpose of this study is compare either using a mask or soft nasal prongs to assist your baby with his/her breathing immediately after birth and continuing in the NICU **to** using a breathing tube, mechanical ventilation and receiving a drug called surfactant into the breathing tube. We want to compare these two to see if there is a difference in the amount of breathing help your baby requires and how long he/she will continue to need this help during the first two weeks of life.

The second purpose of this study is to compare babies who have oxygen saturations kept in the high end of the normal range with babies who have oxygen saturations kept in the low end of the normal range. The doctors, nurses and respiratory therapists will use a study pulse oximeter to monitor your baby during the time he/she requires extra amounts of oxygen.

Study Procedures

Your baby will receive care form the doctors, nurses and respiratory therapists who specialize in newborns to help stabilize him/her in the delivery room.

Your baby will be randomized (assigned by chance similar to a flip of a coin) to 2 treatment assignments.

The first assignment will determine his/her care in the delivery room as follows:

If your baby participates in this study he/she will be randomized (assigned by chance similar to a flip of a coin) to ***either*** the CPAP group ***or*** Intubation group to manage his/her breathing immediately after birth. This will determine if a mask/soft nasal prongs ***or*** a breathing tube will be offered first in the delivery room.

If your baby is randomized to the CPAP group a mask or soft nasal prongs will be used immediately after birth to assist your baby with his/her breathing in the delivery room and continued when he/she is admitted to the NICU. If your baby requires more help with his/her breathing a breathing tube and the ventilator may be offered and your baby will receive all routine care for premature infants with breathing problems. This may include giving a medication called surfactant into the lungs through the breathing tube to help with his/her breathing problems.

If your baby is randomized to the Intubation group your baby will have a breathing tube placed in the delivery room and will be admitted to the NICU. Your baby will receive all routine care for premature babies with breathing problems. This will include giving a medication called surfactant into the lungs through the breathing tube to help with his/her breathing problems.

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Principal Investigator M. Walsh

The second treatment assignment will determine which end of the normal oxygen saturation range (high or low end) as follows:

When your baby is admitted to the NICU, he/she will be randomized (assigned by chance similar to the flip of a coin) to be kept in a certain oxygen saturation range. This will determine if your baby will have his/her oxygen saturation level kept in the high ***or*** low part of the normal oxygen saturation range. The oximeter will be used for as long as your baby is requiring oxygen and until he/she has been in room air (no extra oxygen) for at least 3 days. Your baby will also have his/her oxygen monitored by other routine methods used in the NICU, which may include blood samples to measure the oxygen concentration when the doctors feel it is necessary.

Your infant will have al usual care for infants born before 28 weeks gestation. This includes measuring your child's weight several times weekly, as well as, measuring length and head circumference once each week. If your child is not on a breathing tube or CPAP, your child's length will be performed using a length board [laced inside his/her bed. The length board will remain in your child's bed only long enough to obtain the length measurement.

Usual care for premature infants in the NICU includes head ultrasound examinations to look at the brain. The head ultrasound is convenient, can be done at the bedside and does not require sedation. Routine ultrasounds are done during the first two weeks of life and again close to 36 weeks' corrected age or more often if the doctors feel it is necessary.

Another examination of the brain called an MRI (magnetic resonance imaging) can also give information about your child's brain. The doctors would like to compare results of the routine head ultrasounds to an MRI done close to 36 weeks' corrected age for infants who were treated with CPAP or Intubation and assigned to the high or low end of the normal oxygen saturation range. We will compare these results to see which test will best predict neuromotor (physical abilities such as walking, talking, vision and hearing) and neurodevelopmental (development of intelligence and language) outcome at 18-22 months' corrected age.

Your infant will be taken to the MRI department in a special transporter that provides a protective environment including warmth, oxygen, breathing assistance and I fluids if necessary. Most often infants at this age will sleep during this test and will tolerate the MRI well. If your child does not sleep during the brain MRI, your child may need a mild sedative. If this is necessary, the doctors and nurses will monitor your child's response to the mild sedative.

Follow-up Procedures
In order to understand problems that some former premature infants experience after discharge, we conduct parent interviews in person and by telephone. The interviews ask about breathing problems, especially wheezing and the need for visits to the doctor and/or the hospital for breathing problems. We want to compare infants who are treated with CPAP or Intubation and who are assigned to the high

or low end of the normal oxygen saturation range to better understand breathing problems during early childhood.

The first interview will be conducted in the hospital close to the time your child is scheduled for discharge. We will ask you questions about your home and whether breathing problems run in your family. The next three interviews will be conducted by telephone at 6, 12, and 18 months' corrected age. During each telephone interview we will ask about your child's breathing, especially wheezing and coughing and about your child's need for medical visits and treatments for breathing problems. We also ask how your child is adjusting to his/her new home. These telephone interviews will be scheduled at a time that is convenient for you.

Risks

Possible complications with using soft nasal prongs and/or the ventilator may include trauma to the airway, collapse of airway passages, abnormal lung damage by air getting into the tissues or lung collapse. However, the need for help with breathing may be necessary due to the premature birth.

The oxygen saturation ranges to be used are currently used for usual care in premature infants in the NICU. The known risks associated with the high end of the normal oxygen saturation range may include slow or abnormal growth of blood vessels in the eye causing vision problems. Known risks associated with the low end of the normal oxygen saturation range may include low amounts of oxygen delivered to the tissues.

Risks associated with the use of surfactant may include a temporary drop in the oxygen level during the time the medication is given, brief breathing difficulty while the surfactant is being given and bleeding from the lungs.

Premature babies who have lung problems have a risk of long term breathing problems which may require extra amounts of oxygen.

Risks associated with the MRI examination may include minor skin irritation from the tape used to apply monitoring electrodes (sensors that monitor vital signs during the MRI). If sedation is needed, risks may include less vigorous breathing and lower blood pressure which may require additional monitoring. An intravenous line (IV) may also be required to administer sedation, and if needed, the risk of an IV may include bruising, swelling or rarely an infection. The transport of your child to the MRI department may also represent a possible risk. However, only those patients considered stable for transport will have an MRI performed.

There are no known risks associated with head ultrasounds done in the NICU.

We anticipate no risk to you, your child and your family to participate in interviews in person and by telephone about continued breathing problems in former premature infants.

Project Title: SURFACTANT POSITIVE AIRWAY PRESSURE AND PULSE OXIMETRY IN EXTREMELY LOW BIRTHWEIGHT (ELBW) INFANTS- The SUPPORT Trial

Principal Investigator M. Walsh

There may be unforeseen risks associated with participation in this research study that are not known at this time.

Benefits

There may be no direct benefit to your child to participate in this research study.

Your child's participation in this study may aid in the understanding of the use of a mask/nasal prongs or a breathing tube to help premature babies with breathing immediately after birth and in the NICU. It will also help the doctors to learn more about premature infants managed in the high and low ends of the normal range of oxygen saturation.

An MRI performed for the study may have potential benefit which may include a more detailed view of your child's brain that could show abnormalities not seen with a head ultrasound. This would allow the early identification of possible problems for each individual child.

There will be no benefit to you, your child or your family for participation in the parent interviews. However, information from this study may determine the effect of the different ways to help premature babies with breathing and managing oxygen saturation levels on breathing problems in early childhood.

Participation

You may choose for your baby to have the MRI performed to look at the structure of his/her brain and help identify injury.

Yes, I would like my child to have an MRI performed for this study.* _____
Parent initials/ date

No, I do not want my child to have an MRI performed for this study.* _____
Parent initials/ date

You may choose to participate in the parent interviews before your child's discharge and at 6, 12, and 18 months' corrected age.

Yes, I would like to participate in the parent interviews.* _____
Parent initials/ date

No, I do not want to participate in the parent interviews.* _____
Parent initials/ date

*Your signature will also be required on the last page of this consent form.

Project Title: SURFACTANT POSITIVE AIRWAY PRESSURE AND PULSE OXIMETRY IN EXTREMELY LOW BIRTHWEIGHT (ELBW) INFANTS- The SUPPORT Trial

Principal Investigator M. Walsh

Early Withdrawal From the Study

You may choose to withdraw your child from this research study for any reason and at any time with no penalty or loss of benefit of care. Your child will continue to receive all routine care for premature infants which may include help with breathing, monitoring with a pulse oximeter, head ultrasound examinations and weekly measurements to monitor growth.

Alternatives to Participation

If you do not want your child to participate in this study he/she will not be randomized to soft nasal prongs or a breathing tube to assist with breathing immediately after birth in the delivery room and after admission to the NICU. Also, he/she will not be assigned to the high or low end of the normal oxygen saturation range.

All routine and usual care will be provided to your baby which may include help with his/her breathing in the delivery room and in the NICU. The doctors may use nasal prongs, a breathing tube and the ventilator and the oximeter to monitor my baby's oxygen saturation when they feel it is necessary. Usual care for premature infants includes head ultrasounds. An MRI test may be performed if the doctors feel it is necessary.

Financial Information

There will be no extra cost to you or your insurance company for your child's participation in this research study. You and your insurance company will be responsible for all usual care in the NICU which may include the use of nasal prongs, a breathing tube and the ventilator to assist with your child's breathing, surfactant to help with breathing problems and an oximeter to monitor oxygen saturation.

There is no additional cost to you or your insurance company and your insurance company will not be billed for the MRI done for the study. You and your insurance company will be responsible for all usual care which may which may include head ultrasounds or brain MRI when the doctors feel it necessary.

There is not cost to you or your insurance company for participation in the parent interview prior to discharge and at 6, 12, and 18 months' corrected age of your child. You and your child will not be paid for participation in this research study.

Confidentiality

Information collected for this study will be sent electronically to a central data center via a dedicated computer which is password sensitive. Your child will be identified by a study number and not by name or other identifying information.

UNIVERSITY HOSPITALS CASE MEDICAL CENTE
CONSENT FOR INVESTIGATIONAL STUDIES

Project Title: SURFACTANT POSITIVE AIRWAY PRESSURE AND PULSE OXIMETRY IN EXTREMELY LOW BIRTHWEIGHT (ELBW) INFANTS- The SUPPORT Trial

Principal Investigator M. Walsh

If it is necessary for the study personnel to contact you or your child at a later time, we will contact you at the address and/or telephone numbers you have provided. In the event that we cannot locate you at the address and/or telephone numbers you have provided, we may use other information in your medical record such as social security numbers, your child's pediatrician or other contact information.

Summary of your rights as a participant in a research study

Your participation in this research study is voluntary. Refusing to participate will not alter your usual health care or involve any penalty or loss of benefits to which you are otherwise entitled. If you decide to join the study, you may withdraw at any time and for any reason without penalty or loss of benefits. If information generated from this study is published or presented, your identity will not be revealed. In the event new information becomes available that may affect the risks or benefits associated with this study or your willingness to participate in it, you will be notified so that you can decide whether or not to continue participating. If you experience physical injury or illness as a result of participating in this research study, medical care is available at University Hospitals Case Medical Center (UHCMC) or elsewhere; however, UHCMC has no plans to provide free care or compensation for lost wages.

Disclosure of your study records

Efforts will be made to keep the personal information in your research record private and confidential, but absolute confidentiality cannot be guaranteed. The University Hospitals Case Medical Center Institutional Review Board may review your study records. If this study is regulated by the Food and Drug Administration (FDA), there is a possibility that the FDA might inspect your records. In addition, for treatment studies, the study sponsor and possibly foreign regulatory agencies may also review your records. If your records are reviewed your identity could become known.

Contact information

M.C. Walsh, A.A. Fanaroff, N. Newman, B. Siner has described to you what is going to be done, the risks, hazards, and benefits involved. The researchers conducting this study are M.C. Walsh, N. Newman and B. Siner. You may ask any questions you have now. If you have any questions, concerns or complaints about the study in the future, you may contact them at 216-844-3387.
If the researchers cannot be reached, or if you would like to talk to someone other than the researcher(s) about; concerns regarding the study; research participant's rights; research- related injury; or other human subject issues, please contact University Hospitals Case Medical Center's Chief Medical Officer at (216) 844-3695 or write to:
The Chief Medical Officer, The Center for Clinical Research, University Hospitals Case Medical Center, 11100 Euclid Avenue, Lakeside 1400, Cleveland, Ohio, 44106-7061.

IRB NUMBER: 11-04-29
IRB APPROVAL DATE: 08/15/2011
IRB EXPIRATION DATE: 06/15/2012

UNIVERSITY HOSPITALS CASE MEDICAL CENTE
CONSENT FOR INVESTIGATIONAL STUDIES

Project Title: SURFACTANT POSITIVE AIRWAY PRESSURE AND PULSE OXIMETRY IN EXTREMELY LOW BIRTHWEIGHT (ELBW) INFANTS- The SUPPORT Trial

Principal Investigator M. Walsh

Signature

Signing below indicates that you have been informed about the research study in which you voluntarily agree to participate; that you have asked any questions about the study that you may have; and that the information given to you has permitted you to make a fully informed and free decision about your participation in the study. By signing this consent form, you do not waive any legal rights, and the investigator(s) or sponsor(s) are not relieved of any liability they may have. A copy of this consent form will be provided to you.

_____
Printed Name of Participant

_____ Date_____ _____
Parent or Legal Guardian signature Relationship to Child

_____ Date_____ _____
Signature of Person Obtaining Consent Printed Name of Person Obtaining Consent
(Must be study investigator or individual who has been designated in the Checklist to obtain consent.)

_____ Date_____ _____
Second Parent signature Relationship to Child

_____ Date_____ _____
Signature of Person Obtaining Consent Printed Name of Person Obtaining Consent
(Must be study investigator or individual who has been designated in the Checklist to obtain consent.)

If only one parent can sign this consent, indicate the reason that applies to the other parent.

( ) deceased
( ) unknown
( ) legally incompetent
( ) no legal responsibility for the care and custody of the child
( ) not reasonably available - indicate why _____
(acceptable reasons for this category must not be based on convenience)

_____ Date_____ _____
Signature of Principal Investigator Printed Name of Principal Investigator
(Affirming subject eligibility for the Study and that informed consent has been obtained.)

UNIVERSITY HOSPITALS CASE MEDICAL CENTE
CONSENT FOR INVESTIGATIONAL STUDIES

Project Title: SURFACTANT POSITIVE AIRWAY PRESSURE AND PULSE OXIMETRY TRIAL IN EXTREMELY LOW BIRTHWEIGHT INFANTS- The SUPPORT Trial

Principal Investigator: M.C. Walsh

Consent signed and copy returned to parent/family. Date_____

Name of Person returning consent_____

The University of New Mexico Health Sciences Center
Consent to Participate in Research

The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants (SUPPORT Trial)

Your child is invited to participate in a research study being done by Kristi Watterberg. M.D., who is the Principal Investigator, and her associates, from the Department of Pediatrics. This research is looking at two basic questions: which of two lung treatments used with premature babies is better for the baby's lungs; and what is the appropriate level of oxygen in the blood in premature infants. The two lung treatments are "CPAP" (positive air pressure to help keep the lungs inflated) and "intubation," which involves placement of a breathing tube in the infant's airway with early administration of a medication called surfactant through this breathing tube.

Since 1970 two basic ways to help premature babies breathe have been used in Newborn Intensive Care Units. One method, called "intubation," involves placement of a breathing tube in the infant's airway and attaching it to a machine called a "ventilator" which breathes for the infant. The other method, called "CPAP" or "Continuous Positive Airway Pressure," involves placement of short tubes in the infant's nose and providing air pressure which helps the infant breathe on his/her own. Many studies have been done to see how to make these two methods work as well as possible. Research has shown, regardless of which treatment is used, that all babies who need help with breathing are at risk of developing a type of chronic, or long lasting, lung disease called "Bronchopulmonary Dysplasia," or "BPD" for short. Since 1990 a medication, called "surfactant" has been available to help premature babies breathe easier, but a tube must be placed in the airway to give this medicine.

Oxygen is also used whenever a baby is not able to get enough oxygen into his/her blood by breathing room air. Doctors know that it is important to be sure a baby is getting enough, but not too much oxygen. One possible complication of too much oxygen is an eye disease called "Retinopathy of Prematurity," or "ROP," that may result in poor vision or even blindness.

All of these treatments have been carefully studied and all are used in Newborn ICUs. This is the first study to carefully compare the use of all of these methods starting from the first moments after birth and following the babies until at least 18 months after they would have been born, if they had not been premature.

In this study, infants who receive delivery room CPAP and who have specific guidelines for having a breathing tube placed will be compared to infants who have a breathing tube placed and surfactant given in the delivery room or very soon after birth. The study will also compare keeping a lower range (85-89%) or a higher range (91-95%) of oxygen levels in the blood (saturation). Both of these ranges are within the oxygen saturation range that is currently used for premature infants in the NICU at UNM Hospital (85 – 95%). An alarm will sound if the oxygen saturation goes above or below that range, the same as for other premature infants in our NICU. While it is known that higher oxygen

ranges are associated with more eye disease, the safest oxygen range is still unknown. We hope to find out if a lower range results in less ROP (Retinopathy of Prematurity).

You are being asked to allow your child to be in the study because there is a possibility that (s)he will be born 12-16 weeks early (at 24 to 28 weeks of pregnancy). About 30 babies will take part in this study at the University of New Mexico. 1300 babies will participate in this study across the United States. The National Institutes of Health is funding this study.

This form will explain the research study, and will also explain the possible risks as well as the possible benefits to you. We encourage you to talk with your family and friends before you decide to take part in this research study. If you have any questions right now, please ask one of the study investigators.

What will happen if I decide to participate?

If you decide to allow your child to be in this study, a few minutes before your child is born, (s)he will be randomly assigned, like the flip of a coin, to one of two lung treatments. The treatments are as follows: 1) CPAP in the delivery room immediately after birth and continuing in the intensive care nursery (NICU), or 2) placement of a tube in the windpipe in the delivery room or right after arrival in the NICU, followed by surfactant administration and ventilation (breathing for the baby using a machine). It is not known which of these breathing treatments is better. Infants randomized to the CPAP group may, at some point in their care, require a windpipe tube and a breathing machine. Your baby's doctors will make that decision if they think it is necessary for your baby. Studies have suggested that babies who have a breathing tube placed and surfactant given very early may benefit from the surfactant (Some studies have shown that very early surfactant results in less "air leak", where air escapes from the air spaces of the lungs into the area around the lungs, and less death, but other studies have not found this difference), but they may have a higher risk for developing BPD because of the breathing tube. On the other hand, infants treated with early CPAP may not receive the early benefit of surfactant, but may have a lower risk for developing BPD because no breathing tube is inserted.

In addition to being randomly assigned to one of the two groups described above, your baby will be randomly assigned to having an oximeter (a machine that monitors oxygen in the blood) which reads slightly high or one that reads slightly low. The oximeters used in this study are FDA approved devices which have been adjusted for research purposes to show an oxygen saturation value which is either a little higher or a little lower than the true oxygen reading when the oxygen is in the normal range (between 85 and 95%). Outside the normal range, the oximeter shows the true oxygen level. This will help to protect your baby from oxygen levels that are too high or too low.

Your infant will be assigned to one of the four groups shown below. Neither you nor your baby's doctors will know which oxygen saturation range is being targeted; however, the alarm limits will remain the same as for all premature infants in our NICU. Your baby will not be exposed to lower or higher oxygen saturations than are currently accepted for all premature infants in our NICU. The assignments will be made randomly, like the flip of a coin.

CPAP Higher oxygen level in the blood	CPAP Lower oxygen level in the blood
Breathing tube + breathing machine + surfactant Higher oxygen level in the blood	Breathing tube + breathing machine + surfactant Lower oxygen level in the blood

All the rest of your infant's care will be the standard treatments for premature babies in the UNM Children's Hospital NICU. Information about that care and certain results, such as head ultrasounds and growth measurements, will be collected from your child's medical record. At 6 months and at 12 months we will call you and ask you questions about your child's breathing (especially wheezing and coughing), medication use, and visits to a Doctor, Emergency Room, or Hospital visits for treatment of breathing problems. We will also ask questions about family history of breathing problems, and questions about your home, including things that may increase your child's risk of breathing problems. It will take about 15 minutes to answer these questions. The children enrolled in this study will need to come to Special Baby Clinic for their 18-22 month old assessments of growth, breathing problems, development, and coordinated movement skills.

How long will my child be in this study?

Study guidelines for lung treatments of infants in both groups will be followed for two weeks. Your child will be on a study oximeter until about four weeks before the original "due date". At that time, the oximeter will be changed to a standard one for the remainder of his/her hospital stay. The early part of the project will last until the end of your child's hospital stay. In order to evaluate the long term effects of the treatments in this study, information will be collected about your baby's general health, and any hospitalizations during the first two years of life. By agreeing to participate in this study, you give consent for the release of medical records from other medical facilities and providers of medical care to Dr. Kristi Watterberg and her associates. Follow up at 18-22 months is essential for this study. Families who participate in this project are agreeing to remain in contact with the investigators and to return to the UNM Children's Hospital's Special Baby Clinic with their child when (s)he is 18 months of age.

What are the risks or side effects of being in this study?

Participation in this study may involve some added risks or discomforts. Some unknown risks may be learned during this study. All of these treatments are currently clinically accepted, but haven't been

compared with each other in this manner, so we are not able to predict which group may do better. One or both of these two treatments is the usual clinical practice for all babies who are this premature at UNMH. If your baby is assigned to the group of babies who have a breathing tube placed and surfactant given very early, he/she may benefit from the surfactant, but may have a higher risk for developing BPD because of the breathing tube. If your baby is assigned to the CPAP group, he/she may not receive the early benefit of surfactant, but may have a lower risk for developing BPD because no breathing tube is inserted. The CPAP mask can cause a low heart rate. If this happens, the mask is removed and repositioned. CPAP can cause air to collect in the stomach, so a small tube is placed from the mouth into the stomach. All babies are monitored for these problems.

For this study, there will be no change in the oxygen saturation range from the one that is currently used in the NICU at UNMH. In this study we are trying to further narrow the range that we are currently using. The specific and ideal oxygen range to reduce eye disease is unknown. We hope that this study will help to determine if a lower or higher oxygen range may be better. The higher and lower ranges that are used in this study are both in the oxygen range that is currently used for all babies admitted to the UNM NICU. The only other risk of this study is the risk to confidentiality. Every effort will be made to keep your child's medical record confidential.

What are the benefits to being in this study?

Your child may or may not be benefit from participating in this study. The knowledge learned from this study may help us treat babies in the future.

What other choices do I have if I do not want to be in this study?

The alternative to having your child participate in this project is not to participate. You should not feel obligated to agree to participate. Your questions should be answered clearly and to your satisfaction. If you choose not to have your child participate he/she will receive the standard care for premature infants as needed. This may include oxygen and help to breathe that is similar to the treatments in this study.

How will my information be kept confidential?

We will take measures to protect your privacy and the security of all your personal information, but we cannot guarantee confidentiality of all study data.

Information contained in your study records is used by study staff and, in some cases it will be shared with the sponsor of the study. The University of New Mexico Health Sciences Center Human Research Review Committee (HRRC) that oversees human subject research, the National Institutes of Health which sponsors this study, and the Food and Drug Administration and/or other regulatory entities will be permitted to access your records. There may be times when we are required by law to share your information. However, your name will not be used in any published reports about this study. A copy of this consent form will be kept in your medical record.

What are the costs of taking part in this study?

There are no costs involved in taking part in this study. You or your insurance company will be responsible for the costs incurred in your child's care because that care will not be different from what

is usually provided by the nursery staff. The National Institutes of Health and National Institute of Child Health and Human Development are providing financial support and/or materials for this study.

What will happen if I am injured or become sick because I took part in this study?

No commitment is made by the University of New Mexico Health Sciences Center (UNMHSC) to provide free medical care or money for injuries to participants in this study. If your child is injured or becomes sick as a result of this study, UNMHSC will provide him or her with emergency treatment, at your cost. It is important for you to tell your study doctor immediately if your child has been injured or becomes sick because of taking part in this study. If you have any questions about these issues, or believe that you have been treated carelessly in the study, please contact the Human Research Review Committee (HRRC) at the University of New Mexico Health Sciences Center, Albuquerque, New Mexico 87131, (505) 272-1129 for more information.

Will I be paid for taking part in this study?

No payment will be provided for this project.

How will I know if you learn something new that may change my mind about participating?

You will be informed of any significant new findings that become available during the course of the study, such as changes in the risks or benefits resulting from participating in the research or new alternatives to participation that might change your mind about participating.

Can I stop being in the study once I begin?

Your participation in this study is completely voluntary. You have the right to choose not to participate or to withdraw your participation at any point in this study without affecting your future health care or other services to which you are entitled.

At the discretion of the clinical provider, babies may be taken out of this study due to unanticipated circumstances. Examples of reasons for taking a participant out of the study include: the investigator deciding that continued participation could be harmful to your child or the study being canceled

Who can I call with questions or complaints about this study?

If you have any questions, concerns or complaints at any time about the research study, Kristi Watterberg, M.D., or her associates will be glad to answer them at (505) 272-0180 on Monday through Friday between 9 am and 5 pm. If you would like to speak with someone other than the research team, you may call the UNMHSC HRRC at (505) 272-1129.

Who can I call with questions about my rights as a research subject?

If you have questions regarding your rights as a research subject, you may call the UNMHSC HRRC at (505) 272-1129. The HRRC is a group of people from UNM and the community who provide independent oversight of safety and ethical issues related to research involving human subjects. For more information, you may also access the HRRC website at http://hsc.unm.edu/som/research/hrrc/.

Consent

You are making a decision whether to have your child participate in this study. Your signature below indicates that you read the information provided (or the information was read to you). By signing this consent form, you are not waiving any of your child's legal rights as a research subject.

I have had an opportunity to ask questions and all questions have been answered to my satisfaction. By signing this consent form, I agree to participate or let my child participate in this study. A copy of this consent form will be provided to you.

_____
Name of Parent/Child's Legal Guardian

_____
Signature of Parent/Child's Legal Guardian Date _____

I have explained the research to the subject and his/ her parent/legal representative, and answered all of his/ her questions. I believe that he/she understands the information described in this consent form and freely consents to participate.

_____
Name of Investigator/
Research Team Member

_____ / _____
Signature of Investigator/ Date
Research Team Member

Stanford University Research Consent Form
Cooperative Multicenter Network of Neonatal Intensive Care Units:
The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants (SUPPORT)
Director: Krisa Van Meurs, M.D.

IRB Approval Date: 12/17/08 **IRB Expiration Date: 12/16/09**

Is your child participating in any other research studies? _____ yes _____ no

Informed Consent

Your child is invited to participate in a research study to find out more about treatment with CPAP (positive air pressure to help keep the lungs inflated) and learn the appropriate levels of oxygen in the blood in premature infants. You are being asked to allow your child to be in the study because there is a possibility that (s)he will be born 12-16 weeks early (at 24 to 28 weeks of pregnancy).

The study, funded by the National Institutes of Health, is being conducted at Stanford and other medical centers across the country. The study will compare two ways of assisting premature infants to breathe. Infants who receive delivery room CPAP and who have specific guidelines for having a breathing tube placed will be compared to infants who have a breathing tube placed and surfactant (a liquid which helps babies with immature lungs breath easier by helping keep their lungs from collapsing) given in the delivery room. The study will also compare management of infants in lower range (85-89%) and higher range (91-95%) oxygen levels (saturation). We hope to determine if a lower range results in decreased ROP (Retinopathy of Prematurity, an eye disease that may result in impairment of vision or even blindness, which may be caused by excessive levels of oxygen.) Nationwide, a total of 1300 patients are expected to enroll in this study over about two years. We expect about 60 of those infants will be from Stanford. Children who are enrolled in the study will be involved for about two years.

If you decide to allow your child to be in this study, a few minutes before your child is born, (s)he will be randomly assigned, like the flip of a coin, to one of two lung treatment strategies. The treatments are as follows: 1) CPAP in the delivery room immediately after birth and continuing in the intensive care nursery (NICU), or 2) placement of a tube in the windpipe in the delivery room followed by surfactant administration and ventilation (breathing for the baby using a machine). Infants randomized to the CPAP group may, at some point in their care, require a windpipe tube and a breathing machine. If the attending physician deems this necessary, participation in the study will not affect this decision. Study guidelines for lung treatments of infants in both groups will be followed for two weeks.

In addition to being randomly assigned to one of the two groups described above, your baby will be randomly assigned to having an oximeter (blood oxygen monitor) which reads slightly high or one that reads slightly low. The oximeters used in this study are FDA approved devices which have been modified for research purposes. This modification makes the monitors show a oxygen

Participant ID

STUDY

saturation value which is either a little higher or a little lower than the true oxygen reading when values are in the normal range (between 85 and 95%). Outside those ranges, the oximeter works the same as a standard oximeter. This will allow us to keep the saturations at the high and low ends of the normal range and still protect the study infants from undesirable oxygen levels. The doctors and nurses taking care of your infant will not know if (s)he is in the high or low saturation group. This is to help assure that all patients are cared for in the same way. Your child will be on a study oximeter until about four weeks before the original "due date". At that time, the oximeter will be changed to a standard one for the remainder of his/her hospital stay.

Your infant will be assigned to one of the four groups shown below. Neither you or the doctors taking care of your infant will be able to choose which group your infant is assigned to. The assignments will be made randomly, like the flip of a coin.

CPAP Higher oxygen saturation	CPAP Lower oxygen saturation
Breathing tube + breathing machine Higher oxygen saturation	Breathing tube + breathing machine Lower oxygen saturation

Part of your child's regular care during the first few weeks after birth will include one or more head ultrasounds and, within about four weeks of your child's planned due-date, an MRI of the brain. The ultrasounds and MRI studies create pictures (images) of the brain which are used to look for brain injury. Children who participate in this study will have an ultrasound at the time the MRI is done so the doctors conducting the project can compare the findings and determine if one way of imaging gives more useful information than the other.
Other aspects of your infant's care will be the standard treatments for premature babies in the Stanford NICU. All children who participate in the project will return to the Development and

Participant ID

STUDY

Behavior Unit at regular intervals during the first two years as part of their routine care. When the children enrolled in this study return for their 18-22 month old assessments of growth, development, and coordinated movement skills, the study will collect that outcome information.

Additional Breathing Follow-Up

Many children who were born prematurely and needed help to breathe continue to have breathing problems such as wheezing and coughing in the first two years of life. The study would like to stay in touch with you by telephone beginning when your baby goes home and continuing every six months over the next 18-22 months, a total of four times. At these times, the caller will ask questions about your child's breathing, medication use, and visits to a doctor, emergency room, or hospital for treatment of breathing problems. The caller will also ask several questions about you and your family. Each call should take about 15 minutes of your time, less if your baby has had no breathing problems. The results from your baby's questionnaires will be combined with other babies from around the country. However, your baby's name will not be used.

If you decide you would like to participate in the telephone questionnaires, we will ask for your telephone contact information around the time that your baby is getting ready to go home. Your name and contact information will be given to the study calling center, based at the University of Rochester in Rochester, NY. Although they will have your name, the information you give them will be identified by your baby's study number, not your or your baby's name. Additionally, the study calling center will not disclose your name or contact information to any other person or entity.

Please indicate your decision below:

_____ Yes, I agree to participate in the telephone questionnaires

_____ No, I do not want to participate in the telephone questionnaires

Participation in this study may involve some added risks or discomforts. Because all of the treatments proposed in this study are within standard of care, there is no predictable increase in risk for your baby. There is no known risk or discomfort associated with the extra head ultrasound. Some unknown risks may be learned during the study. You will be told of any new

Participant ID

STUDY

information that is learned which may affect your child's condition or influence your willingness to have him/her continue participation in this study. The only other risk of this study is the risk to confidentiality. Every effort will be made to keep your child's medical record confidential.

There may be benefits to your child directly, including a possible decrease in chronic lung disease (need for extra oxygen near discharge) and/or a decrease in the need for eye surgery as a result of exposure to oxygen. Because we do not know in advance the actual strategies chosen for your child, or which of the treatment strategies is the most effective, it is also possible that your baby will receive no direct benefit. The knowledge learned from this study may help us treat babies in the future. However, each of the 4 possible combinations of treatments is considered by some NICUs to represent their desired approach.

WE CANNOT AND DO NOT GUARANTEE OR PROMISE THAT YOUR CHILD WILL RECEIVE ANY BENEFIT FROM THIS STUDY.

The alternative to having your child participate in this project is not to participate. You should not feel obligated to agree to participate. Your questions should be answered clearly and to your satisfaction. If you choose not to have your child participate, he/she will receive the standard care for premature infants including oxygen, and help to breathe as needed.

Any data that may be published in scientific journals or presented at scientific or medical meetings will not reveal the identity of your child. Patient information may be provided to Federal and regulatory agencies as required. The Food and Drug Administration, for example, may inspect research records and learn your identity if this study falls within its jurisdiction.

Your child's participation in this study is entirely voluntary.
Your decision whether or not to allow your child to participate will not prejudice your child or his/her medical care. If you wish to allow your child to participate in this study, you must sign this consent form and the authorization form. If you decide to let your child participate, you are free to withdraw your consent, including your authorization regarding the use and disclosure of your child's health information, and to discontinue participation at any time without prejudice to your child or effect on your child's medical care. If you decide to terminate your child's participation in this study, you should notify Dr Van Meurs or Dr Stevenson at (650) 723 5711.
The early part of the project will last until the end of your child's hospital stay. In order to successfully evaluate the approaches to lung treatment and oxygen used in this study, Dr. Van Meurs and her associates will want to collect information about your baby's general health, and any hospitalizations during the first two years of life. By agreeing to participate in this study, you

Participant ID

STUDY

give consent for the release of medical records from other medical facilities and providers of medical care to Dr. Krisa Van Meurs and her associates. Follow up at 18-22 months is essential for this study. Families who participate in this project are agreeing to remain in contact with the investigators and to return to the Mary L. Johnson Development and Behavior Unit at Packard Children's Hospital with their child when (s)he is 18 months of age.

While participating in this study, your child should not take part in any other research project without approval from all of the investigators. This is to protect your child from possible injury arising from such things as extra blood drawing, extra x-rays, interaction of research drugs, or similar hazards.

You and your child will not be paid to participate in this research study. You or your insurance company will be responsible for the costs incurred in your child's care because that care will not be different from what is usually provided by the nursery staff. The study will pay for the extra ultrasound obtained around the due-date. The National Institutes of Health and National Institute of Child Health and Human Development are providing financial support and/or materials for this study.

At the discretion of the protocol director subjects may be taken out of this study due to unanticipated circumstances. Examples of reasons for taking a participant out of the study include: *failure to follow the instructions of the Protocol Director and study staff, the investigator deciding that continued participation could be harmful to your child, the study being canceled, some other administrative reason.

If you have any questions, concerns or complaints about this research study, its procedures, risks and benefits, or alternative courses of treatment, you should ask the protocol director, Dr Van Meurs at 650 723 5711. You should also contact her at any time if you feel your child has been hurt by being a part of this study. If you cannot reach the protocol director, please page the research team at 415 607 4326.

If you are not satisfied with how this study is being conducted, or if you have any concerns, complaints, or general questions about the research or your child's rights as a participant, please contact the Stanford Institutional Review Board (IRB) to speak to someone independent of the research team at 650 723 5244 or toll free at 1 866 680 2906. You can also write to the Stanford IRB, Stanford University, Stanford, CA 94305-5401.

Participant ID

STUDY

All forms of medical diagnosis and treatment, whether routine or experimental, involve some risk of injury. In spite of all precautions, your child might develop medical complications from participating in this study. If such complications arise, the protocol director will assist you in obtaining appropriate medical treatment. In the event that your child has an injury or illness that is directly caused by participation in this study, reimbursement for all related costs of care first will be sought from your insurer, managed care plan, or other benefits program. You will be responsible for any associated co-payments or deductibles as required by your insurance. If costs of care related to such an injury are not covered by your insurer, managed care plan or other benefits program, you may be responsible for these costs. If you are unable to pay for such costs, the protocol director will assist you in applying for supplemental benefits and explain how to apply for patient financial assistance from the hospital. Additionally, Stanford is not responsible for research and medical care by other institutions or personnel participating in this study. You do not waive any liability rights for personal injury by signing this form.

As a research participant your child has the following rights. These rights include but are not limited to the participant's right to:

- be informed of the nature and purpose of the experiment;
- be given an explanation of the procedures to be followed in the medical experiment, and any drug or device to be utilized;
- be given a description of any attendant discomforts and risks reasonably to be expected;
- be given an explanation of any benefits to the subject reasonably to be expected, if
- applicable;
- be given a disclosure of any appropriate alternatives, drugs, or devices that might be advantageous to the subject, their relative risks and benefits;
- be informed of the avenues of medical treatment, if any, available to the subject after the experiment if complications should arise;
- be given an opportunity to ask any questions concerning the experiment or the procedures involved;
- be instructed that consent to participate in the medical experiment may be withdrawn at any time and the subject may discontinue participation without prejudice;
- be given a copy of the signed and dated consent form, and be given the opportunity to decide to consent or not to consent to a medical experiment without the intervention of any element of force, fraud, deceit, coercion or undue influence on the subject's decision.

Participant ID

STUDY

IRB Approval Date: 12/17/08 **IRB Expiration Date: 12/16/09**

YOUR SIGNATURE INDICATES THAT YOU HAVE READ AND UNDERSTAND THE ABOVE INFORMATION, THAT YOU HAVE DISCUSSED THIS STUDY WITH THE PERSON OBTAINING CONSENT, THAT YOU HAVE DECIDED TO PARTICIPATE BASED ON THE INFORMATION PROVIDED, AND THAT A COPY OF THIS FORM HAS BEEN GIVEN TO YOU.

Signature of Parent _____ Date _____ Authority to act for participant _____

(If available) Signature of Other Parent _____ Date _____ Authority to act for participant _____

The IRB determined that the permission of one parent is sufficient for research to be conducted under 45 CFR 46.404, in accordance with 45 CFR 46.408(b).

Person Obtaining Consent

I attest that the requirements for informed consent for the medical research project described in this form have been satisfied-that the participant has been provided with the Experimental Subject's Bill of Rights, if appropriate, that I have discussed the research project with the participant and explained to him or her in nontechnical terms all of the information contained in this informed consent form, including any risks and adverse reactions that may reasonably be expected to occur. I further certify that I encouraged the participant to ask questions and that all questions asked were answered.

Signature of Person Obtaining Consent _____ Date _____

Participant ID

STUDY

Informed Consent

Title of Research:	The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants (SUPPORT Study) (Multicenter Network of Neonatal ICU's)
Title of Secondary Research:	Neuroimaging and Neurodevelopmental Outcome (MRI Study) Postnatal Growth of Infants Enrolled in SUPPORT Study (Growth Study)
UAB IRB Protocol Numbers:	F040910010, X060418004 and F050922007
Investigators:	Dr. Wally Carlo and Dr. Namasivayan Ambalavanan
Sponsor:	Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)

You are being asked to give your permission for your baby to participate in a study designed to determine if using positive airway pressure during resuscitation after birth helps decrease the severity of lung disease in premature babies. We will also be looking at the ranges of oxygen saturation that are currently being used with these same babies. You and your baby were selected as possible participants because you are less than 28 weeks pregnant and your baby may be born prematurely. The doctors at UAB, along with 15 other centers across the country, are participating in this project sponsored by the by the National Institute of Child Health and Human Development.

This consent form gives you information about the research study, which a member of the research team will discuss with you. This discussion should go over all aspects of this research: its purpose, the procedures that will be performed, any risk of the procedures, and possible benefits. Once you are informed about this study, you will be asked if you want your baby to participate; if so, you will be asked to sign this form.

Introduction

If born prematurely, your baby is at risk for a breathing problem called **Respiratory Distress Syndrome (RDS).** A baby's lungs are made up of tiny air sacs; each one is supposed to open and close as the baby breathes in and out. Oxygen is supposed to go in and carbon dioxide is supposed to come out. This works well in full term babies and adults; however, in premature babies, the lung sacs don't always work this way. Some lung sacs open and close normally; others collapse and stick together when the baby breathes out making it harder for the baby to breathe. Doctors treat this problem with expanding breaths and pressure to keep the lungs slightly inflated between those breaths. Keeping a little air pressure in the lungs after the baby

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Consent Form Approval 2/25/09
Expiration Date 2/25/10

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breathes out (resting pressure) makes it easier for the baby to take the next breath. Sometimes a medication called *surfactant* is given to try to help keep the lung sacs expanded. After your baby is born, if he/she needs help breathing, the doctor or nurse will place a resuscitation bag over the baby's nose and mouth to provide oxygen and manual breaths. The bag is squeezed to force air into the baby's lungs. The bag and mask may be used to give breaths or give just pressure to keep the lungs inflated between breaths. This resting pressure is called continuous positive airway pressure or CPAP or PEEP.

At the present time, there is no recommendation regarding the early use of CPAP/PEEP in the delivery room and continuing it in the nursery for premature infants. However, some studies have suggested that the use of early CPAP/PEEP may be associated with improved outcomes such as: fewer babies needing to be placed on a breathing machine, less oxygen use in babies at one month of age and longer, and less need for a medication given in the babies lungs called surfactant. This study will begin in the delivery room and continue into the nursery to compare the use of CPAP/PEEP and early placement on the breathing machine along with the early use of surfactant to see if we can help lessen the severity of and even possibly prevent long term lung problems in premature infants.

Another part of the study will be looking at the ranges of oxygen saturation that are currently being used with premature infants. Doctors, nurses, and others taking care of your baby use a machine called a **pulse oximeter** in routine daily care to help them adjust the oxygen to meet the baby's needs. Sometimes higher ranges are used and sometimes lower ranges are used. All of them are acceptable ranges. In this part of the study, we would like to pinpoint the exact range that should be used to help prevent some of the problems that occur with premature babies such as Retinopathy of Prematurity (ROP). This is when there is abnormal blood vessel growth in the eye. It causes scar tissue to build up around the retina and if it pulls on the retina hard enough, it can cause blindness. It is known that ROP is increased by the prolonged use of supplemental oxygen from observations published in the 1950s, but the benefit of higher versus lower levels of oxygenation in infants, especially for premature infants, is not known. In going back and looking at how babies in the past were managed, it is being suggested that the use of lower saturation ranges may result in a lower incidence of severe ROP.

Expanation of Procedures

SUPPORT Study: If your baby is born before a gestational age of 28 weeks, he/she will randomly (like the flip of a coin) be placed into a group that receives early CPAP/PEEP use in the delivery room **or** early placement on the breathing machine (intubation) with the use of surfactant. Both ways are currently used in our hospital and we hope to determine which is the better way for these premature babies.

If your baby is in the Early CPAP group, he/she will be treated with CPAP/PEEP in the delivery room and will remain on it upon admission to the nursery. If, at any time, your baby shows signs of needing intubation for resuscitation purposes, then he/she will be intubated. If this happens within the first 48 hours he/she will also be given surfactant.

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If your baby is in the Early Surfactant and Ventilation group, he/she will be placed on the breathing machine in the delivery room and will be given surfactant within the first hour of birth. For the first 14 days of life, there will be guidelines for the doctors in the nursery to follow. These guidelines help them decide when to place babies on the breathing machines and when to try and take them off the breathing machines. These guidelines will also help decide when to put babies on and take them off of CPAP/PEEP.

The babies in this study will also be placed randomly (again, like the flip of a coin) into a group monitored with lower oxygen saturation ranges or higher oxygen saturation ranges. Oxygen saturation is measured on a baby with a machine called a pulse oximeter. It uses a tiny sensor on the hand or foot of the baby and can give the doctors a measurement of how saturated the baby's blood is with oxygen. Oximeters are not painful and can provide oxygen saturation measurements 24 hours a day. The babies in the lower range group will have a target saturation of 85-89%, while the babies in the higher range group will have a target saturation of 91-95%. All of these saturations are considered normal ranges for premature infants. If the saturation falls below 85% or goes higher than 95% then the pulse oximeter will alarm so that the doctors and nurses know when to turn your baby's oxygen up or down.

If your baby is still receiving oxygen close to the time of discharge (at approximately 36 weeks corrected age) a test will be done to determine the severity of lung disease that may be present. During this test, the oxygen your baby is receiving will be decreased gradually while continuously measuring oxygen saturation with the pulse oximeter. If the saturation falls below an acceptable range, your baby will then be returned to the prior oxygen level.

MRI Study: Part of your baby's regular care during the first few months after birth will include one or more head ultrasounds. The first one usually occurs during the first 2 weeks. There is also one done closer to the time of your baby's due date. In addition to the routine head ultrasound done close to your baby's due date, we would like to ask your permission to also do Magnetic Resonance Imaging (MRI) on your baby. The MRI is a common procedure that uses a magnetic field to make pictures of the inside of the head. It does this by taking a closer look at the tiny particles that are in the brain. Your baby will be placed on a narrow bed for about 20-30 minutes while the machine scans the brain and makes pictures. Your baby will not be exposed to any radiation when having the MRI done. The magnetic fields do not cause any known harmful effects at the levels used in the MRI machine. National and local guidelines have been developed for MRI machines, and these recommendations will be followed.

The ultrasound and MRI pictures of your baby's brain will be looked at by radiologists (doctors who are specialists in X-rays and other pictures of the body). Your doctors will tell you what they find. Because this study will be done in several hospitals across the United States, the ultrasound and MRI pictures from babies who participate will also be seen by other radiologists. They will look at all the pictures from all the babies.

Growth Study: It is routine care in the nursery to weigh and measure babies to watch their growth. With this secondary study to the SUPPORT Study, we will be collecting weight and measurements along with feeding information to take a closer look at how your baby grows.

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Duration of Study

Your baby will be involved in the ventilation part of this study for the first 14 days after birth. After the first 14 days, he/she will still be monitored with the saturation monitor as long as he/she is receiving extra oxygen. Once your baby has been off of oxygen for 72 hours, then the saturation monitor may be discontinued. Information will be gathered from the medical record throughout your baby's hospitalization.

We expect to include about 1310 babies in this study from all the NICHD Neonatal Research Network hospitals over a two year period.

Long Term Follow-up

When your baby is 18-22 months old, he/she will be seen in the Newborn Follow Up Clinic for an evaluation. At this visit, we will ask you a few extra questions about your baby's health. You will then be contacted in the future for further long term follow up for the study.

Benefits

The investigators do not promise or guarantee that your baby will receive any direct benefit from participating in the SUPPORT Study or any of the secondary studies. Participation will, however, benefit the medical community by providing valuable information which may help us treat babies in the future.

SUPPORT Study: If he/she is in the group which receives CPAP/PEEP, he/she might benefit by not needing additional breathing support. He/she may not require surfactant to be given into the lungs.

It is possible that using lower pulse oximeter ranges will result in fewer babies with severe Retinopathy of Prematurity (ROP).

MRI Study: There may be benefits to your baby directly, including findings of brain injury which will allow for earlier intervention than would normally occur.

Growth Study: There is no direct benefit to participating in this secondary study.

Risks and Discomforts

SUPPORT Study: The possible risks of using CPAP/PEEP include stomach bloating and a temporary slowing of the heart rate. Another possible risk is collapsing one or both of the lungs. Use of the CPAP/PEEP at the level used in this study does not increase the risk of collapsed lungs.

Like with the use of CPAP/PEEP, a possible risk of being intubated (placed on the breathing machine) may include a temporary slowing of the heart rate or possibly the collapse of one or

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both lungs. Another risk is the possibility of the airway being punctured. Other possible risks include bruising or cutting of the tongue, gums, or airway.

Other potential risks during resuscitation after birth include; the need for chest compressions, rescue medications, and even death. It is not thought that the use of either of these ways of delivering oxygen to the baby's lungs increases these risks.

There is no known risk to your baby from monitoring with the pulse oximeters used for this study. The possible risk of skin breakdown at the site will be minimized by your baby's nurse moving the oximeter to another arm or leg a couple of times a day.

CPAP/PEEP, intubation, and pulse oximetry are commonly used in the newborn intensive care (NICU). Study participation should not increase these risks because all procedures are carried out by experienced NICU staff.

MRI Study: The risks of participating in this secondary study are minimal. The head ultrasound is a routine part of the care of a premature baby, and the way it is performed will not be changed for this study, nor does it cause any discomfort for the baby. The MRI is often done on babies whenever the doctor feels that it will give him information he needs to treat the baby. For this study, all participants who agree to participate will have an MRI done after getting the approval of the attending physician. The "tapping" noise that the MRI machine makes may agitate your baby. To minimize this, your baby's ears will be covered while the MRI is being done.

Your baby may also need to be given medicine to make him/her drowsy for the MRI. A possible risk of sedation is breathing difficulty. Your baby's heart rate and breathing will be closely monitored by an experienced baby nurse to reduce this risk.

Growth Study: There are no risks to participating in this secondary study.

Alternatives

If you do not want your baby to participate in this study, he/she will receive the routine care given in the delivery room and nursery. The routine care may or may not include the use of CPAP and/or surfactant administration. He/she will most likely have oxygen saturation measured with a pulse oximeter as well. Routine care in the nursery may or may not include MRI.

Confidentiality

Information obtained about your baby for this study will be kept private to the extent allowed by law. However, research information that identifies your baby may be shared with the UAB Institutional Review Board (IRB) and others who are responsible for ensuring compliance with laws and regulations related to research, including people on behalf of the NICHD; the U.S. Food and Drug Administration (FDA); and the Office for Human Research Protections (OHRP). The results of the treatment may be published for scientific purposes. These results could include your lab tests and X-rays. However, your identity will not be given out.

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If any part of this study takes place at University Hospital, or The Children's Hospital of Alabama (TCHA), this consent document will become part of your medical record chart. Information relating to this study, including your name, medical record number, date of birth and social security number may be shared with the billing office of UAB and UAB Health System-affiliated entities, along with the Children's Hospital of Alabama, the Children's Health System, and its billing agents so that claims may be appropriately submitted to either the study sponsor or your insurance company for clinical services and procedures provided to you during the course of this study.

If your baby is transferred to another hospital or discharged before his/her eyes have reached maturity, then we will call the hospital or eye doctor to find out the results of eye exams that are done after discharge.

Refusal or Withdrawal without Penalty
Your taking part in this study is your choice. There will be no penalty if you decide not to be in the study. If you decide not to be in the study, you will not lose any benefits you are otherwise owed. You are free to withdraw from this research study at any time. Your choice to leave the study will not affect your relationship with this institution.

You may be removed from the study without your consent if the sponsor ends the study or if the study doctor decides it is not in the best interest of your baby's health.

Significant New Findings
Any significant new findings discovered during the course of this study, which may influence your decision to allow your baby to continue participation, will be made known to you.

Cost of Participation
The cost of your baby's standard medical care, including surfactant administration and head ultrasounds, will be billed to you and/or your insurance company in the usual manner. The costs of the study, including the MRI that will be done close to your baby's due date, will be covered by a research grant. If any other MRI's are ordered by your baby's doctor as part of clinical care, they will be billed to you or your insurance company. There will be no additional cost to you or your insurance company for expenses related to this study.

Payment for Participation in Research
There will be no payment to you or your baby for participating in this research study.

Payment for Research Related Injuries
If, as a result of your baby's participation, he/she experiences injury from known or unknown risks of the research procedures as described, immediate care and treatment, including hospitalization if necessary, will be available. Neither UAB, The Children's Hospital of Alabama, nor the National Institutes of Health has made provision for monetary compensation in the event of injury resulting from the research, and in the event of such injury, treatment is provided, but is not free of charge. Further information regarding medical treatment can be obtained from Dr. Wally Carlo at 934-4680.

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Questions

If you have questions about this study or experience any problems during the study, you should contact Dr. Wally Carlo at (205) 934-4680. You may also reach Monica Collins, RN, Shirley Cosby, RN, or Vivien Phillips, RN at (205) 934-5771. If you have questions about your baby's rights as a research participant, or concerns or complaints about the research, you may contact Ms. Sheila Moore. Ms. Moore is the Director of the Office of Institutional Review Board for Human Use (OIRB). Ms. Moore can be reached at (205) 934-3789 or 1-800-822-8816. If calling the toll-free number, press the press the option for "all other calls" or for an operator/attendant and ask for extension 4-3789. Regular hours for the Office of the IRB are 8:00 a.m. and 5:00 p.m. CT, Monday through Friday. You may also call this number in the event the research staff cannot be reached or you wish to talk to someone else.

Legal Rights

By signing this consent form, you are not waiving any of your or your child's legal rights.

Optional Participation in Secondary Studies

Please sign your choice below:

Neuroimaging and Neurodevelopmental Outcome (MRI Study)

_____ I agree to allow my baby to participate in the MRI Secondary Study.

_____ I **Do Not** agree to allow my baby to participate in the MRI Secondary Study.

Postnatal Growth of Infants enrolled in the SUPPORT Study (Growth Study)

_____ I agree to allow my baby to participate in the Growth Secondary Study.

_____ I **Do Not** agree to allow my baby to participate in the Growth Secondary Study.

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Signatures

You are making a voluntary decision whether or not to let your baby participate in this study. Your signature below indicates that you have decided to let your baby participate, that you have read (or been read) the information provided above, that you were given the opportunity to ask questions and that they have been answered to your satisfaction. The consent form will remain in the files at UAB Division of Neonatology and a copy will be placed in your baby's medical record. You will receive a copy of this signed consent form.

WAIVER OF ASSENT

The assent of _____ (name of child) has been waived because of age.

_____ _____

Signature of Parent or
Legally Authorized Representative

Date

_____ _____

Signature of Person Obtaining Consent

Date

_____ _____

Signature of Witness

Date

University of Alabama at Birmingham
Authorization for Use/Disclosure of Health Information for Research

What is the purpose of this form? You are being asked to sign this form so that UAB may use and release your health information for research. Participation in research is voluntary. If you choose to participate in the research, you must sign this form so that your health information may be used for the research.

Participant name: _____

UAB IRB Protocol Number: *F040910010, F050922007 and X060418004*

Research Protocol: *The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birthweight Infants; Secondary Studies: Neuroimaging and Neurodevelopmental Outcome and Postnatal Growth of Infants Enrolled in SUPPORT Study (Multicenter Network of Neonatal ICU's)*

Principal Investigator: *Wally Carlo, MD; Namasivayam Ambalavanan, MD;*

Sponsor: ***Eunice Kennedy Shriver*** *National Institute of Child Health Human Development (NICHD)*

What health information do the researchers want to use? All medical information and personal identifiers; including past, present, and future history, examinations, laboratory results, imaging studies and reports and treatments of whatever kind related to or collected for use in the research protocol.

Why do the researchers want my health information? The researchers want to use your health information as part of the research protocol listed above and described to you in the Informed Consent document.

Who will disclose, use and/or receive my health information? The physicians, nurses and staff working on the research protocol (whether at UAB or elsewhere); other operating units of UAB, HSF, The Children's Hospital of Alabama, Callahan Eye Foundation Hospital and the Jefferson County Department of Public Health, as necessary for their operations; the IRB and its staff; the sponsor of the research and its employees; and outside regulatory agencies, such as the Food and Drug Administration.

How will my health information be protected once it is given to others? Your health information that is given to the study sponsor will remain private to the extent possible, even though the study sponsor is not required to follow the federal privacy laws. However, once your information is given to other organizations that are not required to follow federal privacy laws, we cannot assure that the information will remain protected.

How long will this Authorization last? Your authorization for the uses and disclosures described in this Authorization does not have an expiration date.

Can I cancel the Authorization? You may cancel this Authorization at any time by notifying the Director of the IRB, in writing, referencing the Research Protocol and IRB Protocol Number. If you cancel this Authorization, the study doctor and staff will not use any new health information for research. However, researchers may continue to use the health information that was provided before you cancelled your authorization.

Can I see my health information? You have a right to request to see your health information. However, to ensure the scientific integrity of the research, you will not be able to review the research information until after the research protocol has been completed.

Signature of parent or legally authorized representative _____ Date _____

Printed Name of parent/participant's representative: _____

Relationship to the participant: _____

THE SURFACTANT POSITIVE AIRWAY PRESSURES AND PULSE OXIMETRY TRIAL IN EXTREMELY LOW BIRTH WEIGHT INFANTS

The SUPPORT Trial of the NICHD Neonatal Research Network

INVITATION TO TAKE PART

You are invited to enter your infant into a research study conducted at the University of Texas Health Science Center and Memorial Hermann Children's Hospital (MHCH). You are being asked to allow your infant to be in the study because there is a possibility he/she will be born between 16 and 12 weeks early (24-27 weeks gestational age).

Dr. Kathleen Kennedy and Dr. Jon Tyson (doctors who specialize in the care of sick or premature infants) and the National Institutes for Child Health and Human Development (NICHD) Neonatal Research Network are conducting this research study. Your decision to allow your infant to take part is voluntary and may be withdrawn at any time. Refusal to take part in this study or withdrawal at a later date will not affect the care given to your infant by the doctors or any other health professionals. You may refuse to answer any questions asked or written on any forms. This study has been approved by the Committee for the Protection of Human Subjects (CPHS) for the University of Texas Medical School at Houston as HSC-MS-04-415. The CPHS is an independent committee to help make sure that research studies are safe and properly performed.

DESCRIPTION OF RESEARCH

Purpose:
In the delivery room here at MHCH, most infants that are less than 28 weeks gestation routinely have a breathing tube placed and receive a dose of surfactant (a medicine which helps infants with immature lungs breath easier by helping keep their lungs from collapsing). Upon admission into the Neonatal Intensive Care Unit, they are placed on a breathing machine or ventilator which delivers oxygen and mechanical breaths. Additional doses of surfactant may also be given to these infants during the first two days of life. As many as half of the infants that receive this treatment go on to have a significant problem called Bronchopulmonary Dysplasia (BPD). BPD is caused by prematurity and long term exposure to the ventilator. A number of studies have suggested that the use of early CPAP (pressure applied with a face mask/prongs to help keep the lungs inflated) may result in improved outcomes, including a decreased need for mechanical ventilation, a decreased need for surfactant therapy, and a decrease in the amount of extra oxygen the infant requires.

Although additional oxygen is very necessary to the survival of premature babies with very under-developed lungs, studies have shown that too much oxygen can also be harmful. One of the problems that may occur in these tiny premature infants is retinopathy of prematurity or ROP. This eye disease may result in impairment of vision or even blindness and is associated with excessive oxygen therapy. We do not know at what blood oxygen levels ROP occurs.
Growth is another concern for the doctors who care for your infant. Infants that do not have enough oxygen grow poorly however infants that have too much oxygen are predisposed to a breathing problem called brochopulmonary dysplasia (BPD) which has been linked to poor growth.
It is also thought that high amounts of oxygen may actually cause damage to the lungs that could result in impaired growth of the airways. This could predispose infants to having increased respiratory problems during and after hospitalization.

Your infant's doctors have to balance the benefit and risk of using oxygen. We follow the oxygen level in the blood with a machine called an Oxygenation Saturation Monitor. The higher the monitor is reading the more oxygen is in the infant's blood. The highest a monitor can read is 100%. We keep our saturation monitors between 85% and 95% for our premature infants. Studies have suggested that the use of lower saturation ranges may result in a lower risk of severe ROP and BPD. However, oxygen saturations which are too low may result in poor neurological outcomes such as learning disabilities or uncoordinated muscle movements. Currently there is no agreement on the accepted saturation monitor ranges for managing premature infants from birth.

The purposes of this trial are the following:

1) To compare infants who receive delivery room CPAP and who have strict guidelines for having a breathing tube placed with infants who have the tube placed and surfactant given in the delivery room to determine if the use of CPAP from birth results in a decrease in broncopulmonary dysplasia. Broncopulmonary dysplasia or BPD happens

when the lungs grows abnormally because of exposure to high doses of oxygen and mechanical ventilation (breathing machine).

2) To compare low range (85-89%) oxygen saturation levels with high range (91-95%) levels to determine if a lower range results in a decrease in ROP.

3) To compare growth from birth to 18 months adjusted age in the high versus low saturation groups.

4) To compare breathing outcomes at discharge to 18 months adjusted age in the high versus low saturation groups.

DESCRIPTION OF THE STUDY

Procedure:
If you agree for your infant to take part in this study, the following will happen to him/her: If you consent to take part in the study and your infant delivers between 24 and 27 6/7 weeks gestation he/she will be randomized (chosen by chance like the flip of a coin) at the delivery to one of two treatment strategies. At the same time your infant will also be randomized to a "high" or "low" oxygen saturation monitor group. Please note that if you deliver twins, triplets etc they will all be randomized to the same treatment group and oxygen saturation group.
The treatments are as follows:
1) CPAP in the delivery room immediately after birth and continuing in the NICU, or
2) The placement of a tube in his/her trachea in the delivery room followed by a dose of surfactant and ventilation (breathing for the infant using a machine).
We will know if your infant was randomized to receive the breathing tube or CPAP.

The oxygen saturation monitor your infant has been randomized to will be started after he/she gets to the Neonatal ICU. He/she will be place on either a "High" reading or "Low" reading saturation monitor. Within the range of oxygen which we normally use, your infant will either be on the high end of normal or the low end of normal. We will not know what saturation monitor your infant gets. The saturation monitors used in this trial are FDA approved saturation monitors which have been modified for research purposes. This modification makes the monitors show a value which is either slightly higher or slightly lower than the true oxygen level when values are between 85 and 95%. Outside those ranges, the saturation monitor works the same as other oxygen saturation monitors.

Usually all infants in the nursery are weighed daily. Each week as part of routine care your infant's measurements (height and head circumference) are done. The research staff will be doing these measurements at age 1, 2, 3, and 4 weeks, at 32 weeks and 36 weeks adjusted age and at discharge.

To assess your infant's breathing outcomes from discharge until 18 months adjusted age 4 interviews/questionnaires will be conducted by phone or in person in the follow-up clinic.

If you decide to sign this consent and let your infant be in this study, we will collect information from your infant's medical record about his/her medical care and how he/she does throughout his/her hospital stay.

OPTIONAL STUDY COMPARING MRI AND HEAD ULTRASOUND

Premature infants, like yours, have a higher risk for brain injury. Although the way we will be providing breathing support (breathing machine or CPAP) and oxygen are routinely use in our nursery, the doctors in the Neonatal ICU (and those doing the study) do not know if either method could cause brain injury. For this reason a sub-study has been added. It is also not known if the brain ultrasound or the MRI is better at predicting your infant's outcome. Both have been used as part of routine care in neonatal units to help counsel parents and better predict the outcome of high risk infants like yours. You may decide whether you agree to allow your infant to take part in this sub-study by checking one of the boxes below.
Part of your infant's routine care during the first few weeks after birth will include one or more head ultrasounds. Head ultrasounds are done at your infant's bedside and take less than 15 minutes to complete. Also, within about four weeks of your infant's planned due-date, a MRI of the brain is done as part of his/her routine care. The ultrasounds and MRI studies show images (pictures) of the brain which are used to look for brain injury. Infant's who take part in this study will have an extra head ultrasound at the time the MRI is done so the doctors doing the study can compare the findings and see if one way of imaging gives better information than the other. This is another question this sub-study will be able to answer. There are no additional risks, time commitments, or costs to you if you allow your infant to take part in this sub-study. Because your infant would receive both a brain ultrasound and a MRI, you can be sure that he/she is receiving the best diagnostic tests available. His/her doctors

would know the result of both tests which may improve his/her ability to evaluate what your infant's development is likely to be.
Place an X in the box to indicate if you agree or do not agree to allow your infant to take part in this sub-study. If you decide not to take part in the sub-study you can still take part in the main study.

☐ Yes, I agree to allow my infant to take part in the sub-study

☐ No, I do not agree to allow my infant to take part in the sub-study

TIME COMMITMENT

This study begins in the delivery room when your infant is born and if he/she is between 24 0/7 to 27 6/7 weeks gestation. The CPAP/breathing tube part of the study will continue for 14 days. Your infant will remain on the saturation monitor until he/she reaches 36 weeks adjusted age. (e.g. 24 wks gestation plus 12 weeks of age = 36 weeks adjusted age.)
Your infant will be followed in our Infant Follow-up clinic at 6 and 12 months as standard of care for small infant. These visits will take approximately two hours. At 18-22 months corrected age your infant will receive a complete exam. A neonatologist or pediatrician will do a complete physical exam. Also a developmental specialist will do an assessment of his/her muscle movements and learning skills. On this day the evaluation will take approximately 3 hours. Again, this follow-up visit is considered standard of care for small infants.
The breathing outcome interviews will be conducted prior to discharge, and at 6, 12 and 18 months adjusted age. These interviews will be conducted by phone or in the clinic. The interview/questionnaire will be asking about doctor visits, hospitalizations or emergency room visits, medications, diet, and a breathing problems assessment. These interviews should take 15-20 minutes each.

BENEFITS

There may or may not be a benefit to your infant for taking part in this study. Possible benefits to your infant include; a possible decrease in brochopulmonary dysplasia (need for extra oxygen near discharge) and/or a decrease in the need for eye surgery as a result of exposure to oxygen. Because we do not know in advance the actual strategies chosen for your infant, or which of the treatment strategies is the most effective, it is also possible that your infant will receive no direct benefit. The knowledge learned from this study may help us treat infants in the future. However, each of the 4 possible combinations of treatments is currently used by some NICUs as their primary approach to treating premature infants.

RISKS AND/OR DISCOMFORTS

Taking part in a study may involve some added risks or discomforts. Because all of the treatments proposed in this study are standard of care, there is no expected increase in risk for your infant.

Infants randomized to the CPAP group may, at some point in their care, require a breathing tube and ventilation. If the attending doctor deems this necessary, being part of this study will not affect this decision. Some unknown risks may be learned during the study. If these occur, you will be informed by the study personnel.

ALTERNATIVES

This study is voluntary. If you choose not to have your infant take part in the project, he/she will continue to receive routine care.

STUDY WITHDRAWAL

You may withdraw your infant from the study at any time by contacting one of the Research Team at 713-500-5734.

COSTS, REIMBURSEMENTAND COMPENSATION

There will be no additional costs to you or your infant for taking part in this research study

IN CASE OF INJURY

If your infant suffers an injury as a result of taking part in this research study, please understand that nothing has been arranged to provide free treatment of the injury or any other type of payment. However, all needed facilities, emergency treatment, and professional services will be available to your infant, just as they are to the community in

general. You should report any injury to Dr. Kathleen Kennedy at 713-500-5734 and to the Committee for the Protection of Human Subjects at 713-500-7943.

CONFIDENTIALITY

You, or your infant, will not be personally identified in any reports or publications that may result from this study. Any personal information about your infant that is gathered during this study will remain confidential to every extent or the law. A special number will be used to identify your infant in the study and only the investigator(s) at UT Medical School and Hermann Children's Hospital will know your infant's name. Please understand that representatives of the Food and Drug Administration (FDA), the Committee for the Protection of Human Subjects (CPHS), and the sponsor of this research may review your infant's research and/or medical records for the purposes of verifying research data. The FDA representative can see personal identifiers in your infant's record; however his/her identity will be shielded from the view of the sponsor's representative. Your infant's name will not be seen by the sponsor unless the CPHS gives its permission for you to be contacted. You or your infant will not be personally identified in any reports or publications that may result from this study. There is a separate authorization form that you will be asked to sign which details the use and disclosure of your infant's protected health information.

QUESTIONS

You are making a decision whether or not to voluntarily take part in this study. You should not sign until you understand all the information presented in the previous pages and until all your questions about the research have been answered to your satisfaction. If you have any additional questions regarding this study Dr. Kathleen Kennedy or one of the research nurses will be available to answer them for you at any time. You may contact them at 713-500-5734 or 713-704-2900.

SIGNATURES

Sign below only if you understand the information given to you about the research and choose to take part. Make sure that any questions have been answered and that you understand the study. If you have any questions or concerns about your rights as a research subject, call the Committee for the Protection of Human Subjects at 713-500-7943. If you decide for your infant to take part in this research study, a copy of this document will be given to you.

Parent/guardian signature	Date	Time
Printed name of Parent/guardian		
Person obtaining consent	Date	Time
Printed name of person obtaining consent		
Witness	Date	Time

This study (HSC-MS-04-415) has been reviewed by the Committee for the Protection of Human Subjects (CPHS) for the University of Texas Houston Health Science Center. For any inquiries regarding research subject's rights, or to report any research related injury, call the CPHS at (713) 500-7943.

DTF1209

PATIENT INFORMATION

University of California, San Diego

Parent Informed Consent

The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

The SUPPORT Trial of the NICHD Neonatal Research Network

This is a research study. Research studies include only subjects who choose to take part. You are being asked to to allow your child to be in the study because there is a possibility he/she will be born between 16 and 12 weeks early (24-28 weeks gestational age). Please take your time to make your decision. Discuss it with your family. Be sure to ask any questions that you may have.

STUDY INVESTIGATOR AND SPONSOR

Investigator(s): Neil Finer, MD
Sponsor: **Eunice Shriver National Institute of Child Health and Human Development**

WHY IS THIS STUDY BEING DONE?

This reasons this study is being done are:

1) To compare infants who receive delivery room CPAP (Continuous Positive Airway Pressure – a **commonly used method of keeping babies lungs expanded with increased airway pressure)** and who have strict guidelines for having a breathing tube placed with infants who have the tube placed and surfactant (a liquid which helps babies with immature lungs breath easier by helping keep their lungs from collapsing) given in the delivery room.
2) To compare low range (85-89%) oxygen saturation levels with high range (91-95%) levels to determine if a lower range results in decreased ROP (Retinopathy of Prematurity, an eye disease that may result in impairment of vision or even blindness, which may be

5.1 08
5.1 08
4-30 09
7 pgs

12521

caused by excessive levels of oxygen.)

WHAT MAKES THIS DIFFERENT FROM THE USUAL TREATMENT?

The use of CPAP and Intubation/Surfactant are both treatments currently used in the delivery room at UCSD. The decision as to which to use is currently made by the physician attending the delivery.

The oxygen level currently used in the NICU at UCSD is between 85% and 95%. Both treatment groups (85-89% and 91-95%) fall within that range. The study will attempt to keep babies in one of these two smaller ranges.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

50 subjects will be in this study at UCSD, and a total of 1310 nationwide at 16 other academic medical centers.

HOW LONG WILL YOUR CHILD BE IN THE STUDY?

Your child will be in the study for 18-22 months. The part of the study which uses either CPAP or Intubation and Surfactant lasts for 14 days. The part which keeps your baby in one of two levels of oxygen continues until your baby no longer need oxygen, or reach 36 weeks adjusted age. (A baby who was born at 24 weeks gestation will reach 36 weeks adjusted age 12 weeks after birth.) The follow-up part of the study that will see how your baby is doing developmentally will take place at 18-22 months. The NICHD is currently considering following infants in the SUPPORT trial until school age (6-7 years). This consent will include your permission to contact you at that time to re-evaluate you child's development. Because this will occur for some children after 7 years of age, we would also ask your child for their assent at that time.

You can stop your child's participating at any time. However, if you decide to stop your child from participating in the study, we encourage you to talk to the research doctor.

WHAT IS INVOLVED IN THE STUDY?

This is what will happen if your child participates in this study:

Prior to delivery, and after your permission, your baby will be randomized (chosen by chance like the flip of a coin) to one of two lung treatment strategies. The treatments are as follows:
1) CPAP in the delivery room immediately after birth and continuing in the NICU, or
2) The placement of a tube in his/her trachea (windpipe) in the delivery room followed by

surfactant administration and ventilation (breathing for the baby using a machine)
And,
In addition to being randomly assigned to one of the two groups described above, your baby will be randomized to a High reading or Low reading oximeter [a monitor that displays how much oxygen is in the blood.] The oximeters (oxygen monitors) used in this trial are FDA approved oximeters which have been modified for research purposes. This modification makes the monitors show a value which is either slightly higher or slightly lower than the true oxygen level when values are between 85 and 95%. Outside those ranges, the oximeter works the same as the standard of care device.
Which group your baby is randomized to will not be known to the nurse taking care of your baby, or his/her physician. Only the study coordinator will know which group your baby is in. Within the range of oxygen which we normally keep babies in, your baby will either be on the high end of normal or the low end of normal. He/she will remain on this device until he/she reaches 36 weeks adjusted age. (e.g. 24 wks gestation plus 12 weeks of age = 36 weeks adjusted age.) Other care will be conducted as normal during his/her participation in the study.

Your baby will be followed in our Infant Follow-up clinic at 6 and 12 months as standard of care for small babies. At 18-22 months corrected age your baby will receive, at no charge to you, a complete exam of their muscles, nerves, and mental and coordinated movement skills.

We will continue to stay in touch with you and your infant by telephone or in person at one of your visits every 6 months over the next 18-22 months, a total of three times.

WHAT ARE THE RISKS OF THE STUDY?

Participation in this study may involve some added risks or discomforts. Because all of the treatments proposed in this study are standard of care, there is no predictable increase in risk for your baby. Infants randomized to the CPAP group may, at some point in their care, require intubation and assisted ventilation (methods to help them breathe). If the attending physician thinks this is necessary, participation in the study will not affect this decision. Some unknown risks may be learned during the study. If these occur, you will be informed by the study personnel. The only other risk of this study is the risk to confidentiality. Every effort will be made to keep your child's medical record confidential. There will be no name or other patient identification in any study report that may be published after the study is completed. Measures taken to protect you and your baby's identity are described in the confidentiality section of this document.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?
There may be benefits to your child directly, including a possible decrease in chronic lung disease (need for extra oxygen near discharge) and/or a decrease in the need for eye surgery as a result of exposure to oxygen. Because we do not know in advance the actual

strategies chosen for your child, or which of the treatment strategies is the most effective, it is also possible that your baby will receive no direct benefit. The knowledge learned from this study may help us treat babies in the future. However, as noted above, each of the 4 possible combinations of treatments is considered by some units to represent their desired approach.

WHAT OTHER OPTIONS ARE THERE?

As an alternative to participation in this study you may decide to have your baby's doctor decide which treatment your baby will receive. If you decide not to include your child in this study, none of his/her medical information will be included in the study data. Participation in research is entirely voluntary. You may refuse to participate or withdraw at any time without jeopardy to the medical care your child will receive at this institution of other loss of benefits to which your child is entitled. If you withdraw your child from the study, the attending physician will decide whether to maintain current treatment or change it, based on your child's needs at the time of the decision. Data collection for research purposes will stop at that time.

CAN YOUR CHILD BE REMOVED FROM THE STUDY WITHOUT YOUR CONSENT?

Your child's participation in this study may be ended without your consent by the investigator or your baby's doctor if it is in your child's best medical interest, there is a lack of effect, or for other reasons. If your newborn leaves the study early, he/she will continue with whichever treatment the doctor feels is best.

WHAT ABOUT CONFIDENTIALITY?

Every reasonable effort will be made to keep your child's records confidential. Clinical information will be collected from your baby's chart by study personnel at UCSD. Information will be labeled with a code number. Coded information will be sent to the NICHD Neonatal Network's Data Collection Center at Research Triangle Institute (RTI) in Research Triangle Park, North Carolina. The study log linking the code number with your baby's identity will be kept under lock and key at UCSD. Information directly identifying your baby will not leave UCSD. Research records will be kept confidential to the extent provided by law.Your child's records and information will not be released without your consent to the extent the law allows. If the study results are published or presented, your child will not be identified.

WHAT ARE THE COSTS?

There are no costs to participate in this trial.

WHAT IF YOUR CHILD IS INJURED IN THE STUDY?

If your child is injured as a direct result of participation in this research, the University of California will provide any medical care your child needs to treat those injuries. The University will not provide any other form of compensation to you if your child is injured. You may call the UCSD Human Research Protections Program office at (858) 455-5050 for more information about this, or to inquire about your rights as a research subject, or to report research-related problems.

_____ has explained this study to you and answered your questions. If you have other questions or research-related problems, you may reach Wade Rich, the Study Coordinator, or Renee Bridge, the Research Nurse, at 619-543-3759. You may contact the principal investigator Dr. Neil Finer at 619-543-3794

WILL YOU OR YOUR CHILD BE COMPENSATED?

Neither you nor your child will receive compensation for participation in this trial.

WHO DO YOU CALL IF YOU OR YOUR CHILD HAVE QUESTIONS OR PROBLEMS?

For questions about the study or a research-related injury, contact the researcher:

Neil Finer, MD
619-543-3794

WHAT ARE YOUR CHILD'S RIGHTS AS A RESEARCH SUBJECT?

Taking part in this study is voluntary. You may choose not to let your child take part or you or your child may choose to leave the study at any time. Your decision will not result in any penalty or loss of benefits to which your child is entitled. If you have questions about your child's rights you may call:

University of California, San Diego
Human Research Protections Program
(858) 455-5050

You will be told about any new information that may affect your child's health, welfare, or willingness to stay in this study.

SIGNATURE AND CONSENT TO BE IN THE STUDY:

Your signature below means that you have read the above information about the _____ study and have had a chance to ask questions to help you understand

what your child will do in this study and how your child's information will be used.

You or your child can change your minds later if you want to. You will be given a copy of this consent form and a copy of the Subject's Bill of Rights. By signing this consent form you are not giving up any of your or your child's legal rights.

NAME OF PARTICIPANT	AGE
SIGNATURE OF PARENT OR GUARDIAN	DATE
SIGNATURE OF 2nd PARENT OR GUARDIAN	DATE
SIGNATURE OF WITNESS (person explaining this form)	DATE

SUBJECT'S BILL OF RIGHTS

It is important that the purpose and procedures of the research study are fully understood and that consent is offered willingly. A subject in a research study or someone, who is asked to give consent on behalf of another person for such participation, has the right to:

1. Be informed of the nature and purpose of the research.
2. Be given an explanation of all procedures to be followed and of any drug or device to be used.
3. Be given a description of any risks or discomforts, which can be reasonably expected to result from this research study.
4. Be given an explanation of any benefits, which can be reasonably expected to the subject as a result of this research study.
5. Be informed of any appropriate alternative procedures, drugs, or devices that may be advantageous and of their relative risks and discomforts.
6. Be informed of any medical treatment, which will be made available to the subject if complications should arise from this research.
7. Be given an opportunity and encouraged to ask any questions concerning the study or the procedures involved in this research.
8. Be made aware that consent to participate in the research may be withdrawn and that participation may be discontinued at any time without affecting continuity or quality of medical care.
9. Be given a copy of the signed and dated written consent form if requested.
10. Not be subjected to any element of force, fraud, deceit, duress, coercion, or any influence in reaching the decision to consent or to not consent to participate in the research.

If you have any further questions or concerns about your child's rights as a research subject, please contact your research doctor, the Children's Hospital Office for Human Subjects Protection at (858) 966-4008 or the UCSD Human Research Protections Program.

The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

Background

You are being asked to allow your baby to be in the study because there is a possibility he/she will be born between 24 and 27 weeks gestation. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, and relatives if you wish. Ask us if there is anything that is not clear or if you would like more information. Please take time to decide whether or not you volunteer your baby to take part in this research study.

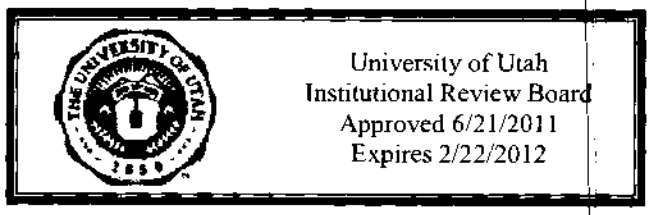
Our hospital is conducting this study in cooperation with the National Institutes for Child Health and Human Development (NICHD) Neonatal Research Network to try to determine the optimal means for managing early breathing support in the extremely premature infant (CPAP or a breathing tube) and to determine the appropriate level of oxygen saturation (oxygen levels in the blood) in extremely premature babies. CPAP stands for Continuous Positive Airway Pressure. The pressure is provided by the flow of oxygen and air through prongs or a tube in the nose, and the purpose of the pressure is help keep the lungs inflated making it easier for the baby to breathe and to get adequate oxygen into the blood.

Study Procedures

Prior to delivery, and after your permission, your baby will be randomized (chosen by chance, like a flip of a coin) to one of two lung treatment strategies. The use of early CPAP and Intubation/Surfactant are both treatments currently used immediately after delivery at this hospital. The decision as which to use is currently made by the physician attending the delivery. The randomized treatments are as follows:

1) CPAP immediately after delivery continuing in the neonatal intensive care unit (NICU), or
2) The placement of a breathing tube (ETT) in the airway immediately after delivery followed by surfactant administration and assisted ventilation (breathing for the baby using a machine)
And,
3) Oxygen saturation levels (O2-SAT's) maintained between 85-89% (low range), or
4) Oxygen saturation levels (O2-SAT's) maintained between 91-95% (high range)
The box below indicates the 4 possible treatment combinations your infant can be randomized to.

CPAP and Higher range oxygen saturation	CPAP and Lower range oxygen saturation
Breathing tube + Surfactant and Higher range oxygen saturation	Breathing tube + Surfactant and Lower range oxygen saturation



The physician or nurse caring for your baby will not know which oxygen saturation group the baby is randomized to.

Your baby will remain on the specially modified O2-SAT monitor until he/she reaches 36 weeks corrected age (example: 24 weeks gestation plus 12 weeks of age = 36 weeks adjusted age) or until the monitor is no longer needed because your baby is in room air.

Other care will continue as normal during his/her participation in the study.

A secondary purpose to this study is to determine the longer term effect of different approaches to breathing and oxygen support in the very premature baby. In that regard, this study includes several other planned follow-up evaluations of all study baby's during the first two years of life including:

a. follow up at 6 and 12 months in our high-risk infant follow-up clinic
b. follow-up for subsequent lung problems
c. follow-up at 18-22 months of age for neurodevelopmental function (a complete exam of their muscles, nerves, mental and coordinated movement skills)
d. a comparison of currently applied radiology studies (MRI and Ultrasound) obtained at 36-42 weeks corrected gestation for predicting later neurodevelopmental function

Some of these follow-ups may be by phone and some may be in our special follow-up clinic for very premature infants. The costs of all follow-up evaluations and the MRI examination are covered by the NIH Neonatal Research Network.

Our study coordinator will keep track of how your baby is doing up to 40 weeks gestational age (the babies original due date) or until discharge. Once your baby reaches 36 weeks gestational age we will record if he/she is still being treated with oxygen and/or a ventilator. If your baby is still on nasal cannula oxygen we will try to wean him/her off the oxygen using a standard protocol. If he/she successfully weans off oxygen, your baby's medical team may decide to take him/her completely off oxygen. All information will have a code number and, after discharge, this information will be sent to the NICHD Neonatal Network's Data Collection center at Research Triangle Park, North Carolina.

A further planned follow-up will occur when your baby is about 6 – 7 years old. This will involve neurological, developmental and intelligence testing at a Follow-Up clinic appointment. With your permission we will maintain contact with you in order for your baby to attend the Follow Up appointment when he/she is in grade school.

Risks

All treatments proposed in this study are currently accepted standard of care. All of these treatment options may have risks but there is no known predictable increase in risk to your baby from any one approach. We don't know which approach to treatment is better or safer – that is why we are doing this study. Infants randomized to the CPAP group may, at some point in their care, require intubation and assisted ventilation. If the attending physician deems necessary, participating in this study will not effect this decision. Some unknown risks may be learned during the study. If this occurs, you will be informed by the study personnel. The only other risk in this study is the risk to confidentiality. Every effort will be made to keep your child's medical

record confidential. There will be no names or other patient identification in any study report that may be published after the study is complete. Measures taken to protect you and your baby's identity are described in the confidentiality.

Benefits

There may be benefits to your child directly, including a possible decrease in chronic lung disease (need for extra oxygen at discharge) and decrease in the need for eye surgery as a result of exposure to oxygen. However, we cannot promise any benefits to your baby from being in this study. The knowledge learned from this study may help us treat babies in the future.

Confidentiality

As an alternative to participation in this study you may decide to have your baby's doctor decide which treatment your baby will receive. If you decide not to include your baby in this study, none of his/her medical information will be included in the study data. Participation in research is entirely voluntary. You may refuse to participate or withdraw at any time without jeopardy to the medical care your baby will receive at this institution. Data collection for this study will stop at that time.

Person to Contact

If you have concerns or questions about this research or any related matter, you can contact the primary investigator, Dr. Bradley Yoder @ 801-581-7052 or co-investigator, Dr. Roger Faix@ 801-587-7500, in the Department of Pediatrics/Neonatology, University of Utah School of Medicine. After hours, please call the NICU directly (University Hospital: 801-581-2775; or Primary Children's Medical Center: 801-588-3800) and ask for the doctor on call. They will be able to answer your questions or contact the above investigators. If you believe your child has been harmed as a result of participation, or if you have any complaints or concerns, please contact the study team.

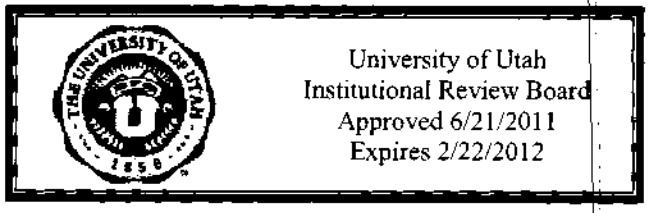
Institutional Review Board

Contact the Institutional Review Board (IRB) if you have questions regarding your child's rights as a research participant. Also, contact the IRB if you have questions, complaints or concerns which you do not feel you can discuss with the investigator. The University of Utah IRB may be reached by phone at (801) 581-3655 or by e-mail at irb@hsc.utah.edu.

Research Participant Advocate: You may also contact the Research Participant Advocate (RPA) by phone at (801) 581-3803 or by email at participant.advocate@hsc.utah.edu.

Research-Related Injury

If your infant is injured from being in this study, medical care is available at either the University of Utah Hospital or Primary Children's Medical Center, as it is to all sick or injured people. The University of Utah Hospital and Primary Children's Medical Center do not have a program to pay you if your infant is hurt or has other bad results from being in the study. The costs for any treatment or hospital care would be charged to you or your insurance company (if you have insurance), to the study sponsor or other third party (if applicable), to the extent those parties are responsible for paying for medical care you receive. Since this is a research study, some health insurance plans may not pay for the costs.



The University of Utah is a part of the government. If your child is injured in this study, and you want to sue the University or the doctors, nurses, students, or other people who work for the University, special laws may apply. The Utah Governmental Immunity Act is a law that controls when a person needs to bring a claim against the government, and limits the amount of money a person may recover. See Section 63G-7-101 to -904 of the Utah Code. .

Voluntary Participation
It is up to you to decide whether or not your baby will take part in this study. If you do decide to have him/her take part you will be asked to sign this consent form. You are free at any time to withdraw from this study without giving a reason. Whether your baby joins this study or not, your baby will receive the same medical and nursing care as needed and it will not affect the relationship you have with the investigator or other medical staff.

Unforeseeable Risks
The particular treatment or procedure may involve risks to the baby that are currently unforeseeable but because all of the treatments proposed in this study are standard of care, there is no unpredictable increase. If unknown risks are learned during the study, you will be informed by the study personnel. The only other risk of this study is a risk to confidentiality. Every effort will be made to keep your baby's medical record confidential.

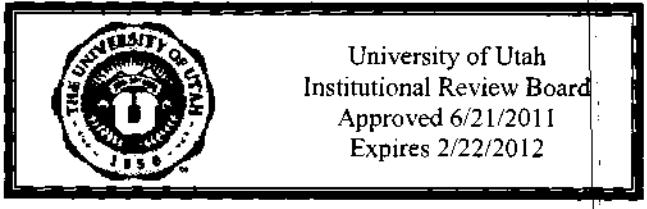
Right of Investigator to Withdraw
Your baby may withdraw from the study at any time without penalty. Dr. Bradley Yoder or his associate investigators can withdraw your baby without your approval. Possible reasons for withdrawal include a need to transfer care to a different hospital not involved in this study or early termination of this study for safety considerations.

Costs to Subjects and Compensation
There is no cost to parents nor is there any compensation for participating in this study. Standard costs for care will be billed to you and your insurance company in the usual manner. The exception to this is that the cost of the MRI scan to be obtained at 36 weeks corrected age will be covered by study funds obtained from the NIH Neonatal Research Network and will not be billed to you.

New Information
Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, your research doctor will tell you about it and discuss with you whether you want to continue in the study. If you decide to continue your baby in the study, you will be asked to sign an updated permission form. Also, on receiving new information your research doctor might consider it to be in your baby's best interest to withdraw him/her from the study. They will explain the reasons and arrange your baby's care to continue.

Number of Subjects
We expect to include about 1310 babies in the study from the fifteen NICHD Neonatal Research Network hospitals over a two- year period. The University of Utah and LDS Hospital will enroll around 60 babies over the two year period.

Approval to Use Your Child's Protected Health Information



Signing this document means you allow us, the researchers in this study, and others working with us to use information about your baby's health for this research study. You can choose whether or not to will participate in this research study. However, in order to participate you have to sign this consent and authorization form.

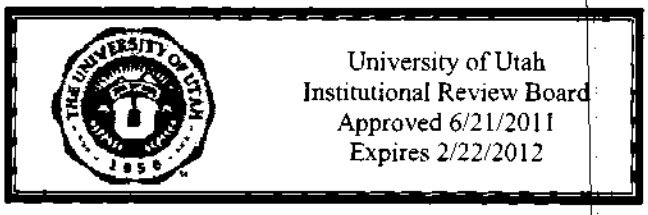
This is the information we will use:

- Name
- Address
- Telephone number
- Current and past medications or therapies
- Information from a physical examination, such as blood pressure reading, heart rate, breathing rate, and temperature
- Information related to the use of any device for support of lung function such as ventilator pressures, oxygen concentration and blood oxygen levels; any pertinent x-ray studies including head ultrasounds; information related to other neonatal diagnoses.

Others who will have access to your child's information for this research project are the University's Institutional Review Board (the committee that oversees research studying people) and authorized members of the University's and/or Primary Children's Medical Center workforce who need the information to perform their duties (for example: to provide treatment, to ensure integrity of the research, and for accounting or billing matters). The sponsor of the study does not have the right to inspect patient records.

If we share your child's information with anyone outside the University of Utah Health Sciences Center and/or Primary Children's Medical Center, your child will not be identified by name, social security number, address, telephone number, or any other information that would directly identify him/her, unless required by law. In records and information disclosed outside of the University of Utah Health Sciences Center and/or Primary Children's Medical Center, your child's information will be assigned a unique code number. We will keep the key to the code in a password protected computer. We will destroy the key to the code at the end of the research study.

You may revoke this authorization at any time. **This must be done in writing.** You must either give your revocation in person to the Principal Investigator or the Principal Investigator's staff, or mail it to Dr. Bradley A. Yoder, Department of Pediatrics/Neonatology, University of Utah School of Medicine, and PO Box 581289, Salt lake City, UT 84158-1289. If you revoke this authorization, we will not be able to collect new information about your child and they will be withdrawn from the research study. However, we can continue to use information we have already started to use in our research, as needed to maintain the integrity of the research. You have a right to information used to make decisions about your baby's health care. However, your baby's information from this study will not be available during the study; it will be available after the study is finished. This authorization lasts until this study is finished.



Consent

I confirm that I have read and understand this consent and authorization document and have had the opportunity to ask questions. I understand that my child's participation is voluntary and that I am free to withdraw my child at any time, without giving any reason, without my medical care or legal rights being affected. I will be given a signed copy of the consent and authorization form to keep.

I agree to allow my child to participate in this research study and permit you to use and disclose health information about my child for this study, as you have explained in this document.

_____
Child's Name

_____
1st Parent/Guardian's Name

_____ _____
1st Parent/Guardian's Signature Date

_____
Relationship to Child for 1st Parent/Guardian

_____
2nd Parent/Guardian's Name

_____ _____
2nd Parent/Guardian's Signature Date

_____
Relationship to Child for 2nd Parent/Guardian

Permission cannot be obtained from 2nd parent/guardian because *(please check which one applies to the situation. 45 CFR 46.408):*

____ The parent/guardian is deceased.
____ The parent/guardian is unknown.
____ The parent/guardian is incompetent.
____ The parent/guardian is not reasonably available.
____ Only one parent/guardian has legal responsibility for the care and custody of the child.

_____
Name of Person Obtaining Authorization and Consent

_____ _____
Name of Person Obtaining Authorization and Consent Date

INTERMOUNTAIN HEALTH CARE

PARENTAL PERMISSION and AUTHORIZATION DOCUMENT IHC INSITUTIONAL REVIEW BOARD

INTERMOUNTAIN HEALTH CARE
URBAN CENTRAL REGION
IRB
FEB 3 2009 APPROVED
DEC 11 2009 EXPIRATION DATE

TITLE: The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weigh Infants (SUPPORT Trial)

PRINCIPAL INVESTIGATOR: Bradley A. Yoder, MD (801) 581-7052

CO-INVESTIGATOR(S): Roger Faix, MD (801) 581-7052
Susan Wiedmeier, MD (801) 408-3435

LOCATION: Intermountain Medical Center and Primary Children's Medical Center

BACKGROUND:

You are being asked to allow your baby to be in this research study because there is a possibility he/she will be born between 24 and 27 weeks gestation. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, and relatives if you wish. Ask us if there is anything that is not clear or if you would like more information. Please take time to decide whether or not you volunteer your baby to take part in this research study.

Our hospital is conducting this study in cooperation with the National Institutes for Child Health and Human Development (NICHD) Neonatal Research Network to try to determine the best way to manage early breathing support in the extremely premature infant and to determine the most appropriate level of oxygen in the blood of extremely premature babies.

STUDY PROCEDURES:

Prior to delivery, and after your permission, your baby will be randomized (chosen by chance, like a flip of a coin) to one of four treatment strategies as shown below. There are two breathing support strategies: 1) early CPAP (giving pressurized gas by small plastic tubes in the nose) and 2) Intubation/Surfactant (placing a breathing tube and giving a medicine through the tube to try to help the lungs work better). Both treatments are currently used immediately after delivery at this hospital. The decision as which to use is currently made by the physician attending the delivery. There are also two oxygen support strategies: 1) a low normal range (85-89%) and 2) a high normal range (91-95%). The box on the following page indicates the four possible treatment combinations your infant can be randomized to. There is an equal chance (1 in 4) for randomization to each treatment group.

CPAP and Higher oxygen saturation	CPAP and Lower oxygen saturation
Breathing tube + Surfactant and Higher oxygen saturation	Breathing tube + Surfactant and Lower oxygen saturation

Your baby will remain on a specially modified oxygen saturation monitor (measures oxygen levels in the blood through the skin without needle sticks) until he/she reaches 36 weeks corrected age (example: 24 weeks gestation plus 12 weeks of age = 36 weeks corrected age) or until the monitor is no longer needed because your baby is in room air. Because of the design of these monitors none of the nurses, doctors, or study personnel taking care of your baby will know if he/she is in the lower or higher oxygen saturation group.

Other care will continue as normal during his/her participation in the study.

A secondary purpose to this study is to determine the longer term effect of different approaches to breathing and oxygen support in the very premature baby. In that regard, this study includes three planned follow-up evaluations of all study baby's during the first two years of life including:

a. follow-up for subsequent lung problems

b. follow-up of neurodevelopmental function (a complete exam of their muscles, nerves, mental and coordinated movement skills) at 18-22 months age

c. a comparison of currently applied radiology studies (MRI and Ultrasound) obtained at 36-42 weeks corrected gestation for predicting later neurodevelopmental function

Some of these follow-ups may be by phone and some may be in our special follow-up clinic for very premature infants routinely provided at 6, 12 and 18-22 months age.

Our study coordinator will keep track of how your baby is doing up to 40 weeks gestational age (the babies original due date) or until discharge. Once your baby reaches 36 weeks gestational age we will record if he/she is still being treated with oxygen and/or a ventilator. If your baby is still on nasal cannula oxygen we will try to wean him/her off the oxygen using a standard protocol. If he/she successfully weans off oxygen, your baby's medical team may decide to take him/her completely off oxygen.

RISKS:

Because all treatments proposed in this study are currently accepted standard of care, there is no predictable increase in risk to your baby. Infants randomized to the CPAP group may, at some point in their care, require intubation and assisted breathing. This will be determined by your baby's attending physician and participating in this study will not effect this decision.

BENEFITS:

We cannot promise any direct benefits to your baby from being in this study. However, possible benefits to your child may include decrease in chronic lung disease (need for extra oxygen at discharge) and decrease in the need for eye surgery as a result of exposure to oxygen. The information we learn from this study may help us treat premature babies in the future.

ALTERNATIVE PROCEDURES:

As an alternative to participation in this study you may decide to have your baby's doctor decide which treatment your baby will receive. If you decide not to include your baby in this study, none of his/her medical information will be included in the study data. Participation in research is entirely voluntary. You may refuse to participate or withdraw at any time without jeopardy to the medical care your baby will receive at this institution. Data collection for this study will stop at that time.

PERSON TO CONTACT:

If you have concerns or questions about this research or any related matter, you can contact the primary investigator, Dr. Bradley Yoder @ 801-581-7052 (pager 801-339-0092) or co-investigator, Dr. Roger Faix@ 801-587-7500 (pager 338-2228), in the Department of Pediatrics/Neonatology, University of Utah School of Medicine.

INSTITUTIONAL REVIEW BOARD:

If you have questions regarding your child's rights as a research subject, or if problems arise which you do not feel you can discuss with the Investigator, please contact the Institutional Review Board Office at the LDS Hospital @ 801-408-6781.

INJURY NON-COMPENSATION STATEMENT:

In the event your child sustains an injury resulting from your participation in the research project, Intermountain Medical Center can provide to him/her, emergency and temporary medical treatment and will bill your insurance company. Since this is a research study, payment for any injury resulting from participation in this research study may not be covered by some health insurance plans. If you believe that your child sustained an injury as a result of your participation in this research program, please contact the Institutional Review Board Office at the LDS Hospital @ 801-408-6781.

VOLUNTARY PARTICIPATION:

It is up to you to decide whether or not your baby will take part in this study. If you do decide to have him/her take part you will be asked to sign this consent form. You are free at any time to withdraw from this study without giving a reason. Whether your baby joins this study or not, your baby will receive the same medical and nursing care as needed and it will not affect your relationship with the investigator or other medical staff.

UNFORESEEABLE RISKS:

A particular treatment may involve risks to the baby that are currently unforeseeable. However, because all of the treatments proposed in this study are currently accepted as standard of care, there is no unpredictable increase expected. Unknown risks may be learned during the study, and is so you will be informed by the study personnel. The only other risk of this study is a risk to confidentiality. Every effort will be made to keep your baby's medical information confidential.

RIGHT OF INVESTIGATOR TO WITHDRAW:

You may withdraw your baby from this study at any time without penalty. Dr. Bradley Yoder or his associate investigators can withdraw your baby without your approval. Possible reasons for withdrawal include a need to transfer care to a different hospital not involved in this study or early termination of this study for safety considerations.

COSTS TO SUBJECTS AND COMPENSATION:

There is no cost to parents nor is there any compensation for participating in this study.

NEW INFORMATION:

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, your research doctor will tell you about it and discuss with you whether you want your baby to continue in the study. If you decide to continue your baby in the study, you will be asked to sign an updated permission form. Also, on receiving new information your research doctor might consider it to be in the best interest of your baby to withdraw him/her from the study. They will explain the reasons and arrange your baby's care to continue.

INTERMOUNTAIN HEALTH CARE
URBAN CENTRAL REGION
IRB

FEB 3 2009 APPROVED

DEC 11 2009 EXPIRATION DATE

NUMBER OF SUBJECTS:

We expect to include about 1300 babies in the study from the sixteen NICHD Neonatal Research Network hospitals over a two-year period. Intermountain Medical Center, Primary Children's Medical Center, and the University of Utah Hospital will enroll around 80 babies over the two year period.

CONFIDENTIALITY/ APPROVAL TO USE YOUR CHILD'S PROTECTED HEALTH INFORMATION

IHC has a commitment to protect your child's confidentiality. Federal regulations require that you understand how your child's protected health information (PHI) is used for this study.
Signing this document means you allow us, the researchers in this study, and others working with us to use information about your baby's health for this research study. You can choose whether or not to participate in this research study. However, in order to participate you have to sign this consent and authorization form.

This is the information we will use:
Name
Address
Telephone number
Current and past medications or therapies
Information from a physical examination, such as blood pressure, heart rate, breathing rate, and temperature
Information related to the use of any device for support of lung function such as ventilator pressures, oxygen concentration and blood oxygen levels; any pertinent x-ray studies including head ultrasounds and MRI's; and information related to other neonatal diagnoses.

In records and information disclosed outside of IHC to the NICHD Neonatal Network Data Collection center at Research Triangle Park, North Carolina, your child's information will be assigned a unique code number. We will keep the key to the code in a secure file maintained in the Division of Neonatology, University of Utah School of Medicine.

Others who will have access to your child's protected health information for this research project include IHC's Institutional Review Board (the committee that oversees research studying people) and authorized members of the IHC's workforce who need the information to perform their duties (for example: provide treatment, to ensure integrity of the research, and for accounting or billing matters), the Food and Drug Administration, and others as required by law.

You may revoke this authorization at any time. **This must be done in writing.** You must either give your revocation in person to the Principal Investigator or the Principal Investigator's staff, or mail it to Dr. Bradley A. Yoder, Department of Pediatrics/Neonatology, University of Utah School of Medicine, and PO Box 581289, Salt lake City, UT 84158-1289. If you revoke this authorization, we will not be able to collect new information about your baby, and will be withdrawn from the research study. However, we can continue to use information we have already started to use in our research, as needed to maintain the integrity of the research.
You have a right to information used to make decisions about your baby's health care. However, your baby's information from this study will not be available during the study; it will be available after the study is finished. This authorization lasts until this study is finished.

For more information about rights to your child's protected health information, how to revoke this authorization, and how IHC uses your child's health information, you may ask to see or obtain a copy of the IHC Notice of Privacy Practices.

I hereby acknowledge that I have received or been offered a copy of IHC's Notice of Privacy Practices.

INTERMOUNTAIN HEALTH CARE
URBAN CENTRAL REGION
IRB

FEB 3 2009 — APPROVED
DEC 11 2009 — EXPIRATION DATE

CONSENT:

I confirm that I have read and understand this consent and authorization document and have had the opportunity to ask questions. I understand that my child's participation is voluntary and that I am free to withdraw my child at any time, without giving any reason, without his/her medical care or legal rights being affected. I will be given a signed copy of the consent and authorization form to keep.

INTERMOUNTAIN HEALTH CARE
URBAN CENTRAL REGION
IRB

FEB 3 2009 APPROVED

DEC 11 2009 EXPIRATION DATE

I agree to allow my child to participate in this research study and permit you to use and disclose health information about my child for this study, as you have explained in this document.

_____
Child's Name

(Please Note: Both parents must give their permission unless one parent is deceased, unknown, incompetent, not reasonably available, or when only one parent has legal responsibility for the care and custody of the child. If both parents are not able to sign, please list the name of the parent and the reason why they are not able to sign in the signature line.

Parent/ Guardian Name	Parent/ Guardian Signature	Title	Date

_____
Name of Person Obtaining Authorization and Consent

_____ _____
Signature of Person Obtaining Authorization and Consent Date

_____
Name of Witness

_____ _____
Signature of Witness Date

The University of Texas Southwestern Medical Center at Dallas
Parkland Health & Hospital System and Children's Medical Center

CONSENT TO PARTICIPATE IN RESEARCH

Title of Research: The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

Sponsor: National Institute of Child Health and Human Development Neonatal Research Network

Investigators:	Telephone No. (regular office hours)	Telephone No. (other times)
Pablo J. Sánchez, MD	214-648-3753	972-206-9021
Luc P. Brion, MD	214-648-2060	972-326-1145
Lijun Chen, RN, PhDDiana Vasil, RNC-NIC	214-648-3780	214-590-6500
	214-648-3789	972-206-9148
Lizette Torres, RN	214-456-2585	972-206-9174
Roy Heyne, MD	214-648-3753	972-206-8791
Jaclyn LeVan, MD	214-648-2098	972-601-0011
Alicia Guzman	214-456-8041	972-206-9458

INVITATION: You/your newborn infant are invited to participate in this research because there is a possibility he/she will be born 12 to 16 weeks early and could possibly develop a lung problem called bronchopulmonary dysplasia (an abnormal formation of the lungs in premature infants leading to a need for oxygen treatment for a long time) and an eye problem called retinopathy of prematurity (an eye disease that may result in poor vision or loss of sight in premature infants), which may be caused by high oxygen treatment.

Medical research involves offering a plan of care to a group of patients, collecting and studying information about each patient's experience, and using that information to develop the best possible care for future patients.

NUMBER OF PARTICIPANTS: The sponsor plans to include 1300 newborn infants in the study from all the National Institute of Child Health and Human Development Neonatal Research Network hospitals over a two-year period.

PURPOSE: This study has three purposes and they are:
1) To compare newborn infants, in the delivery room, who receive breathing support through their nose with a cannula with newborn infants who have a tube placed in their windpipe (a process called intubation) and surfactant (a liquid which helps babies with immature lungs breathe easier by keeping their lungs from collapsing) given in the first hour of life.

2) To compare newborn infants, in the intensive care nursery, treated with low range (85-89%) oxygen saturation levels (a measure of the amount of oxygen in the blood) with newborn infants treated with high range oxygen saturation (91-95%) levels.

3) To measure the effects of the oxygen therapies used in the study on the growth of premature infants.

PROCEDURES
Breathing support through the nose with a cannula blowing air (also called nasal continuous positive airway pressure), or intubation with surfactant are both treatments currently used in the delivery room at Parkland Health and Hospital System. The decision to use one or the other on any newborn infant is made by the doctor who is in the delivery room.

Screening: The study doctor will ask you questions on whether you are admitted to the hospital in premature labor and

whether we can approach you to be in this study.

Randomization: If you agree for your newborn infant to be in this study, your infant will be randomized (chosen by chance like the flip of a coin) to one of two lung treatment groups:

1) Nasal continuous positive airway pressure through the nose or the mouth in the delivery room immediately after birth and continuing in the intensive care nursery, or
2) The placement of a tube in his/her windpipe in the delivery room followed by giving surfactant and mechanical ventilation (breathing for the baby using a machine).

After admission to the intensive care nursery, your newborn infant will also be randomized to a low or a high oxygen saturation group using a specially designed oximeter (a monitor that displays blood oxygen level).

Your infant will have a 1 in 4 chance of being in one of these groups:

Group 1: the nasal continuous positive airway pressure /low saturation,
Group 2: the nasal continuous positive airway pressure /high saturation,
Group 3: oral intubation with surfactant/low saturation, or
Group 4: oral intubation with surfactant/ high saturation.

Treatment:

Groups 1 and 2 (nasal continuous positive airway pressure):

Delivery Room Care: In the delivery room the doctor resuscitating your newborn infant will try using nasal continuous positive airway pressure on your baby. If your baby responds to nasal continuous positive airway pressure, he/she will continue on nasal continuous positive airway pressure and will be transferred to the intensive care nursery. If your baby does not improve with nasal continuous positive airway pressure, the doctor resuscitating your baby will intubate your baby in the delivery room. If intubated in the delivery room, your infant will receive one dose of surfactant within one hour of life. Your infant may receive more than one dose of surfactant in his/her first day of life, but your infant's doctor, based on your infant's condition, will decide this.

Care in the Neonatal Intensive Care Nursery: The doctor may intubate your infant if he/she believes your infant is not doing well on the nasal continuous positive airway pressure. The study sponsor has guidelines for your infant intubation or extubation (the process of removing the tube from the windpipe) to safeguard your infant. Your infant's doctor will follow the sponsor guidelines for intubating or extubating your infant in the first two weeks of life. However, if your infant requires intubation three times, he/she will be out of the study and further intubations or extubations will be decided solely by your infant's doctor. After two weeks of life all intubations and extubations are decided only by your infant's doctor.

Groups 3 and 4 (oral intubation with surfactant):

Delivery Room Care: In the delivery room, the doctor resuscitating your newborn infant will place a tube in his/her windpipe after delivery and will give a dose of surfactant in the first hour of life. Your infant will be transported to the intensive care nursery on a breathing machine.

Care in the Neonatal Intensive Care Nursery: Your newborn infant will be admitted to the intensive care nursery on a breathing machine. The study sponsor has specified guidelines for the first two weeks of life at which your infant will be taken off the breathing machine and your infant's doctor will follow those criteria to decide on extubating your infant. Once your infant is extubated for the first time, further intubations or extubations will be decided only by his/her doctor.

All study infants will be placed on the study oximeter within two hours of birth. (An oximeter is an object placed on the skin to measure oxygen in the blood). Which oxygen saturation group your infant is randomized to will not be known to the nurse taking care of your infant, or his/her doctor. Only the study coordinator will know which group your infant is in. However, your infant will either be on the high end or the low end of the normal oxygen saturation that we normally use in our intensive care nursery. Your infant will remain on the study oximeter until he/she reaches 36 weeks adjusted age (e.g. 24 wks gestation plus 12 wks of age = 36 wks adjusted age) or until he/she is discharged home.

We will measure your infant's weight, length, and head at birth, day of life 7, 14, 21, 28, and at 32 and 36 wks of age and at home discharge to evaluate the effects of the study procedures on his/her growth.

All other care will be conducted as normal during your infant's participation in the study. The studies to be done on your baby's blood will be performed on blood already drawn in the standard care and no additional blood draws will be done for the research. Your baby will be followed in our infant follow-up clinic at Children's Medical Center after discharge from the intensive care nursery as we usually do for all babies his/her size.

Follow-up after discharge from the Neonatal Intensive Care Nursery: At the time of a regular follow-up visit, following your infant's discharge from the NICU, our follow-up staff (Dr. Roy Heyne or his designee) will interview you (or your designee) to find out about your child's diet, breathing problems in the family, and things in the home that may increase your child's risk of breathing problems. This interview will take about 15 minutes and will include questions about the air quality at your home, your home location, your infant's exposure to infections, your family history of asthma and allergies, and any recent hospital or doctor office visits. You do not need to answer any questions that make you uncomfortable. The follow-up staff will be in touch with you and your infant, either by telephone or in person at one of your follow-up visits every 6 months for a total of three times. At these times, they will ask questions about your child's breathing (especially wheezing and coughing), medication use, and visits to a Doctor, Emergency Room, or Hospital for treatment of breathing problems. They will also ask you several questions about things in the home or day care setting that may affect your child's breathing. The entire call should take about 15 minutes of your time, less if your baby has had no breathing problems. If your infant is followed in the Low Birth Weight Clinic at Children's Medical Center, the follow-up staff will arrange to meet you during the clinic visit to ask you these questions. Otherwise, they will schedule the telephone calls at a time that is convenient for you. The telephone calls will occur when your infant is 6, 12, and 18 months after his/her expected delivery at full term. The results from your baby's questionnaire will be combined with those of other infants from around the country. However, your baby's name will not be used.

At 18-22 months of age your baby will receive, at no charge, a complete exam of their muscles, nerves, intelligence and motor function. We will also measure his/her weight, length, and head size. This exam is done at the Children's Medical Center Follow-up Clinic.

Evaluations during the Research: Dr. Sánchez and his research staff will closely monitor your infant's response to the study in the delivery room and in the intensive care nursery. Dr. Sánchez and his research staff will review your infant's medical record to gather information on your infant's date, time and place of birth, delivery room events, birth weight, length, head circumference, age at birth, gender, results of lab tests performed by your infant's doctor, results of the physical exam performed by your infant's doctor, type and name of medicines your infant receives during his hospitalization, duration and

type of respiratory support and mechanical ventilation, duration and degree of oxygen therapy, complications during hospitalization, amounts of milk and intravenous nutrition, duration of hospital stay, results of the head ultrasounds performed during the hospital stay (head ultrasounds, also called head sonograms, are pictures taken of the baby's brain by

a special machine that is brought to the baby's bedside), results of the eye exam performed during the hospital stay, results of the neurologic exams and the Bayley tests performed in the follow-up clinic(the neurologic and Bayley tests are a complete evaluation of your infant's muscles, nerves, intelligence, and motor function). Dr. Roy Heyne and his research staff will review the results of the interview to gather information on your infant breathing problems and conditions that may affect his/her breathing following the study.

Investigational Procedures: The oximeters (oxygen monitors) used in this trial are FDA approved oximeters, but have been modified for this study. The FDA is a government agency that oversees new drugs and medical equipment.

POSSIBLE RISKS

All the treatments in this study are currently used in the intensive care nursery and most infants born at the same age as your infant will receive all those treatments during their stay in the intensive care nursery.

The risk of intubation includes injury to your infant's throat and windpipe, but this is unusual. The risk of surfactant treatment includes bleeding in the lung but this is rare. Infants receiving nasal continuous positive airway pressure in the delivery room may have problems breathing and their heart-beat may abnormally slow down. If this happens to your infant, your infant's doctor in the delivery room will intubate your infant and place him/her on a breathing machine. Infants placed on nasal continuous positive airway pressure for a long time, may have damage to their nose; our nurses and doctors are very aware of this possible problem and are careful to prevent it. The weight, length, and head measurements of your infant are performed by experienced nurses and do not add any risk. Some unknown risks may be learned during the study. If these occur, you will be informed by the study personnel.

Following discharge from the NICU, you (or your designee) will be involved in a series of interviews about factors related to your child's breathing; and while answering interview questions you may experience some anxiety or emotional discomfort; but you do not have to answer questions you do not feel comfortable responding to.

Another risk of this study is the risk to confidentiality. Every effort will be made to keep your infant's medical record confidential. There will be no name or other patient identification in any study report that may be published after the study is completed. Measures taken to protect you and your infant's identity are described in the confidentiality section.

Blood samples: Your infant will have the same amount of blood collected whether your infant receives standard medical care for your infant's health problems or participates in this research. Therefore, your infant's risk of complications from collecting the blood is the same.

Your infant may experience discomfort, bleeding and/or bruising. On a rare occasion, an infection could develop at the site where the blood was collected.

Unforeseen risks: A previously unknown problem could result from your newborn infant's participation in this research. It is not possible to estimate the changes of such problems or how serious problems could be.

POSSIBLE BENEFITS

Benefit to your infant: Your study doctor cannot guarantee that your newborn infant will benefit from participation in this research.

Benefit to other premature infants: The information learned from this study may help us better treat premature infants in the future. However, your infant's study doctor will not know whether there are benefits to other premature infants until all of the information obtained from this research has been collected and analyzed.

ALTERNATIVES TO YOUR INFANT'S PARTICIPATION IN THIS RESEARCH: Your infant does not have to participate in this research to receive care for your infant's medical problem. If you decide not to participate in this research, your infant will receive the standard of care at Parkland Health and Hospital System and Children's Medical Center intensive care nurseries. The standard of care at the Parkland Health and Hospital System and Children's Medical Center neonatal intensive care nurseries varies with the attending doctor taking care of your infant and may be similar to any of the above 4 groups of therapies that the research is studying.

Please ask your infant's study doctor as many questions as you wish. The doctor's answers to your questions could help you decide whether your infant will participate in this research or receive the standard care that is currently available for your infant's medical problem.

If you decide now that your infant will participate in research, and later change your mind, your infant may stop participation in the research then and receive the standard of care.

THE STUDY DOCTOR'S DECISION TO STOP YOUR INFANT'S PARTICIPATION: Your infant's study doctor or the sponsor may stop your infant's participation in this research without your or your infant's permission under any one of the following conditions:

- Your infant's study doctor believes participation in the research is no longer safe for your infant.
- Your infant's study doctor believes that other treatments may be more helpful.
- The sponsor or the FDA stops the research for the safety of the participants.
- The sponsor cancels the research.

PROCEDURES AFTER STOPPING PARTICIPATION IN THIS RESEARCH: If you, the study doctor, or the sponsor stops your infant's participation in the research, it is your responsibility to do the following:

- Let the study doctor know immediately that you wish that your infant withdraw from the research.
- Return to the research center for tests that may be needed for your infant's safety.
- Discuss your infant's future medical care with the study doctor and/or your infant's regular doctor.

INCENTIVE TO TAKE PART IN THIS RESEARCH: You will not be paid for your infant's participation in this research.

COSTS TO YOU: The sponsor will pay the expenses for the neurodevelopmental testing (tests that evaluate the function of nerves, muscles and intelligence of your infant) which are part of the research.

Expenses related to standard medical care for prematurity are your responsibility (or the responsibility of your insurance provider or government program). Since nasal continuous positive airway pressure, intubation, mechanical ventilation, surfactant treatment, and the use of a pulse oximeter are all part of the routine care of preterm infants, the research will not pay for those therapies.

You, your insurance or your government program will be responsible for the cost of delivery room care, the costs of the day-to-day care in the intensive care nursery, the using cost of all respiratory equipments (mechanical ventilation machine, nasal continuous positive airway machine, pulse oximeter) used in the day-to-day care of your infant, and the costs of the daily physician care.

COMPENSATION FOR INJURY: Compensation for an injury resulting from your infant's participation in this research is not available from the University of Texas Southwestern Medical Center at Dallas, Children's Medical Center, or Parkland Health & Hospital System. You and your infant retain your legal rights during your infant's participation in this research.

VOLUNTARY PARTICIPATION IN RESEARCH: You and your infant have the right to agree to or refuse participation in this research. If you decide that your infant will participate and later change your mind, you are free to discontinue participation in the research at any time.

Your refusal to participate in this research will involve no penalty or loss of benefits to which you and your infant are otherwise entitled. Your refusal to participate in this research will not affect your legal rights or the quality of health care that you and your infant receive at this center.

NEW INFORMATION: Any new information which becomes available during your infant's participation in the research and may affect your infant's health and safety or your willingness for your infant to continue in the research will be given to you.

RECORDS OF YOUR INFANT'S PARTICIPATION IN THIS RESEARCH: You and your infant have the right to privacy. Any information about you or your infant that is collected for this research will remain confidential as required by law. In addition to this consent form, you will be asked to sign an "Authorization for Use and Disclosure of Protected Health Information for Research Purposes."

YOUR QUESTIONS: Your infant's study doctor, Dr. Pablo J. Sánchez and his research staff are available to answer your questions about this research; and Dr. Roy Heyne and his research nurse, Lizette Torres, RN, are available to answer questions about the breathing interview. The Chairman of the IRB is available to answer questions about your rights and your infant's rights as a participant in research or to answer your questions about an injury or other complication resulting from your infant's participation in this research. You may telephone the Chairman of the IRB during regular office hours at 214-648-3060.

YOU WILL HAVE A COPY OF THIS CONSENT FORM TO KEEP.

Your signature below certifies the following:

- You have read (or been read) the information provided above.
- You have received answers to all of your questions.
- You have freely decided that your infant may participate in this research.
- You understand that you and your infant are not giving up any of your legal rights.

_____
Participant's Name (printed)

_____
Legally authorized representative's name (printed)

_____ _____
Legally authorized representative's signature Date

_____
Name of person obtaining consent (printed)

_____ _____
Signature of person obtaining consent Date

DO NOT DISCLOSE

WAKE FOREST UNIVERSITY SCHOOL OF MEDICINE AND FORSYTH MEDICAL CENTER

The SURfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants (The SUPPORT Trial)

Michael O'Shea, MD, MPH, Principal Investigator

Introduction

You, as a parent or legal guardian of _____, are invited to enter your child in a research study conducted at Forsyth Medical Center and Wake Forest University Baptist Medical Center and sponsored by the National Institutes of Child Health and Human Development (NICHD) Neonatal Research Network. You are being asked to allow your child to be in the study because there is a possibility he/she will be born between 24 and 28 weeks of gestation. Babies born this early frequently develop chronic lung disease (prolonged difficulty with breathing) and retinopathy of prematurity (a condition in which there is overgrowth of the blood vessels in the back of the eye). This study is being carried out to test the benefit of two treatments which may decrease the risk of developing chronic lung disease and retinopathy of prematurity. Approximately 1310 infants, cared for at one of sixteen medical centers in the United States will participate in this study, and about 74 of these babies will be born at Forsyth Medical Center.

Research studies are designed to gain scientific knowledge that may help other babies in the future. Your child may or may not receive any benefit from being part of this study. Participation is voluntary. Please take your time to make your decision, and ask your doctor or the study staff to explain any words or information that you do not understand.

Why Is This Study Being Done?

One of the primary purposes of this study is to find out if the risk of chronic lung disease can be reduced by treatment with continuous positive airway pressure (CPAP) applied immediately after birth while the baby is in the delivery room and continued in the neonatal intensive care unit (NICU). Also, strict guidelines will be used for having a breathing tube placed and mechanical ventilation started. There is no standard way to use CPAP for resuscitation in the delivery room for premature infants. This pressure is given using a mask placed on the baby's face. The pressure may also be given using prongs placed in the infant's nostrils. The pressure is produced using current breathing machines (ventilators). There are also special devices that are designed to deliver such pressures. At the current time very few infants who are born at Forsyth Medical Center and 24 to 27 completed weeks gestation are resuscitated using only CPAP, but this approach has been used for hundreds of babies in other hospitals.

The other purpose of this study is to find out if the risk of retinopathy of prematurity can be reduced by using a lower range for oxygen saturation levels (85-89%) instead of a higher range

(91-95%). Retinopathy of prematurity (ROP) is a common eye problem in tiny premature infants. Blood vessels that nourish the preterm infant's eyes are not fully developed. Small vessels in the retina (part of the eye) may have periods of increased or rapid growth. Over time ROP can get better or get worse. Usually ROP will heal without any problems. If the ROP is worse than usual, there is a chance that the blood vessels will grow out of control. If this happens, surgery may be needed to prevent scars inside the eye. These scars can cause severe vision loss. The oxygen saturation level currently used in the neonatal intensive care units at Forsyth Medical Center and Brenner Children's Hospital is between 85% and 94%, so both treatment groups (the group for whom the target for oxygen saturation levels will be 85-89% and the group for whom the target for oxygen saturation levels will be 91-95%) will be treated with oxygen in a manner that is very similar to that currently used at both hospitals.

What Is Involved in the Study?

If you give permission for your child to be in this research study, the following will happen:

1) Prior to delivery your baby will be assigned to one of two treatments for babies with respiratory distress. Assignment will be random, like the flipping of a coin. In the first treatment group, your baby will be placed on CPAP in the delivery room immediately after birth and CPAP will continue after transfer of your baby to the NICU. If your baby is in the second treatment group, a tube will be placed in his/her trachea (windpipe) and your baby will be receive help with his/her breathing with a ventilator (a breathing machine). After the tube is placed, a dose of surfactant will be given in the tube. Surfactant is produced by the normal full-term baby lung. It is lacking in very preterm baby lungs and its use has been connected with a decrease in respiratory problems and death.

Both of these treatment groups are current standards of care for preterm babies in the delivery room. The other aspects of the resuscitation will be managed according to the Neonatal Resuscitation Program (NRP) guidelines and follow current hospital practice. Infants randomized to the CPAP group may, at some point in their care, require intubation, assisted ventilation (methods to help them breathe), and surfactant. If the attending physician deems this necessary, participation in the study will not affect this decision. After your infant is admitted to the NICU the study guidelines for intubation, extubation and re-intubation will be in effect for the first 14 days of your baby's life. After 14 days, the ventilation care will be the same as the standard practices in your baby's nursery.

2) Your baby will also be randomized to a high reading or low reading pulse oximeter (a monitor that displays how much oxygen is in the blood). We will start this monitoring of oxygen saturation by 2 hours of age. These oximeters have been modified for use in our research study so that they show a value that is either slightly higher or slightly lower than the true oxygen level when the values are between 85 and 95%. The ranges used in this study are in common use in NICU's across the country. When the true oxygen level is outside those ranges, the actual number will be displayed. This type of oximeter will be used the entire time your baby is on oxygen while he/she is in the NICU until he/she reaches 36 weeks corrected age (age adjusted for prematurity). None of the professionals caring for your baby will know which type of pulse oximeter (high or low reading) your baby is using. This information will be known only by the research coordinator.

The oximeter group your baby is randomized to will not be known to the nurse, respiratory therapist or physician/s taking care of your baby. Only the study coordinator will know which group your baby is in.

3) If your baby is still receiving oxygen therapy at around 36 weeks corrected age and qualifies for testing, he/she will have an Oxygen Reduction Test. Your baby will stay in his/her bed and a neonatal research nurse will always be present at the bedside. The level of oxygen in the blood will be measured using a standard pulse oximeter. The test will begin with a measurement of the pulse oximeter value at the amount of oxygen your child is receiving. The oxygen level will be lowered in small steps. If the oxygen saturation (or level of oxygen in the blood) remains high, your baby will be placed in room air and monitored for 30 minutes. If your baby's oxygen level goes below the acceptable level (less than 90% for five minutes or 80% or less for 15 seconds), the test will be ended. At the end of the test, your baby will be returned to the oxygen level that he or she was in before the test.

4) As part of the study we will collect information about eye exams. If your baby is transferred to another hospital before discharge home, or requires follow-up eye examinations after discharge we will request a copy of your child's exam.

5) Prior to the time when your infant is discharged from neonatal intensive care, we will contact you to ask about your family, yourself, and your home. We will contact you three more times, either at the time of a visit to our outpatient clinic or by telephone, every 6 months over the next 18-22 months. At these times, we will ask questions about your child's breathing (especially wheezing and coughing), medication use, and visits to a doctor, emergency room, or hospital visits for treatment of breathing problems. We will also ask you several questions about your family and yourself. We expect that answering these questions will take no more than 15 minutes at each contact.

How Long Will My Baby Be in the Study?

The study begins with your agreement to allow your baby to participate in this study. During the initial hospitalization there is no time commitment required from the parent/legal guardian. The treatments that are being tested in this research study will end when your child is discharged. The collection of data will end when your child comes for his/her 18-22 months corrected age visit at the Infant Follow-Up Program at Amos Cottage in Winston-Salem for an evaluation of motor skills, mental development, health and physical growth. These assessments are a part of routine follow-up care for infants born very prematurely. That visit takes approximately 2-3 hours.

In the future we may wish our study participants to return for additional follow-up assessments. Your signature on the line below indicates that you give permission for us to contact you about any further opportunities for follow-up evaluations, after the 18-22 months of age visit.

_____ _____

Signature of parent or legal guardian Date of signature

What Are the Risks of the Study?

Participation in this study may involve some added risks or discomforts. Because all of the treatments proposed in this study are standard of care, there is no predictable increase in risk for your baby. Some unknown risks may be learned during the study. If these occur, you will be informed by the study personnel.

Are There Benefits to Taking Part in the Study?

There may be benefits to your child directly, including a possible decrease in chronic lung disease and/or a decrease in the need for eye surgery as a result of exposure to oxygen. Because we do not know in advance the actual strategies chosen for your child, or which of the treatment strategies is the most effective, it is also possible that your baby will receive no direct benefit. The knowledge learned from this study may help us treat babies in the future.

What Other Choices Are There?

Your decision to permit your child to participate in this study is voluntary. Your alternative is to not participate in this study.

What about the Use, Disclosure and Confidentiality of Health Information?

Taking part in this research study will involve collecting health information that you consider confidential or private and that directly identifies your baby. Information that identifies your baby includes, but is not limited to, such things as name, address, telephone number, and date of birth. Personal health information includes all information about your baby which is collected or created during the study for research purposes. It also includes your baby's health information that is related to this study and that is maintained in medical records at Forsyth Medical Center, Brenner Children's Hospital and at other such places as additional hospitals or clinics where your baby may have received medical care. Examples of personal health information include health history, the family health history, how your baby responds to study procedures, laboratory and test results, and medical images and information from study-related visits, interactions, and questionnaires. The information gathered from this study will be kept strictly confidential but will be submitted to the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network **without any identification of you or your baby**.

Personal health information and information that identifies you and your baby ("your health information") may occasionally be given to others during and after the study. This is only for reasons such as to carry out the study, to make sure the study is being done correctly, to and to provide required reports.

The health information of your baby **without any identification of you or your baby** may be used by the research team, other researchers and their staff involved with this study or by data management centers; the sponsor of this study, the NICHD, the Federal Office of Human Research Protection, the Food and Drug Administration (FDA), the Wake Forest University School of Medicine Institutional Review Board, The Forsyth Medical Center Institutional Board, or the Office of Clinical Trials, Novant Health Triad Region. The health information of your baby may be disclosed if required by state or federal laws. The results of this study may be published in medical journals, presented at medical meetings, or exchanged between medical investigators; **however your name or your child's name will not be used.** If you have never received a copy of the Wake Forest University Baptist Medical Center Health Insurance Portability and Accountability Act (HIPAA) notice, please ask for one.

When you sign this consent and authorization you give permission for the use of the health information of your baby as described in this consent form. This authorization does not have an expiration date. You may decide to withdraw your consent at any time by providing written notification of your decision to Dr. Michael O'Shea at the following address: *Department of Pediatrics, Wake Forest University School of Medicine, Medical Center Boulevard, Winston-Salem, NC 27157.* If you withdraw your authorization your baby will not be able to be in this study. If you withdraw your authorization, no new health information will be gathered after that date, however the information already collected will continue to be used to the extent that it has already been relied on for the study, as necessary to maintain the integrity of the research study or as required by law. Refusal to participate in this study or withdrawal at a later date will not affect the care given to your child by your physician or any other health professionals. This study has been approved by the Wake Forest University Baptist Medical Center Institutional Review Board and Forsyth Medical Center Institutional Review Board, which are committees to help assure that research studies are safe and properly performed.

Although every effort will be made to keep your baby's research-related information private, absolute confidentiality and protection of the information cannot be guaranteed. If information is disclosed to a person or entity that is not covered by the federal privacy regulations it may be re-disclosed. Your baby's research-related information **without any identification of you or your baby** may be used or disclosed until the end of the research study. If the information is included in a research database there is no scheduled date at which it will be destroyed or no longer used. This is because research information continues to be analyzed for many years and it is not possible to determine when this will be complete.

What Are the Costs?

There are no costs to you for taking part in this study. All of the costs related directly to the study, will be paid for by the study. Costs for your regular medical care, which are not related to this study, will be your own responsibility.

Will You Be Paid for Participating?

You will receive no payment or other compensation for taking part in this study. However, you will receive $100 after completion of the follow-up visit at 18-22 months corrected age to compensate you for time and expenses related to that visit. If your child's birth weight is between 401 (about 14 ounces) and 1000 grams (about two pounds and 3 ounces), this money will be paid as a part of the Follow Up Study. If your child's birth weight is less than 401 grams or more than 1000 grams, this money will be paid as a part of the SUPPORT Trial. In addition, we will assist with travel expenses. To receive payment, you must provide your social security number, name, and address, so that we can comply with Internal Revenue Service (IRS) reporting requirements. When payments are reported to the IRS we do not let them know what the payment is for, only that you have been paid. If you do not wish to provide this information, you can still take part in the study but you will not be paid.

What Happens If My Child Experiences an Injury or Illness As a Result of Participating in This Study?

Should your child experience a physical injury or illness as a direct result of his or her participation in this study, Wake Forest University School of Medicine maintains limited research insurance coverage for the usual and customary medical fees for reasonable and necessary treatment of such injuries or illnesses. To the extent research insurance coverage is available under this policy the reasonable costs of these necessary medical services will be paid, up to a maximum of $25,000. Wake Forest University Baptist Medical Center holds the insurance policy for this coverage. It provides a maximum of $25,000 coverage for each claim, and is limited to a total of $250,000 for all claims in any one year. The Wake Forest University School of Medicine, and The North Carolina Baptist Hospitals, Incorporated do not assume responsibility to pay for these medical services or to provide any other compensation for such injury or illness. Additional information may be obtained from the Medical Center's Director of Risk Management, at (336) 716-3467.

You do not give up any legal rights as a research participant by signing this consent form. For more information on medical treatment for research related injuries or to report a study related illness, adverse event, or injury you should call Dr. Michael O'Shea at (336) 716-2529. After hours you may call (336) 716-7654 or 1-800-277-7654 and ask for Dr. O'Shea to be paged.

What Are My Child's Rights as a Research Study Participant?

Taking part in this study is voluntary. If you choose not to have your baby participate in this study, he/she will receive routine care. You may choose not to take part or you may leave the study at any time. The investigators also have the right to stop participation in the study at any time. You will be given any new information we become aware of that would affect your willingness to continue to have your baby participate in the study.

Whom Do I Call if I Have Questions or Problems?

Questions about your baby's participation in this research study can be directed to Dr. Michael O'Shea at (336) 716-2529) during business hours and (336) 716-7654 or 1-800 277-7654 before or after business hours. The Institutional Review Board (IRB) is a group of people who review the research to protect your rights. If you have a question about your rights as a research participant, you may contact the Chairman of the Wake Forest University Health Sciences IRB at (336) 716-4542 and/or the Chairman of the Forsyth Medical Center IRB at (336) 718-5960.

Consent

I agree to let my child take part in The SUPPORT Trial. (The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants. I authorize the use and disclosure of my child's health information as described in this consent and authorization form. I have had a chance to ask questions about being in this study and have those questions answered. By signing this consent and authorization form, I am not releasing or agreeing to release the investigator, the sponsor, the institution or its agents from liability for negligence.

(You will receive a copy of this consent form after all signatures have been obtained.)

_____ _____

Signature of parent or legal guardian Date of signature

_____

Printed name of parent or legal guardian

_____ _____

Signature of person administering consent Date of signature

_____

Printed name of person administering consent

From: Luc Brion
To: Keszler, Martin; Kristi Watterberg
Cc: Carl_Dangio@URMC.Rochester.edu; dwallace@rti.org; Higgins, Rosemary (NIH/NICHD) [E]; Pablo Sanchez
Subject: RE: revised protocol
Date: Monday, January 23, 2012 7:25:49 PM
Attachments: Secondary - predicting ext success - Protocol 01232012 rev 2.docx

Thanks, Martin.

All:

I attach the revised version, in which I eliminated several manuscripts, which are not needed anymore. I also eliminated Martin's comments except the one for Dennis

Please let me know if you have any additional suggestions by January 27th so I can I send the protocol to the review committee at least one week before the next protocol review standing committee call (February 7th).

Dennis:

Please could you extract the data from SUPPORT as indicated in my previous email sent Fri 1/20/2012 8:58 AM. This information is for the bottom of page 7 of the version without the Word tracking [Results pending from Dennis].

Please let us know if we are planning too many secondary analyses.

Thanks for your help,

Luc

Luc P. Brion, MD
Professor of Pediatrics
Director, Fellowship Training Program in Neonatal-Perinatal Medicine
University of Texas Southwestern Medical School Program
The University of Texas Southwestern Medical Center at Dallas
5323 Harry Hines Boulevard, STOP 9063
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Office: (214) 648-3903
Fax: (214) 648-2481
luc.brion@utsouthwestern.edu

From: Keszler, Martin [mailto:MKeszler@Wihri.org]
Sent: Monday, January 23, 2012 5:37 PM
To: Luc Brion; Kristi Watterberg
Cc: Carl_Dangio@URMC.Rochester.edu; dwallace@rti.org; Rose (higginsr@mail.nih.gov); Pablo Sanchez
Subject: RE: revised protocol

Luc, here are my edits and comments. Sorry I could not get this back to you sooner.
Keep up the good work. We're almost there!
Cheers,
M.

Martin Keszler MD
Mkeszler@WIHRI.org
(401) 274-1122, x7490

From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
Sent: Monday, January 23, 2012 5:14 PM
To: Kristi Watterberg
Cc: Carl_Dangio@URMC.Rochester.edu; Keszler, Martin; dwallace@rti.org; Rose (higginsr@mail.nih.gov); Pablo Sanchez
Subject: RE: revised protocol

Kristi:

Oops! I missed a few more mistakes! Thanks a lot for taking the time to read the documents and thanks your comments.

Kristi: Carl, Martin, Dennis, Rose:

I looked carefully at the printout and edited the text further; corrections should come in blue this time; this will allow you to detect changes I made today.

Best regards,

Luc

Luc P. Brion, MD
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From: Kristi Watterberg [mailto:KWatterberg@salud.unm.edu]
Sent: Monday, January 23, 2012 2:42 PM

To: Luc Brion
Cc: Carl_Dangio@URMC.Rochester.edu; MKeszler@Wihri.org
Subject: Re: revised protocol

A lot of work in a short time, Luc! A couple of minor points:

Background: this must be a typo: "extubation predicted by a positive SBT was 3/43 (93%), compared with a success rate of 39/50 (78%) in the"

The two statements below seem to conflict - in each, you are looking at the SBT vs. clinical factors to predict successful extubation, even though they're stated a little differently.

The null hypothesis is that the percentage of successful extubation among patients with positive SBT is not different from that in those extubated based on criteria established for extubation in the main hydrocortisone study.

The primary question is not to determine whether SBT is better predictive than clinical information; this would be best studied by a randomized trial.

There seems to be a missing clause in the following sentence: "If an occasional infant requires more than this, e.g., bag and mask ventilation or additional resuscitation."

Kristi

>>> Luc Brion <Luc.Brion@UTSouthwestern.edu> 1/21/2012 4:59 PM >>>
Martin, Carl, Kristi, Dennis, Rose:

Thanks a lot for all the feedback at the meeting.

Here is the updated protocol, taking into account all the suggestions from the protocol review committee and a first draft of the revised sample size analysis (not seen by Dennis yet).

Please let me know your suggestions (if possible by January 27th) so I can I send the protocol to the review committee at least one week before the next protocol review standing committee call (February 7th).

Thanks and best regards,
Luc

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UT Southwestern Medical Center
The future of medicine, today.

PREDICTING SUCCESS OF EXTUBATION DURING HYDROCORTISONE THERAPY IN PRETERM INFANTS < 30 WEEKS OF GESTATIONAL AGE~~AND THE EFFECT OF DIFFERENT MODES OF SYNCHRONIZED VENTILATION~~

Luc P Brion, UT Southwestern at Dallas

Martin Keszler, Brown University

Kristi Watterberg, University of New Mexico

Dennis Wallace, RTI

Carl d'Angio, University of Rochester

Rose Higgins, RTI

Protocol

Rev 01~~11~~/22~~15~~/12~~1~~

Proposed secondary study to

"A RANDOMIZED CONTROLLED TRIAL OF THE EFFECT OF HYDROCORTISONE ON SURVIVAL WITHOUT BRONCHOPULMONARY DYSPLASIA AND ON NEURODEVELOPMENTAL OUTCOMES AT 18 – 22 MONTHS OF AGE IN INTUBATED INFANTS <30 WEEKS GESTATIONAL AGE",

Referred to as "Main Hydrocortisone Study" in this protocol

Kristi Watterberg, PI

Thanks to: Diana Vasil, RN, Coordinator at UT Southwestern at Dallas, and Glenn Metoyer, RT, Parkland Memorial Hospital

1. ABSTRACT (SYNOPSIS)

This observational study is primarily designed to evaluate whether a short endotracheal continuous positive airway pressure (ET CPAP) test ~~(also called spontaneous breathing test, (SBT)~~ may help predict the success of extubation of ~~very~~ premature infants ≤30 weeks estimated gestational age at birth who remain intubated at 14 - 28 days postnatal age. ~~-~~For this purpose, we will use the 3-minute ET CPAP test (also called "spontaneous breathing test" or SBT) described by Kamlin in a single center.[1] The primary aim of this study is to compare the percentage of successful extubation among patients with positive SBT with that in those who failed the SBT and were extubated based on criteria established for extubation in the main hydrocortisone study. The secondary aim is to evaluate the point estimates and confidence intervals of sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio of a positive test, and likelihood ratio of a negative test for the SBT. The large number of patients we plan to recruit will allow us to test the external validity of the SBT in different centers using different types of ventilators, ~~and~~ different modes of ventilation and different modes post-extubation therapy.

~~We will also assess if ventilation modes that support every breath, i.e., assist control (AC), pressure regulated volume control (PRVC), pressure support ventilation (PSV) or synchronized intermittent mandatory ventilation (SIMV) with PSV, are associated with shorter duration of mechanical ventilation than SIMV. Since there are many center and individual differences in approach to therapy we will use multivariate analysis ventilation to attempt to account for possible confounder. Shorter intubation will in part depend on approaches to fluids, volumes, sodium administration and nutritional management, caffeine, etc.~~

2. STATEMENT OF PROBLEM

Prediction of successful extubation in preterm infants remains a challenge. This question has not been addressed by the NRN, and specific data were not collected during the SUPPORT trial. Previous single-site studies suggested that successful extubation can be predicted by the SBT in preterm infants during the first days of life. However, validity of this test has not been established in a multicenter study, using different types of ventilators, ~~and~~ different modes of ventilation and different modes post-extubation therapy, in a population of infants of greater post-natal age than in the original study by Kamlin et al.[1].

~~There is limited information about the relative merits of SIMV vs. ventilation modes that support every breath as weaning modes of mechanical ventilation. There are important physiological considerations suggesting that SIMV, although widely used, may not provide optimal support in very premature infants during weaning.~~

3. HYPOTHESIS

~~Since this is an observational study there is no primary hypothesis.~~

~~The study is primarily designed to test the external validity of the SBT in a multicenter study, with multiple institutions, using different types of ventilators and different modes of ventilation, in a population of infants of greater post natal age than in the original study by Kamlin et al.~~[1]Previous studies suggest that the success of extubation may be higher in patients with a positive SBT[1]. Therefore, we hypothesize that the percentage of successful extubation among patients ~~with positive~~who pass the SBT is greater than that in those who failed the SBT and were extubated based on criteria established for extubation in the main hydrocortisone study.

The null hypothesis is that the percentage of successful extubation among patients with positive SBT is not different from that in those who failed the SBT and were extubated based on criteria established for extubation in the main hydrocortisone study.

Secondary n~~Secondary null~~ -hypotheses include :

1. The predictive value of the SBT is not affected by whether the baby is supported by a ventilator using a mode supporting all breaths or by SIMV.

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2. The predictive value of the SBT is not affected by whether the baby is randomized to hydrocortisone or placebo. Hydrocortisone may affect lung compliance and laryngeal edema and thus improve success rate of extubation compared with placebo.

3. The predictive value of the SBT is not affected by the resistance of the endotracheal tube (ETT). While on CPAP small diameter and long length of the ETT may increase work of breathing and contribute to failing of the SBT while not affecting success of extubation.

4. The predictive value of the SBT is not affected by postnatal age (within the ranges expected in the hydrocortisone trial).

4-5. The predictive value of the SBT is not affected by the mode of respiratory support after extubation. We would expect that success of extubation will be greater on patients extubated to NIPPV than on CPAP or high-flow nasal cannula, and lowest on those extubated to low flow nasal cannula or room air.

~~5. Modes of ventilation supporting all breaths and SIMV are associated with a similar duration of mechanical ventilation.~~

4. SPECIFIC AIMS

Primary aim:

To compare the percentage of successful extubation among patients with positive SBT with that in those extubated based on criteria established for extubation in the main hydrocortisone study.

~~To evaluate the point estimates and confidence intervals of sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio of a positive test, and likelihood ratio of a negative test for the SBT.~~

~~1.~~ *Secondary aims:*

1. To evaluate the point estimates and confidence intervals of sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio of a positive test, and likelihood ratio of a negative test for the SBT.

2. To evaluate point estimates and confidence intervals of sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio of a positive test, and likelihood ratio of a negative test for the SBT in various ~~two~~ subgroups: ~~infants ventilated with SIMV and infants ventilated using modes supporting all breaths~~.

~~3. To determine if ventilation modes that support every breath are associated with shorter duration of mechanical ventilation than SIMV.~~

5. RATIONALE/JUSTIFICATION

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Success of elective extubation is one of the quality measures in neonatal intensive care. This study is designed

~~1.~~ ~~1~~To assess the external validity of the SBT to predict successful extubation in very premature infants. This proposal is the first multicenter study that will assess whether the predictive value of the SBT is better (or not) than other information available to the clinician (Fi02, PIP, PEEP, rate, presence of atelectasis, physiologic stability) to predict successful extubation~~,~~ ~~and~~

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~~2.~~ ~~To add to the limited body of knowledge regarding relative merits of various forms of synchronized ventilation during weaning.~~ Very little additional coordinator time will be needed to collect information that will be used in multivariate analysis that could build the basis for a future randomized trial.

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6. BACKGROUND AND SIGNIFICANCE

Success of extubation is around 60-73% in extremely low birth weight infants.[2,3]~~;~~ Higher success rates (80-86%) have been reported in series including all preterm infants,[4,5]~~;~~ Infants who require re-intubation, with its attendant risks, may experience deterioration of their respiratory status due to atelectasis. Intermittent hypoxemia and/or hypercapnia prior to re-intubation may expose them to additional risks. On the other hand, a relatively large number of infants who self-extubate and remain extubated subsequently.[6,5] Those infants may be exposed to mechanical ventilation and potential ventilator-induced lung injury for longer than necessary or for elective reasons such as to facilitate growth or to prepare for surgery. The latter will be limited in the main hydrocortisone study, since extubation is expected when the baby reaches specific criteria.

Thus, a test that improves the clinician's ability to predict readiness for extubation is highly desirable. Kamlin et al[1] compared three tests to predict success of extubation (no reintubation within 72 hours) in 50 infants with birth weight < 1250 grams using a 3-minute ET CPAP trial: (a) expired minute ventilation (VE) during ET CPAP; (b) ratio of minute ventilation during ET CPAP to minute ventilation during mechanical ventilation (VE ratio); (c) the spontaneous breathing test (SBT). The infant passed the SBT if there was no hypoxia or bradycardia during ET CPAP. The median age at the time of the study was 4 and 5 days,~~;~~ respectively, for successful extubations and for extubations followed by reintubation within 72 hours~~;~~. Kamlin concluded that the SBT had the highest sensitivity (97%), specificity (73%), positive predictive value (93%), negative predictive value (89%), likelihood ratio of a positive test (3.6) and the smallest likelihood ratio of a negative test (0.04) among the three tests.[1] Success rate of extubation predicted by a positive SBT was 403/43 (93%), compared with a success rate of 39/50 (78%) in the total cohort. Limitations of this study included small sample size (n=50) and failure to separate infants ventilated by different synchronized modes. In that study infants were weaned by reducing the tidal volume to 3.5 ml/kg using AC or by reducing ventilator rates to 20–30 breaths/minute on SIMV.

A subsequent study (n=180) provided a degree of validation of the SBT, but compared this test to a historical cohort, which differed substantially from the practice at the time of the validation study. Once more, various modes of ventilation were used, and there was no subanalysis by mode.[26] Most babies in the validation cohort were on volume guarantee ventilation (94% vs 26% in the controls), and most of them were ventilated using AC at the time of extubation (81%, compared with 93% using SIMV in controls). The median age at extubation was 0 days (range 0-27) for babies undergoing the SBT and 0 days (range 0-11 days for controls). Compared with historical controls, infants were extubated at significantly higher ventilator rates and airway pressures using the SBT, but the success rate of extubation was not significantly different (78% with SBT versus 72% in historical controls). The sensitivity of the SBT was 83% (compared with 97% in the first study).

It is not known if the SBT is equally predictive in infants with evolving chronic lung disease and prolonged ventilator dependence. It is also not known if the SBT is equally predictive in infants on different modes of

synchronized ventilation. It is possible that modes in which every breath is supported mask significant respiratory control center immaturity or afford less respiratory muscle training compared to SIMV. SIMV remains the most widely used mode of assisted ventilation in newborn infants,[7] despite its potential disadvantages related to high work of breathing resulting from the high resistance of small endotracheal tubes (ETT) in extremely low birth weight (ELBW) infants.[8-10] This is especially true as the SIMV rate is decreased during the weaning process. In contrast, AC and PSV (when used as a sole mode of ventilation) support each patient breath, thereby resulting in more even tidal volume, less tachypnea, lower work of breathing and lower tidal volume compared to SIMV.[11-13]

There is no information in the literature describing the success of extubation from various modes of ventilation. A practice survey of NRN investigators conducted in July 2011 yielded data from 10 centers. Ventilators include Draeger 8000 (n=6), Maquet Servo I (n=5), Draeger Evita XL (n=2), Draeger VN500 (n=2), Avea (n=2), and Bird VIP (n=1). Pressure-controlled ventilation is predominantly used in 6 NRN centers, and volume-targeted ventilation in 3 centers, while both are used equally in 2 centers. Volume-targeted ventilation is used either often or most of the time in 7 centers, and is used both during the acute phase and during weaning; it is used during weaning by 5 of 10 centers. During weaning and for extubation SIMV is used predominantly by 5 centers and modes supporting all breaths are used predominantly by 5 centers. Extubation from high-frequency ventilation is either rarely or never used. Eight of 10 centers would be ready to perform a 3-min SBT in patients on high-frequency ventilation. In summary the survey showed substantial heterogeneity across centers, with approximate equal distribution of SIMV and modes supporting all breaths.

~~There are limited data regarding the relative efficacy of ventilation modes that support every breath vs. SIMV in weaning from mechanical ventilation and no large clinical trials to evaluate their effect on survival or the risk of bronchopulmonary dysplasia. Three small studies compared SIMV and AC during weaning. In two of these studies SIMV rate was reduced to 10 breaths/min; these studies showed shorter duration of ventilation when using AC. In the third trial, SIMV rate was not reduced below 20 breaths/minute, and the authors showed no difference in duration of ventilation between the two modes.[14,15] These findings support the physiologic explanation that the narrow ETT of ELBW infants increases work of breathing and impairs weaning from mechanical ventilation. Reyes et al showed faster weaning from mechanical ventilation in ELBW infants using SIMV+ PSV, compared to SIMV alone, suggesting that PSV may obviate this problem to some extent.[16] However, this option is not available on all ventilators and may not be widely used. One larger randomized trial enrolled 212 VLBW infants (birth weight 500-1249 g) from initiation of mechanical ventilation through extubation on AC or SIMV.[17] The study showed no differences between the groups in survival, BPD, age at extubation, or length of ventilation in survivors. This study used pressure regulated volume control using the Siemens Servo 300 ventilator, in which the volume targeted mode uses tidal volume measurement at the ventilator end of the circuit, in contrast with ventilator adjusting volume closer to the endotracheal tube. Cross-over for failure occurred in 33% of the infants receiving SIMV and 20% of those who received PRVC.~~

~~A practice survey of NRN investigators conducted in July 2011 yielded data from 10 centers. Ventilators include Draeger 8000 (n=6), Maquet Servo I (n=5), Draeger Evita XL (n=2), Draeger VN500 (n=2), Avea (n=2), and Bird VIP (n=1). Pressure-controlled ventilation is predominantly used in 6 NRN centers, and volume-targeted ventilation in 3 centers, while both are used equally in 2 centers. Volume-targeted ventilation is used either often or most of the time in 7 centers, and is used both during the acute phase and during weaning; it is used during weaning by 5 of 10 centers. During weaning and for extubation SIMV is used predominantly by 5 centers and modes supporting all breaths are used predominantly by 5 centers. Extubation from high-frequency ventilation is either rarely or never used. Eight of 10 centers would be ready to perform a 3-min SBT in patients on high-frequency ventilation. In summary the survey showed substantial heterogeneity across centers, with approximate equal distribution of SIMV and modes supporting all breaths.~~

7. METHODS AND PROCEDURES

a) Study design

This is an observational study (prospective cohort) ~~with prospective data collection~~in a selected group of patients enrolled in a randomized trial (the main hydrocortisone study).
The study will involve analysis of (1) the frequency of successful elective extubation and (2) the operational characteristics of a diagnostic test (SBT) ~~and retrospective analysis of a cohort study (using two cohorts: babies ventilated using SIMV and babies ventilated using modes supporting all breaths)~~.
The spontaneous breathing test (SBT) will be performed by the study team just before elective extubation decided by the clinicians according to the protocol of the main hydrocortisone study~~trial~~. Clinicians will remain blinded to the
results.

b) Study population

We will use the same population as that for the ~~main study~~main hydrocortisone study. All patients enrolled in the ~~main study~~main hydrocortisone study will be approached for informed consent. It is up to each center to decide whether to use a separate consent for the sub-study, or ~~an optional consent, indicated by~~ a check on the consent form of ~~to~~ the ~~main study~~main hydrocortisone study.

c) Inclusion and exclusion criteria

Inclusion criteria:

These will be the same as for the ~~main study~~main hydrocortisone study, i.e.,:
Patients eligible for this study will be infants between 14 – 28 postnatal days who:
(a) are <30 weeks estimated gestational age, to be randomized in two strata: $\leq 26^{6/7}$ and $27^{0/7} - 29^{6/7}$ weeks);
(b) were inborn at an NRN site or were admitted to an NRN site before 72 hours postnatal age;
(c) have received ≥ 7days of mechanical ventilation;
(d) are receiving mechanical ventilation through an endotracheal tube .

We anticipate a starting time for this sub-study to be at the earliest 6/1/2012.

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Exclusion criteria:

Same as for the ~~main study~~main hydrocortisone study, i.e.:

(a) Major congenital anomalies
(b) Decision to limit support
(c) Indomethacin or ibuprofen treatment within 48 hours of study drug
(d) Previous corticosteroid treatment for BPD
(e) Hydrocortisone treatment for hypotension in the first week of life is common (35) and will not be an exclusion; however, infants will be excluded if they have received hydrocortisone:
    (i) for ≥ 14 cumulative days OR
    (ii) within 7 days of study entry.

In addition, we will exclude for this secondary study patients who have at the time of extubation an ETT size <2.5.

d) Enrollment centers and PIs

Case Western	Michele Walsh
Dallas	Luc P Brion

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Wayne State	Seetha Shankaran
Emory	Barbara Stoll
Cincinnati	Kurt Schibler
Indiana	Brenda Poindexter
Brown	Martin Keszler
Stanford	Krisa Van Meurs
Alabama	Waldemar Carlo
Houston	Kathleen Kennedy
Duke	Ronald Goldberg
Iowa	Edward Bell
New Mexico	Kristi Watterberg
Pennsylvania	Barbara Schmidt
Rochester	Carl D'Angio
UCLA	Uday Devaskar
Ohio State	Leif Nelin
Missouri	William Truog

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c) Study intervention and procedures

We will perform a maximum of 2 SBTs per patient: one at the time of the first elective extubation and one at the time of the second elective extubation, if any. Spontaneous unplanned extubations will not be analyzed since SBT will not be performed.

Extubation criteria in the main hydrocortisone study are as follows: "Extubation must be attempted within 72 hours of starting study drug and within 24 hours after meeting the following criteria: the FiO2 is ≤0.40 to maintain a saturation of 88%, the mean airway pressure is ≤ 8, and the infant is hemodynamically stable (as defined for the SUPPORT trial: "clinically acceptable blood pressure and perfusion in the opinion of the clinical team")."

We will request that the clinical team inform the NRN coordinator of any ~~of a~~ pending extubation after the baby has been enrolled to this sub-study.

The intervention (SBT) will be similar to that described by Kamlin et al.[1] Specifically, when the clinicians decide a baby is ready to be extubated, the investigator will perform the SBT within 4 hours of the planned extubation. This intervention will be masked in order to prevent bias that would occur if the clinical provider knew the result of the SBT. We propose that the SBT be conducted after rounds in centers that review the monitoring tracing during rounds.

The infant's ETT will be suctioned prior to the SBT if suctioning is clinically indicated. The SBT will be done no less than 10 minutes after suctioning to ensure adequate re-recruitment of lung volume.

The researcher will silence any alarms and will place screens around the bedside before initiating the test -to minimize the chance of unblinding. After ensuring that the clinical care team, including the patient's nurse, is away from be bedside (to maintain blinding) the investigator (respiratory therapist, fellow, nurse practitioner or attending), who must not be involved with the patient's clinical care, will switch the ventilator to CPAP for 3 minutes at the

same pressure as the positive end-expiratory pressure setting. ~~The infant's ETT will be suctioned prior to the SBT if clinically indicated,~~ T~~and the~~ intervention will be done when the infant is in a quiet state, taking care to minimize stimulation and disturbance during the study.

The baby succeeds the SBT if he or she requires no more than a 15% increase in FiO_2~~FiO2~~ for isolated hypoxemia and does not develop bradycardia (HR <100) for more than 15 seconds. After 3 minutes on CPAP the study will be stopped, and ventilation will be restarted.

The baby fails the SBT if he or she develops a bradycardia (HR <100) for more than 15 seconds and/or a fall in SpO2 below 85% despite ~~a~~ 15% increase in FiO_2. If isolated hypoxemia develops, FiO_2 ~~FiO2~~ will be increased according to unit protocol. If hypoxemia does not respond to a 15% increase in FiO_2~~FiO2~~, or if bradycardia develops, manual breaths are given through the ventilator and mechanical ventilation is restarted at the previous settings.

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~~because of bradycardia or desaturation, this will be considered a failed test. At this point the study will be stopped, and ventilation will be restarted. If manual breaths are given through the ventilator because of bradycardia or desaturation, this will be considered a failed test. Data on the mode of ventilation, success and time of extubation will be collected for subsequent analysis.~~

The baby will be placed back on previous ventilatory settings for~~to~~ 30 minutes, to limit the risk of derecruitment that could have resulted from performing the SBT. The investigator will document in the chart and communicate to the clinical team that the SBT was performed, the exact time of the procedure and the earliest time of extubation (30 min after the SBT). The results of the SBT will not be disclosed to the clinician or documented into the chart unless additional therapy is required as indicated below.

In rare circumstances, the baby may not respond well to the usual intervention described above. In that case, manual bagging will beis initiated and additional treatment will be provided according to NRP guidelines~~for 30 seconds~~, and the clinical team will be ~~is~~ informed. NRP guidelines will be followed if the infant requires more extensive intervention. Once stable, the infant will be placed back on mechanical ventilation.

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~~If the baby responds well, mechanical ventilation is restarted; otherwise appropriate treatment is initiated.~~

f) *Required follow-up*

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None beyond 72 hours after the second elective extubation

g)f) Primary and secondary outcomes

Primary outcomes:

Comparison of the ~~Point estimates and confidence intervals of sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio of a positive test, and likelihood ratio of a negative test to predict successful (defined as no reintubation within 72 hours) extubation using SBT~~ percentage of successful extubation among patients with positive SBT with that in those extubated based on criteria established for extubation in the main hydrocortisone study

Comment [MK1]: I think Dennis will tell us we are doing too many secondary analyses.....

Secondary outcomes:

1. Point estimates and confidence intervals of sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio of a positive test, and likelihood ratio of a negative test to predict successful (defined as no reintubation within 72 hours) extubation using SBT

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a) In the entire cohort undergoing SBT ~~Point estimates and confidence intervals of sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio of a positive test, and likelihood ratio of a negative test to predict successful (defined as no reintubation within 72 hours) extubation using SBT~~

b) In two subgroups: infants with gestational age ≤ $26^{6/7}$ versus those with gestational age $27^{0/7}$ – $29^{6/7}$ weeks

~~1.~~ ~~c) Point estimates and confidence intervals of sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio of a positive test, and likelihood ratio of a negative test to predict successful extubation using SBT~~ In two subgroups: infants ventilated with SIMV and infants ventilated using modes supporting all breaths at the time of the SBT

d) ~~Point estimates and confidence intervals of sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio of a positive test, and likelihood ratio of a negative test to predict successful extubation using SBT~~ By primary study group (hydrocortisone versus placebo)

~~2.~~

~~3. Point estimates and confidence intervals of sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio of a positive test, and likelihood ratio of a negative test to predict successful extubation using SBT~~ According to ETT diameter, since resistance is proportionate to: $R \propto L / r4$, where L is the length of the tube and r is its radius~~ETT resistance calculated according to the formula:~~

~~$R \propto L / r^4$,~~

~~where L is the length of the tube and r is its radius~~

e)

f) ~~Point estimates and confidence intervals of sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio of a positive test, and likelihood ratio of a negative test to predict successful extubation using SBT~~ According to postnatal age

g) ~~Point estimates and confidence intervals of sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio of a positive test, and likelihood ratio of a negative test to predict successful extubation using SBT~~ According to the mode of respiratory support used after extubation: NIPPV;, CPAP or, high-flow nasal cannula;, low flow nasal cannula, or room airoxihood or ambient air.

h) ~~Point estimates and confidence intervals of sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio of a positive test, and likelihood ratio of a negative test to predict successful extubation using SBT~~ Using different definitions of failed extubation (at 12, 24 and 48 hours instead of 72 hours after extubation)

2. Odds ratio of successful extubation taking into account the SBT and multiple possible confounders

~~4. Odds ratio of successful extubation taking into account the SBT and multiple possible confounders~~

~~5. Duration of mechanical ventilation in two subgroups: infants ventilated with SIMV and infants ventilated using modes supporting all breaths for the majority of the time on the ventilator starting at the time of randomization~~

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~~1.~~ Data to collect for this study beyond those in the main trial (see Appendix B):

~~2.~~ Information about the situation before the SBT: ~~At the time of randomization we will obtain the respiratory severity score, which will be calculated as mean airway pressure X FiO2.18~~

~~3.~~ Mode of ventilation, ventilatory settings, vital signs, m~~between the time of randomization and the SBT~~.

1. ~~M~~ost recent blood gas, ~~ventilatory settings and~~ ETT size
2. Response to SBT
3. Respiratory support after the elective ~~second~~ extubation

~~4. just before SBT~~

g) Sample size and power estimate

~~h)~~

Criteria used for elective extubation in the main hydrocortisone trial were targeted toward the lower end of the criteria in the SUPPORT trial. The percentage of successful elective extubation in the main hydrocortisone trial was estimated from data in the surfactant arm of the SUPPORT trial [Results pending from Dennis]. In Kamlin's original study[1] 86% of the infants had a positive SBT, and the success rate of extubation predicted by a positive SBT was 93%, compared with a success rate of 78% in the total cohort. ~~Therefore sample size was determined assuming 65% success rate using extubation criteria used for the main hydrocortisone trial and 75% for patients with a positive SBT. Using two-sided chi-square analysis, a p value of 0.05, and a power of 80% we would need 320 patients in each group; using a power of 90% we would need 420 patients in each group. Since not all patients will have a positive SBT, the denominator will not be identical in the 2 groups.~~

To the extent possible, we will use all available subjects from the total sample size of 800 available in the main trial. By the time the sub-study is expected to start, 100 of 800 patients will have been enrolled into the main trial. Patients who self extubate before the SBT and remain off mechanical ventilation will not be available for this analysis. Those who are reintubated will have another SBT performed before attempting elective extubation. We estimate that about 70% of the total sample size available in the main trial will be available for the analysis of this secondary study; thus sample size is estimated at 420.

Power was calculated using two-tailed chi-square analysis and an alpha error of 0.05. The following grid shows the estimated power ~~using the estimated number of patients we will have available for the analysis (see next section).~~ ~~The table~~ assuminge that 420 patients will undergo elective extubation, that 70-80% will have a positive SBT, that the success of extubation will be 60-75% in the whole group, and 10-15% higher among those with a positive SBT. We will have at least 79% power to detect a 10% difference success rate of extubation using clinical criteria and patients with a positive SBT.

% successful extubation if SBT is positive	Sample size with positive SBT (%)	% successful extubation using criteria using in the main hydrocortisone study	Sample size undergoing elective extubation	Power
70%	336 (80%)	60%	420	82%
75%	336 (80%)	60%	420	99%
70%	294 (70%)	60%	420	79%
75%	294 (70%)	60%	420	99%
75%	336 (80%)	65%	420	85%
80%	336 (80%)	65%	420	100%
75%	294 (70%)	65%	420	82%
80%	294 (70%)	65%	420	99%
80%	336 (80%)	70%	420	89%
85%	336 (80%)	70%	420	100%

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80%	294 (70%)	70%	420	86%
85%	294 (70%)	70%	420	100%
85%	336 (80%)	75%	420	93%
90%	336 (80%)	75%	420	100%
85%	294 (70%)	75%	420	91%
90%	294 (70%)	75%	420	100%

The Kamlin study,[1] which compared three tests, had a sample size of 50. This study was powered to detect a difference of one standard deviation in mean VE in the group failing extubation but not to detect differences in dichotomous outcomes between the three tests. This was a single-center study with a relatively uniform approach to ventilation. The high degree of variability of clinical practice within the NRN will impact the outcome measures in this proposed multicenter trial, thus clearly requiring a much larger sample size to detect a comparable effect size.

~~The Reyes study,[16] which was also a single center study, focused on a similar population demonstrated no significant difference in duration of mechanical ventilation (median [interquartile range] 22 [10-52] vs 34 d [19-59]). This study was powered to detect a 30% difference in the duration of oxygen dependency between groups at an alpha of 0.05 with a power of 90%; it did not reach statistical significance with n=107.~~

~~To the extent possible, we will use all available subjects from the total sample size of 800 available in the main trial. At the current date of this proposal, 40 of 800 patients have been enrolled into the main trial. Patients who self extubate before the SBT and remain off mechanical ventilation will not be available for this analysis. Those who are reintubated will have another SBT performed before attempting elective extubation. We estimate that about 570% of the total sample size available in the main trial will be available for the analysis of this secondary study; thus sample size is estimated at 373550.~~

The secondary ~~primary~~ aim ~~goal~~ of this study is to generate estimates of the operating characteristics (sensitivity [Se], specificity [Sp], positive predictive value [PPV] and negative predictive value [NPV]) of the 3-minute ET CPAP test ("spontaneous breathing test" or SBT) for predicting successful extubation in this population of infants. Each of the operating characteristics of interest is a conditional probability (where the calculation is conditioned on a either success or failure of the extubation or the positive or negative value for the SBT), and the primary sample size consideration for the study is the precision with which these probabilities can be estimated with the available sample sizes. Based on information provided earlier that suggests that 60% to 80% of the extubations are likely to be successful, we assume that between 20% and 80% of the 550 subjects will be used in the denominator of each of the calculations. Furthermore, operating characteristics in the range of 0.7 to 1 are of greatest interest. Given those assumptions the available sample sizes are sufficient to provide confidence intervals with half widths, where a 95% confidence interval is typically computed as the estimate of the sensitivity ± the half width, shown in the table below.

Estimates of Confidence Interval Half Width for Different Levels of True Measure Prevalence and Conditional Denominator							
Se, Sp, PPV, NPV Value	Half Interval Width for Available Denominator						
	110	165	220	275	330	385	440
0.70	0.084	0.069	0.059	0.053	0.048	0.045	0.042
0.72	0.082	0.067	0.058	0.052	0.047	0.044	0.041
0.74	0.082	0.067	0.058	0.052	0.047	0.044	0.041
0.76	0.080	0.065	0.056	0.050	0.046	0.043	0.040
0.78	0.077	0.063	0.055	0.049	0.045	0.041	0.039
0.80	0.075	0.061	0.053	0.047	0.043	0.040	0.037
0.82	0.072	0.059	0.051	0.045	0.041	0.038	0.036
0.84	0.069	0.056	0.048	0.043	0.040	0.037	0.034
0.86	0.065	0.053	0.046	0.041	0.037	0.035	0.032
0.88	0.061	0.050	0.043	0.038	0.035	0.032	0.030
0.90	0.056	0.046	0.040	0.035	0.032	0.030	0.028
0.92	0.051	0.041	0.036	0.032	0.029	0.027	0.025
0.94	0.044	0.036	0.031	0.028	0.026	0.024	0.022
0.96	0.037	0.030	0.026	0.023	0.021	0.020	0.018
0.98	0.026	0.021	0.019	0.017	0.015	0.014	0.013

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i) Available population/compatibility with other ongoing protocols

Same as for the ~~main study~~main hydrocortisone study: Based on GDB data 06-07, and assuming 60% consent rate, 800 infants could be recruited to the ~~main study~~main hydrocortisone study over 3 years. Since the secondary study will start at the earliest 6/1/2012 we estimate 100 infants will have been recruited already in the main hydrocortisone study. Patients who self extubate before the SBT and remain off mechanical ventilation will not be available for this analysis. Those who are reintubated will have another SBT performed before attempting elective extubation. Since some centers may use a separate consent form for the current study while other centers may use an embedded consent w~~W~~e estimate that about 70% of the total sample size available in the main trial will be available for the analysis of this secondary study; thus sample size is estimated at 420~~550~~.

~~Since the secondary study will start after the beginning of the main study, the total number of patients in this secondary study will be probably 10% smaller, i.e. 500 patients.~~

j) Projected recruitment time

The projected recruitment time for the ~~main study~~main hydrocortisone study was~~is~~ 30 months. However, as of November 2011, only 16 had been randomized per month (versus an original main trial estimate of 27 recruited per month). Initiation of the secondary study could be expected within 6 months (i.e., by 6/1/2012). ~~Therefore, projected recruitment time for the main study is estimated to be 24 months.~~Since recruitment into the main hydrocortisone study is slower than expected, recruitment may last longer than initially expected.

k) Data Analysis Plan

We will use chi-square analysis to compare the success of extubation in patients who will successively pass the SBT with that among all patients who are electively extubated and undergoing the SBT.

~~1. We will determine the point estimates and 95% confidence intervals for the operating characteristics (sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio of a positive test, and likelihood ratio of a negative test) of successful extubation using the SBT.~~

We will ~~We will~~ determine the point estimates and 95% confidence intervals for the operating characteristics (sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio of a positive test, and likelihood ratio of a negative test) of successful extubation using the SBT in all patients undergoing SBT.

We will

~~use the same~~ determine the same point estimates and 95% confidence intervals for the operating characteristics tests in the following subgroups: ___ ___ ___ ___ ___ ___ ___ ___ ___ ___ ___

a) In the entire cohort undergoing SBT

b) In two subgroups: infants with gestational age $\leq 26^{6/7}$ versus those with gestational age $27^{0/7}$ – $29^{6/7}$ weeks

c) In two subgroups: infants ventilated with SIMV and infants ventilated using modes supporting all breaths at the time of the SBT

d) By primary study group (hydrocortisone versus placebo).

e) According to ETT diameter, since resistance is proportionate to: $R \propto L / r^4$, where L is the length of the tube and r is its radius

f) According to postnatal age

g) According to the mode of respiratory support used after extubation: NIPPV; CPAP or high-flow nasal cannula; low flow nasal cannula, oxihood or ambient air

h) Using different definitions of failed extubation (at 12, 24 and 48 hours instead of 72 hours after extubation)

~~1.~~

~~2. infants ventilated with SIMV versus infants ventilated using modes supporting all breaths at the time of the SBT.~~

~~infants with gestational age $\leq 26^{6/7}$ versus those with gestational age $27^{0/7}$ – $29^{6/7}$ weeks~~

~~2. primary study group~~

~~3. infants ventilated with SIMV and infants ventilated using modes supporting all breaths at the time of the SBT~~

~~4. according to the mode of respiratory support used after extubation: NIPPV, CPAP, high-flow nasal cannula, low-flow nasal cannula or room air~~

~~5. using different definitions of failed extubation (at 12, 24 and 48 hours instead of 72 hours after extubation)~~

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We will use Receiving operator characteristic curve (ROC) to analyze whether the operating characteristics of the SBT vary according to ETT resistance and to postnatal age.

~~Duration of mechanical ventilation will be compared in the two subgroups using non-parametric tests (two-sided Mann-Whitney test, alpha < 0.05) because this variable has a non-normal distribution. We will use multiple regression analysis of the duration of ventilation using as factors the gestational age, the center, the respiratory severity score at the time of randomization, the randomization arm (hydrocortisone versus control), and the mode of ventilation. Additional factors that differ by p < 0.10 on univariate analysis will be tested for significance in the multiple regression analysis.~~

The likelihood of success of extubation may depend on multiple factors other than SBT, including patient characteristics, mode of ventilation, individual clinician and center. For this purpose we will use multivariate logistic regression analysis using as predictors:[1] gestational age, weight for age at birth, postnatal age, PEEP, mode of ventilation and ventilation settings at the time of SBT (SIMV vs. ventilation supporting every breath), SBT, hydrocortisone (vs. placebo), caffeine,- symptomatic patent ductus arteriosus, center, and mode of respiratory support after extubation (NIPPV, CPAP, high flow nasal cannula, low flow nasal cannula, room air). Additional factors that differ by $p < 0.10$ on univariate analysis will be tested for significance in the multiple regression analysis.

l) Data safety monitoring plan:

Eight interim blocks are planned in the ~~main study~~main hydrocortisone study. The DSMC will review data from the main trial and from this secondary study at the same time. For this secondary study, the DSMC will review the frequency of required treatment (bagging, resuscitation) related to the SBT. Serious adverse events to be reported to NICHD within 24 hours include death that would occur after a code related to the SBT.

m) Stopping limits for protocol termination:

The DSMC may decide to stop the main trial or this secondary study.

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8. RISK, BENEFITS, LIMITATIONS

Ethical issues

Benefit: There is no direct benefit to participating in this secondary study.

Risks: Some babies may develop bradycardia or desaturation and may require increase in FiO_2 or manual breaths on the ventilator ~~bagging~~ at the time of SBT. It is possible that an occasional infant may require additional interventions. However, ~~n~~No case of resuscitation related to the SBT has been described in the two published studies. Any baby requiring resuscitation will be reported to the IRB as an adverse event.

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Blinding: SBT failure may be fairly predictive of failure of extubation. However, it is not part of standard practice in centers in the NRN. If the results of the SBT were provided to the clinical care team, it would result in bias in decision of extubation time. The SBT as described has been reported in two studies involving a total of 230 neonates, ~~more than~~ Since reported infants undergoing the SBT had an uneventful course even if failing the SBT, ;

~~therefore~~ blinding the clinical care team to the results of this test is defensible, except in the rare circumstance of ~~lack of response to ventilator breaths through the ventilator and re-initiation of mechanical ventilation~~ a more serious deterioration that required more than a few ~~manual~~ breaths through the ventilator and resumption of mechanical ventilation (in which case the clinical team will be informed of the event).

~~A consent form will be obtained for participation in this study. There is a slight possibility that asking for permission for this secondary study would affect enrollment rate in the primary study. We think it is unlikely with the opt-in checkbox.~~

Consent form: A consent form will be obtained for participation in this study. There is a slight possibility that asking for permission for this secondary study would affect enrollment rate in the primary study. Each center PI will decide whether to use a separate ~~This~~ consent for this secondary study or to ~~could be~~ embedded it in the consent form for the ~~main study~~main hydrocortisone study.

Limitations

Since this is an observational rather than a randomized study, success of extubation ~~the duration of mechanical ventilation~~ may be affected by multiple factors, biases and confounders, some of which we may not be able to quantify. Based on our survey, it appears that selection of the ventilation mode depends in large part on center and care provider/attending choice than on patient characteristics. For this purpose we will conduct multivariate analysis using patient characteristics (GA, prenatal steroids, disease severity), and information about individual patients. ~~NICU and providers' practices (fluid and salt administration, therapy for PDA, diuretics, caffeine, type of ventilator, choice of ventilator mode, blood gases at the time of extubation).~~

There may be inter-institutional and inter-individual variability in the decision about when to extubate. Variability will be limited by criteria set by Kristi Watterberg in the main trial protocol: "Extubation must be attempted within 72 hours of starting study drug and within 24 hours after meeting the following criteria: the FiO2 is <0.40 to maintain a saturation of 88%, the mean airway pressure is < 8, and the infant is hemodynamically stable (as defined for the SUPPORT trial: "clinically acceptable blood pressure and perfusion in the opinion of the clinical team"). The infant may be extubated from higher settings at the discretion of the attending physician. If the infant does not meet these criteria within 72 hours, he/she will be reassessed every 24 hours during the intervention period and extubation will be attempted within 24 hours of those criteria being met."

Success of extubation depends on absence of apnea. Apnea may not be detected during the 3 minutes during which the SBT will be performed. We expect that a majority but not all patients in the current trial may be on caffeine at the time of extubation, since a large multicenter randomized trial has shown it reduces the rate of bronchopulmonary dysplasia (oxygen requirement at 36 weeks postmenstrual age)[14,20] and improves the rate of survival without neurodevelopmental disability at 18 to 21 months but not in early childhood in infants with very low birth weight infants.[21,15,16,22]

Success of extubation will be limited in case of laryngeal edema, which may be more prevalent in the control arm. Hydrocortisone may limit this risk. We will record documentation of stridor and failure of successful extubation related to stridor.

We will not use VE as a predictor for extubation because the tidal volume cannot reliably be measured when the leak around the endotracheal tube is ≥ 30%. In spontaneously breathing infants, the tidal volume is not stable and the number of r breaths over which the VE is averaged varies among different types of ventilators.

SIMV with PS will be classified as a mode ~~modes~~ supporting all breaths; however this mode supports some breaths fully (SIMV) and other breaths to a lower extent (PS), in contrast with AC or PS.

~~Since subgroups for duration of mechanical ventilation will be based on the mode of respiratory support for the majority of the time on the ventilator from the time randomization, there will be possible overlap between the two groups, since some babies may be exposed to more than one mode. However, most changes in mode occur between the acute phase and beginning of weaning. Starting the count at the time of primary study entry (at least 14 d) will minimize this overlap.~~

We did consider alternatives to Kamlin's SBT.

1. During the SBT the baby will need to breathe against the resistance of the endotracheal tube. The resistance of the tube is proportional to L / r^4, where L is the length of the tube and r is its radius. We will record length and radius to assess whether the predictive value of the SBT decreases with increased resistance of the tube. An alternative to the SBT would be to design a modified SBT using PSV with minimal pressure instead of CPAP. Since no complications have been described with the SBT, this may not be necessary. Since this has not been tested in the past, we will not use this option.

2. Wilson et al[17,22] described a minute ventilation test (MVT) of 10 minutes duration instead of the 3-minute test described by Kamlin. In a single institution, a spontaneous minute ventilation ≥ 50% of the ventilator-generated minute ventilation correctly predicted successful extubation in 86% of preterm infants with birth weight < 2 kg and requiring mechanical ventilation for > 24 hours.[22] In a subsequent randomized trial[18,23] (mean GA 30 weeks), babies undergoing the MVT were extubated sooner than those in the control group. The positive predictive value of the MVT for extubation was 76% (95% CI, 55 to 89%) and the success of extubation was similar to the control group.[19,23] Kamlin's SBT is more appropriate for our study for several reasons: ~~H~~his studies only included smaller babies; the SBT only uses 3 minutes and does not require minute ventilation measurement and thus could be used in multicenter setting with various ventilators, and appears at least as good as the 10 minute MVT.

3. Dimitriou et al[5] have described composite indices such as the diaphragmatic pressure–time index and the noninvasive respiratory muscle pressure–time index to predict success of extubation in preterm with mean gestatational age of 30 weeks and mean birthweight of 1.36 kg. The test had ~86% positive predictive value of successful extubation in the validation group. Kamlin's SBT is more appropriate for our study for the same -reasons as described for -the 10 minute MVT.

~~There is a slight possibility that asking for permission for this secondary study would affect enrollment rate in the primary study. We think it is unlikely with the opt-in checkbox.~~

9.5 BUDGET

Direct Costs

Cost per patient: $ 190413

Respiratory therapist: 3015 minutes x $530 per hour = $ 508

Coordinator time: 43 hours x $35 per hour = $ 140105

Consent: ~~assuming consent for this secondary study is embedded in the consent for the main trial:~~ 3010 minutes

Screening for subjects who qualify for extubation: 6020 minutes

SBT: 6060 minutes

Data collection/entry/transmission: 90 minutes

Total Capitation ~~Direct~~ Cost for 436533 patients:
$8259,840963

Training session at NRN steering committee *$ 2,000*

Total direct costs $84,840

Indirect costs (52.6%): $44,626

Total costs: $129,466

Note: there is no CPT code for the SBT test

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Appendix A: Authorship Plan:

We will follow the Policies and Procedures of the NICHD Neonatal Research Network

For abstracts, Authors of the Secondary Study with be the authors followed by "for the NICHD Neonatal Research Network.

For publications, authors will include Authors of the Protocol Subcommittee, Remaining participating Center PIs (those not serving on the Protocol Subcommittee), listed in order by the Center's combined ranking of the number of infants enrolled and the percent of eligible infants enrolled in the study by the Center, Followed by the phrase "for the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network."

Appendix B1: Data sample sheet

Data obtained for the ~~main study~~main hydrocortisone study and location on GDB or main hydrocortisone study forms:

Center: _____ HCO2

Gestational age~~,~~ _____ HCO1

Bbirth weight~~,~~ _____ GDB

Date of birth _____ HCO1

~~date and time of birth, prenatal steroids,~~ Ddate of ~~and time of~~ randomization~~,~~ _____ HCO2

Rrandomization ~~arm~~code _____ ~~,~~ _____ HCO2

Information about first extubation~~center~~ HCO5

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Appendix B2: Data sample sheet

~~1.~~ **Data obtained for the secondary study: first elective extubation:**

~~2. Exclusion criterion: ETT size < 2.5~~

~~3. At the time of randomization: FiO2 ____ Mean airway pressure: ____~~

~~4. Ventilation mode and duration:~~

~~From~~	~~Until~~	~~SIMV~~	~~PS/SIMV +PS/AC/PRVC~~

~~SBT~~ Planned extubation date and time: _____ ETT diameter (mm): ____ ~~total length: ___~~

Symptomatic PDA: Yes ____ No ____

Caffeine: yes ____ No ____

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~~6.~~ SBT: ~~(when quiet, change to CPAP at same pressure as prior PEEP for 3 min):~~ date and time:_____

~~Planned extubation date and time:~~

Immediately before SBT	During SBT
~~PS/SIMV +PS/AC/PRVC SIMV~~ Ventilation mode: PS SIMV SIMV with PS AC Volume mode Pressure control	~~Date:~~ From until
ETT diameter: length at lips:	
Latest pH: pCO2: BE:	
PIP: MAP: Ventilator rate: PEEP: cm FiO2: Sat:	CPAP: cm
HR > 100: yes no	Min HR < 100 for > 15 sec: Yes No
FiO2: Sat:	Fall < 85% despite 15% increase in FiO2: Yes No
	Max FiO2 Manual breaths through ventilator: number: Resuscitation needed: bagging minutes: chest compressions: minutes: epinephrine:

Exbutation to: NIPPV CPAP high-flow nasal cannula low flow nasal cannula oxihood ambient air

Stridor: Racemic epinephrine:

Reintubation: no yes date: time

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Comment [MK3]: This is stuff after extubation. We also need to document treatment after extubation (CPAP, NIPPV, HFNC, etc!)

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Appendix B3: Data sample sheet

Data obtained for the secondary study: second elective extubation:

Planned extubation date and time: _____ ETT diameter (mm): ____ ~~total length: ____~~

Symptomatic PDA: Yes ____ No ____

Caffeine: yes ____ No ____

SBT: date and time: _____

Immediately before SBT	During SBT
Ventilation mode: PS ____ SIMV ____ SIMV with PS ____ AC ____ Volume mode ____ Pressure control ____	~~Date:~~ _____ From ____ until ____
ETT diameter: ____ length at lips: ____	
Latest pH: ____ pCO2: ____ BE: ____	
PIP: ____ MAP: ____ Ventilator rate: ____ PEEP: ____ cm FiO2: ____ Sat: ____	CPAP: ____ cm
HR > 100: yes ____ no ____	Min HR < 100 for > 15 sec: Yes ____ No _____
FiO2: ____ Sat: ____	Fall < 85% despite 15% increase in FiO2: Yes ____ No ____
	Max FiO2 Manual breaths through ventilator: number: ____ Resuscitation needed: bagging ____ minutes: ____ chest compressions: ____ minutes: epinephrine: ____

HCO5: same data form as for first extubation in the main trial

Extubation to: NIPPV__CPAP__ high-flow nasal cannula__ low flow nasal cannula__ oxihood__ ambient air__

Stridor: Racemic epinephrine:

Reintubation: no yes date: time

~~HCO5: same data form as for first extubation in the main trial~~

~~7. Reintubation within 72 hours after extubation: no yes:~~

~~If yes: date and time:~~

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From: Luc Brion
To: Kristi Watterberg
Cc: Carl_Dangio@URMC.Rochester.edu; MKeszler@Wihri.org; dwallace@rti.org; Higgins, Rosemary (NIH/NICHD) [E]; Pablo Sanchez
Subject: RE: revised protocol
Date: Monday, January 23, 2012 5:14:28 PM
Attachments: SBT response 23Jan12.doc
Secondary - predicting ext success - Protocol 01232012 rev.docx

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Kristi:

Oops! I missed a few more mistakes! Thanks a lot for taking the time to read the documents and thanks your comments.

Kristi: Carl, Martin, Dennis, Rose:

I looked carefully at the printout and edited the text further; corrections should come in blue this time; this will allow you to detect changes I made today.

Best regards,

Luc

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Director, Fellowship Training Program in Neonatal-Perinatal Medicine
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luc.brion@utsouthwestern.edu

From: Kristi Watterberg [mailto:KWatterberg@salud.unm.edu]
Sent: Monday, January 23, 2012 2:42 PM
To: Luc Brion
Cc: Carl_Dangio@URMC.Rochester.edu; MKeszler@Wihri.org
Subject: Re: revised protocol

A lot of work in a short time, Luc! A couple of minor points:

Background: this must be a typo: "extubation predicted by a positive SBT was 3/43 (93%), compared with a success rate of 39/50 (78%) in the"

The two statements below seem to conflict - in each, you are looking at the SBT vs. clinical factors to predict successful extubation, even though they're stated a little differently.

The null hypothesis is that the percentage of successful extubation among patients with positive SBT is not different from that in those extubated based on criteria established for extubation in the main hydrocortisone study.

The primary question is not to determine whether SBT is better predictive than clinical information; this would be best studied by a randomized trial.

There seems to be a missing clause in the following sentence: "If an occasional infant requires more than this, e.g., bag and mask ventilation or additional resuscitation."

Kristi

>>> Luc Brion <Luc.Brion@UTSouthwestern.edu> 1/21/2012 4:59 PM >>>
Martin, Carl, Kristi, Dennis, Rose:

Thanks a lot for all the feedback at the meeting.

Here is the updated protocol, taking into account all the suggestions from the protocol review committee and a first draft of the revised sample size analysis (not seen by Dennis yet).

Please let me know your suggestions (if possible by January 27th) so I can I send the protocol to the review committee at least one week before the next protocol review standing committee call (February 7th).

Thanks and best regards,

Luc

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DATE: January 19, 2012

TO: Brenda Poindexter
Chair, Protocol Review Subcommittee

FROM: Luc Brion

RE: Itemized response to the Protocol Review Subcommittee re: "Predicting Success of Extubation During Hydrocortisone Therapy and the Effect of Different Modes of Synchronized Ventilation"

We thank the protocol review subcommittee for a careful review of our proposal. We added itemized responses to each comment that required either a response or a change in the protocol. We modified the protocol considerably along the guidelines provided by the committee.

The Protocol Review Subcommittee reviewed this protocol during its conference call on January 3, 2012. Written comments were provided by Kurt Schibler, Brenda Poindexter, and Stephanie Archer and are included below.

The Subcommittee discussed differences between the population of infants studied in the Melbourne trial of spontaneous breathing versus those that will be in the hydrocortisone trial. It was noted that the investigators in Melbourne who described this test were using it every day on rounds, the purpose being to extubate VLBW infants as soon as possible (median age 4-5 days). On the other hand, infants in the hydrocortisone trial are a unique subgroup of babies who are stuck on the ventilator. The investigators need to explain how the results of the spontaneous breathing test (SBT) in the hydrocortisone cohort will be generalizable in the typical NICU setting.

We agree that the postnatal age of patients in the hydrocortisone study is different from those in the Melbourne study. We also agree data in the proposed study will not be generalizable to all patients in the NICU. The proposed study is specifically designed to address the current knowledge gap in the literature, i.e., vailidity of the SBT at later postnatal age. We have clarified the protocol to indicate this dand expanded the rationale for the study.

The specific aim related to modes of ventilation was discussed at length by the Subcommittee. Given center differences in the use of assisted modes of ventilation, the consensus of the Subcommittee is that this aim is not feasible. In addition, only a limited amount of data is currently being collected for the Hydrocortisone trial (see HCO4 respiratory data collection form); in order to address the aim related to assisted ventilation, a significant increase in data collection would need to be incorporated into the study design.

We have removed the specific aim related to duration of ventilation based on different modes of ventilation.

Finally, the Subcommittee discussed the potential confounding of post-extubation management. In the current protocol, it is not clear how differences in clinical management following extubation will be handled (many which could significantly impact the success of extubation).

This may actually be a strength of the proposed study, which is aimed at finding out if the SBT is better or not to clinical decision about readiness to extubation across multiple centers using ~~and~~ multiple approaches to post-extubation therapy (CPAP, high-flow nasal cannula, NIPPV). We will collect this information and analyze it by secondary subgroup analysis and by multivariate analysis.

As currently written, the Subcommittee had low enthusiasm for the proposed secondary. However, the Subcommittee would be willing to review a revised version of the protocol which addresses the concerns outlined below.

Comments submitted by Kurt Schibler:

This observational study is primarily designed to evaluate whether a short endotracheal continuous positive airway pressure (ET CPAP) test may help predict the success of extubation of very premature infants.

1) The primary aim of this study is evaluate the point estimates and confidence intervals of sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio of a positive test, and likelihood ratio of a negative test for the spontaneous breathing test (SBT).

2) Secondary aims are 1) To evaluate point estimates and confidence intervals of sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio of a positive test, and likelihood ratio of a negative test for the SBT in two subgroups: infants ventilated with SIMV and infants ventilated using modes supporting all breaths and 2) To determine if ventilation modes that support every breath are associated with shorter duration of mechanical ventilation than SIMV.

Methods

Study design - This is an observational study with prospective data collection.

The study will involve analysis of the operational characteristics of a diagnostic test (SBT) and retrospective analysis of a cohort study (using two cohorts: babies ventilated using SIMV and babies ventilated using modes supporting all breaths).

The spontaneous breathing test (SBT) will be performed by the study team just before extubation decided by the clinicians. Clinicians will remain blinded to the results.

Study population - We will use the same population as that for the main study. All patients enrolled in the main study will be approached for an optional consent, indicated by a check on the consent to the main study

Study intervention - when the clinicians decide a baby is ready to be extubated, the investigator will perform the SBT within 4 hours of the planned extubation.

The researcher will silence any alarms and will place screens around the bedside before initiating the test to minimize the chance of unblinding. After ensuring that the clinical care team, including the patient's nurse, is away from be bedside (to maintain blinding) the investigator (respiratory therapist, fellow, nurse practitioner or attending), who must not be involved with the patient's clinical care, will switch the ventilator to CPAP for 3 minutes at the same pressure as the positive end-expiratory pressure setting. The infant's ETT will be suctioned prior to the SBT if clinically indicated, and the intervention will be done when the infant is in a quiet state, taking care to minimize stimulation and disturbance during the study. The baby fails the SBT if he or she develops a bradycardia (HR <100) for more than 15 seconds and/or a fall in SpO2 below 85% despite a 15% increase in FIO2. At this point the study will be stopped, and ventilation will be restarted. If manual breaths are given through the ventilator because of bradycardia or desaturation, this will be considered a failed test. Data on the mode of ventilation, success and time of extubation will be collected for subsequent analysis.

The baby will be placed back on previous ventilatory settings to 30 minutes, to limit the risk of derecruitment that could have resulted from performing the SBT.

Sample size

The investigators estimate that about 70% of the total sample size available in the main trial will be available for the analysis of this secondary study; thus sample size is estimated at 550. Since the secondary study will start after the beginning of the main study, the total number of patients in this secondary study will be probably 10% smaller, i.e. 500 patients.

Analysis plan

The investigators will determine the point estimates and 95% confidence intervals for the operating characteristics (sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio of a positive test, and likelihood ratio of a negative test) of successful extubation using the SBT.

Investigators will use the same tests in subgroups:

1. infants ventilated with SIMV versus infants ventilated using modes supporting all breaths at the time of the SBT.
2. infants with gestational age ≤ $26^{6/7}$ versus those with gestational age $27^{0/7} - 29^{6/7}$ weeks

Receiving operator characteristic curve (ROC) will be used to analyze whether the operating characteristics of the SBT vary according to ETT resistance and to postnatal age.

Comments

1. Allowing time after suctioning and after the SBT for potential re-recruitment of alveoli is important particularly in the lower gestational age strata. – We added a minimum of 10 minutes between suctioning and the SBT.

2. The reasons for failure to remain extubated for 72 hours are multifactorial including individual infant associate factors and factors related to providers or center. – This fact is acknowledged in the protocol and in the limitations. We will use multivariate analysis for this purpose; however we wil not control for individual providers. We may actually consider this heterogeneity of approach to patient care as one of the strength of this study: this will enhance external validation of the SBT test, which so far has only been tested in single-center studies.

3. It may not be possible to have SBT performed by someone not involved in clinical care of the study infant. We believe it is important to maintain blinding of SBT. The study cannot be done without masking the clinical team. If the caregivers know whether the baby has passed or failed the SBT, they will be biased by the study, and therefore it will be impossible to determine the outcomes described for the study. It would be up to each center to decide whether the study PI, coordinator, respiratory therapist, fellow, attending, or NNP would be involved in theSBT. Centers who are not able to perform blinding SBT should not participate.

4. The effects of the study medication in the main trial may influence the utility of the SBT to predict extubation success. The study is designed to determine this as one of the secondary outcomes and by using multivariate analysis. We realize that steroids may improve lung compliance and reduce the risk of laryngeal edema.

5. The study forms and additional data to be collected should be included with the protocol in order to determine how time intensive the secondary study will be. Appendix B includes all the additional information required for the study, and was edited to include all the comments and suggestions from the reviewer. Further development of the forms will be done in the manual.

6. The respiratory support variable collected around the time of the test may have little bearing on modes of support and their influence on extubation success or failure. We agree with the reviewer that this variable may not affect the validity of the SBT. This will be one among many variables we will test.

7. Whether consent should be imbedded or not should be at the discretion of the centers. We changed the protocol accordingly.

Comments submitted by Brenda Poindexter:

SUMMARY: The proposed study is a secondary study to the hydrocortisone trial to assess the sensitivity, specificity, positive and negative predictive value of the spontaneous breathing test (SBT) in predicting successful extubation in ELBW infants.

~~1.~~ The authors state that because this is an observational study, there is no primary hypothesis. This needs to be revised to reflect the analyses that will be done (hypothesis could be that the SBT will be more useful than clinical information alone). Thank you for this suggestion. The null hypothesis is that the percentage of successful extubation among patients with positive SBT is not different from that in those extubated based on criteria established for extubation in the main hydrocortisone study.

~~2.~~1. In the methods and procedures section of the protocol the authors state that the study will involve analysis of the operational characteristics of the SBT and retrospective analysis of a cohort study. The retrospective analysis is not mentioned anywhere else in the protocol. As currently written, it seems that all infants enrolled as part of the hydrocortisone for extubation main trial will all receive the SBT, so it is is not clear where the retrospective cohort will come from. Thank you for this comment; we agree with you. We have removed this sentence from the study design. This was a mistake we have overlooked; there is no retrospective data in this study. If the primary question is whether the SBT has better predictive ability than typical clinical information (such as FiO2, PIP, PEEP, etc.) as stated in the rationale/justification, then wouldn't there need to be a control group of infants who are subjected to the SBT? We changed the primary aim of the study: "To compare the percentage of successful extubation among patients with positive SBT with that in those extubated based on criteria established for extubation in the main hydrocortisone study.", ~~The primary question is not to determine whether SBT is better predictive than clinical information; this would be best studied by a randomized trial.~~

~~3.~~2. Secondary aim – the second secondary aim is to determine if ventilation modes that support every breath are associated with shorter duration of mechanical ventilation than SIMV. Although data will be collected related to mode of ventilation at time of extubation, it would seem that detailed data related to respiratory support prior to the time of extubation would be required. The HC04 respiratory form collects only very limited information related to type of ventilator support on study days 1, 3, 5, 7, 10, and 14 and collects no information related to assist control or pressure support. If modes of assisted ventilation shorten the duration of mechanical ventilation, wouldn't the duration of being on an assisted mode also contribute to the outcome? In other words, I would think there would be a difference between infants whose entire course on the ventilator is in SIMV versus those who are only changed to SIMV during the final stages of weaning (for 12-24 hrs) prior to extubation. In the data analysis plan, the subgroups are only divided by mode of ventilation at the time of the SBT. How will duration of time in assisted ventilation mode be dealt with in the analyses? The investigators state that "very little additional coordinator time will be needed to collect information that will be used in multivariate analysis that could build the basis for a future

randomized trial" but have not provided a draft of the proposed data collection forms to be utilized in the secondary study. The wide range of practice variation in modes of ventilator management at NRN centers provided by the survery results in the protocol highlight the likelihood that center differences will bias the ability to evaluate this secondary aim (this concern was also raised in the concept comments). We agree with the reviewer's concerns and eliminated this part of the study.

4.3. Unplanned extubations – the investigators have not taken into account unplanned extubations (some of which are likely to be successful). How will these infants be handled in the analyses? These events will be excluded from the analysis, since SBT is not performed.

5.4. Post-extubation management – the role of post-extubation management is not addressed in the protocol as a potential confounder to prediction of extubation success. What type of data will be collected during the immediate post-extubation period and what variables (such as extubation to CPAP versus HFNC or SiPAP, use of racemic epinephrine, etc.) will be considered in the analytic plan. This information was added to the protocol and to appendix B.

6.5. Treatment group – one of the secondary null hypotheses is that the predictive value of the SBT is not affected by whether the baby is randomized to hydrocortisone or placebo. This hypothesis needs to be justified as hydrocortisone, if efficacious as defined by the primary outcome measure of the main trial, could significantly confound the primary outcome of likelihood of extubation success (in addition to the other potential confounders mentioned in the protocol including fluid management, caffeine, etc.). We agree with the reviewer's comments. In this protocol we describe null hypotheses. "2. The predictive value of the SBT is not affected by whether the baby is randomized to hydrocortisone or placebo. Hydrocortisone may affect lung compliance and laryngeal edema and thus improve success rate of extubation compared with placebo."~~We hypothesize that hydrocortisone might improve lung compliance and reduce laryngeal edema, thereby improving the success rate of extubation in comparison to the control group.~~ We will analyze potential confounders by using multivariate analysis, which is now listed as~~in the~~ secondary outcome.

7.6. Masking – the protocol states that the individual performing the SBT should not be involved in the clinical care of the infant. Clarification is needed regarding the duration of time that this individual cannot be involved in the clinical care (before and after performance of the SBT). Regardless of who performs the test, it may be impossible to avoid having this person involved in the clinical care of the infant. It would be helpful to specify the period of time that the person administering the SBT should not be involved in the clinical care of the infant. The issue of clinical documentation and masking also needs to be addressed in the protocol. If an infant has significant hypoxia and/or bradycardia during the SBT, how will the documentation in the medical record be addressed? Given that data from our monitors in the NICU is recorded and reviewed on rounds on a daily basis, significant episodes of desaturation and/or bradycardia will be difficult to not relay to the clinical team; in addition, if the infant does require PPV or other intervention following a failed SBT, the clinical team will need to be informed. I would think that the IRB would question the plan to not inform the clinical team of a significant desaturation or bradycardia event knowing that an

extubation attempt is being planned by the clinical team in the immediate future. In this regard, I disagree with the investigators that blinding the clinical team of a failed SBT (at least in the case of significant bradycardia or need for resuscitation) is "defensible". Thank you for your comments. The study cannot be done without masking the clinical team. If the caregivers know whether the baby has passed or failed the SBT, they will be biased by the study, and therefore it will be impossible to determine the outcomes described for the study. The large majority of the babies undergoing an SBT tolerate the procedure well and those who fail the SBT respond rapidly to manual breaths on the ventilator. If an occasional infant requires more than this, e.g., bag and mask ventilation or additional resuscitation. We have modified the protocol accordingly. We propose that the SBT be conducted after rounds in centers that review the monitoring tracing during rounds.

~~8.~~ 7. Budget – Two areas of the proposed budget warrant further consideration – first, there is a budget for a respiratory therapist for 15 minutes – does this mean that the SBT must be performed by a study respiratory therapist? I would assume that the majority of centers do not have respiratory therapists on their paid research team. For other NRN studies requiring support from respiratory therapists (such as SUPPORT, Benchmarking, and the iNO studies), we have always relied on respiratory therapists at the centers providing their time without reimbursement. The protocol leaves to each center the choice of who will be involved in performing the SBT; in some centers only respiratory therapists are allowed to change ventilator settings. The second point that requires clarification is the 20 minutes of coordinator time for screening for subject who qualify for extubation. This would not be a one-time event, but rather would require daily screening until the infant met criteria for consideration of extubation. In addition, the decision to extubate is often made during morning rounds – therefore, this protocol will require that the clinical team inform the research coordinator of the intent to extubate in a timely manner (within the required 4 hours) or the opportunity to perform the SBT may be missed. In addition, for infants who require reintubation, the protocol states that a second SBT will be performed prior to the next extubation attempt; this effort for continuing to follow the infant after the first reintubation is not accounted for in the budget (nor is it required for the main RCT); the protocol is also inconsistent in this regard as the required follow-up is listed as being none beyond 72 hours after extubation (First extubation? Second if first one fails?). -Finally, the budget needs to be adjusted to reflect the additional data collection for type of respiratory support (as mentioned above, HC04 does not record whether infant is on assist control, SIMV, or pressure support). Thus, the time estimate for coordinator effort for this secondary study is markedly underestimated in the current budget. We now indicate in the protocol that we will use only the first 2 elective extubations after randomization. Sample size analysi s is based on the first elective extubation only. The coordinator time was increased to 4 hours based on your recommendations. We increased the time by only one hour because we have eliminated the collection of ventilator mode and support between randomization and the day of the SBT. We further revised the budget to follow Stephanie Archer's recommendations. We propose to leave the respiratory therapist in the budget. At Parkland, the plan is that one of the 2 respiratory therapists on call (the one is not assigned to take care of the baby as a provider) assigned to the NICU will perform the SBT. Each center will decide who could do the SBT; some centers may use the

coordinator, the PI, the alternate PI, another attending, fellow or NNP for this purpose. Alternatively, we may further revise the budget if we decide that respiratory therapists will not be involved in the study.

~~9.~~8. Consent – the authors state that they do not feel that the imbedded consent will affect enrollment in the main trial because of the opt-out ability, but I do think that this issue will need to be prospectively monitored to ensure that enrollment in the main trial is not compromised. I am not in favor of imbedding consent for this secondary into the main trial; I would suggest that the decision of whether or not to imbed consent be left to the individual centers. We changed the protocol accordingly and will let each center choose whether to use a separate consent from or to imbed it into the consent for the main trial.

~~10.~~9. Data collection forms – drafts of the proposed data collection forms need to be included in the protocol; without these, it is impossible to ascertain whether the time estimates in the budget are appropriate or not. The data collection form is included in Appendix B and was updated based on all the comments from the review subcommittee.

Comments submitted by Stephanie Archer:

Questions:

- Estimated Start Date. I'm assuming no earlier than 6/1/12. Obviously, the later this is, the smaller the sample size, and the cheaper the cost. We modified the protocol accordingly.
- Consent rate. Not sure how you can say you will capture 70% of the original study population with only a 60% consent rate. I've used 70% in this estimate. We selected 70% because some centers may select centers may select a separate consent form for the secondary study while other centers may select an embedded consent.
- Sample size. This will depend on the start date, consent rate, and the rate of recruitment for the Main trial. As of November 2011, only 16 randomized (versus an original main trial estimate of 27 recruited per month). We changed the protocol accordingly.
- Respiratory therapist. This rate is too low. For IPGE, we used $100/hour, which is probably still too low. We changed the budget accordingly.
- Training costs. Assuming no need for extensive training for this secondary – with any training done at a Steering Committee meeting or via teleconference. We changed the budget accordingly.

Comments submitted during Concept Presentation (17 yes, 3 no votes):

Comments with yes votes

- This study can add critical information to the steroid tria.
- AC vs SIMV length of ventilation comparison is unlikely to yield useful results.
- Simple, inexpensive, important study.
- We'd enthusiastically test this hypothesis.

- Validation of SBT particularly among subgroups would be very valuable. Comparison of ventilator modes will b e hopelessly biased by center difference. It might be worth looking at multiple definitions of failure at 12, 24 and even 48 hours. Comparison of duration of ventilation support by ventilator modes was eliminated from the protocol. We ~~will~~ added various definitions of failure, as suggested, to secondary outcomes.
- Will PDA influence SBT? This will be one of the variables assessed in the multivariate analysis.
- Where is ref 4 cited? All references are cited.
- Good use of the HC extubation main trial to gain additional information.
- Consent should not be embedded as it may decrease consent into main trial. This was changed; each center PI will decide whether to embed the consent into that of the main trial or to use a separate consent form.
- Coordinator and RTI seemed to be an under-estimate. The budget was revised accordingly.
- SBT validation more worthwhile than trying to get at length of ventilation. Focus on SBT component. The length of ventilation was removed from the protocol.

Comments with no votes

- Not easy to predict by ~ 3 minute of CPAP. Previous studies have shown that the SBT is superior to clinical parameters to predict successful extubation in preterm infants. Issues with upper airway obstruction and apnea despite caffeine. This information is being collected in this study.
- Post extubation variation HFNC/CPAP ;this information will be collected and analyzed.

From: Laroia, Nirupama
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)
Date: Monday, January 23, 2012 4:55:10 PM

I will get it out today.
Thanks.

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, January 23, 2012 3:52 PM
To: Laroia, Nirupama; Phelps, Dale
Cc: Maddox, Yvonne (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Hirschfeld, Steven (NIH/NICHD) [E]
Subject: RE: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)

Yes – see address below -

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Laroia, Nirupama [mailto:Nirupama_Laroia@URMC.Rochester.edu]
Sent: Monday, January 23, 2012 3:49 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Phelps, Dale
Cc: Maddox, Yvonne (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Hirschfeld, Steven (NIH/NICHD) [E]
Subject: RE: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)

Hi Rosemary,
Could I mail you a copy of the last consent form we used for this study? The form is from 2007.
Thanks.

Nirupama

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, January 20, 2012 2:42 PM
To: Phelps, Dale; Laroia, Nirupama
Cc: Maddox, Yvonne (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Hirschfeld, Steven (NIH/NICHD) [E]
Subject: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)

Dale and Nirupama-

As you are aware the Neonatal Research Network (NRN) continues to support studies under common protocols, but which require individual institutional IRB review prior to the conduct of these studies at each of the NRN sites. This is to inform you that The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), which provided the Federal support to the NRN, has been requested by the Office of Human Subjects Protection, to provide to the Office the most current consent form approved by your IRB and the corresponding IRB approval for the main SUPPORT Study, including any revisions, as soon as possible. As the NICHD Program Director of the NRN, I am requesting that the most recent consent form with IRB approval for your site for SUPPORT be submitted to me as soon as possible, but no later than January 26, 2012. Thank you for your cooperation.

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Laroia, Nirupama"; "Phelps, Dale"
Cc: Maddox, Yvonne (NIH/NIMHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Hirschfeld, Steven (NIH/NICHD) [E]
Subject: RE: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)
Date: Monday, January 23, 2012 3:52:00 PM

Yes – see address below -

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Sent: Monday, January 23, 2012 3:49 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Phelps, Dale
Cc: Maddox, Yvonne (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Hirschfeld, Steven (NIH/NICHD) [E]
Subject: RE: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)

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Nirupama

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Sent: Friday, January 20, 2012 2:42 PM
To: Phelps, Dale; Laroia, Nirupama
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higginsr@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Zaterka-Baxter, Kristin"
Cc: "Das, Abhik"; "Cunningham, Meg"; "Gabrio, Jenna"
Subject: RE: Support Consents as requested at the SCM
Date: Monday, January 23, 2012 11:11:00 AM
Attachments: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT).msg

I have about 6 of them so far (with the IRB approvals). I sent out 20 individual emails on Friday and have attached one. I also sent to all of the sites that are no longer in the network and have Wake, UCSD so far and a response back from Tufts – they are getting theirs.

Bottom line – you don't need to do anything for this request.

Thanks
Rose

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From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Monday, January 23, 2012 11:07 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik; Cunningham, Meg; Gabrio, Jenna
Subject: Support Consents as requested at the SCM

Hi Rose,

We can definitely compile/track the requested most recent SUPPORT consents but I have a few questions:

- Do we also want the most recent IRB approval (we have most on them but a few are delinquent)
- Do we need the collaborating centers that enrolled in SUPPORT (Yale, UCSD, Utah, Tufts, Miami WF or Rochester; these are primarily the delinquent IRBs)

Thanks,
Kris

Kris Zaterka-Baxter, RN, BSN, CCRP
RTI International
Res Clinical Study Specialist

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Research Triangle Park, NC 27709
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Fax: 919-485-7762

From: Newman, Nancy S [mailto:Nancy.Newman2@UHhospitals.org]
Sent: Monday, January 23, 2012 10:34 AM
To: Zaterka-Baxter, Kristin
Subject:

Hey- Here is a copy of our SUPPORT consent.....good seeing you.....NN

From: Luc Brion
To: Wally Carlo, M.D.; Kennedy, Kathleen A; KWatterberg@salud.unm.edu; ambal@uab.edu; bpoindex@iupui.edu; dwallace@rti.org
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Changes to Sodium Diuretic Proposal
Date: Monday, January 23, 2012 9:53:53 AM
Attachments: jp2011144a.pdf

Kathleen:
Great job!
I agree with all the changes.
I agree with 2 mg/kg furosemide. I would be careful with higher doses of furosemide. There are some publications showing association between furosemide and hearing loss in preterm infants, with potential cumulative effect of loop diuretics and aminoglycosides (see attached).
Could you please email the powerpoint presentation.
Luc

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From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Monday, January 23, 2012 8:06 AM
To: Kennedy, Kathleen A; KWatterberg@salud.unm.edu; ambal@uab.edu; bpoindex@iupui.edu; Luc Brion; dwallace@rti.org
Cc: Higgins, Rosemary (NIH/NICHD)
Subject: RE: Changes to Sodium Diuretic Proposal

Kathleen:

Great job. I agree with the changes. I am ok with 2 mg/kg. Even higher doses have been recommended by some.

I am not sure why make such a big deal about interaction when we are not powering the study for it. I agree we should look at it.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
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From: Kennedy, Kathleen A [mailto:Kathleen.A.Kennedy@uth.tmc.edu]
Sent: Sunday, January 22, 2012 2:14 PM
To: Kristi Watterberg (KWatterberg@salud.unm.edu); Wally Carlo, M.D.; 'ambal@uab.edu'; Brenda Poindexter (bpoindex@iupui.edu); Brion, Luc; Dennis Wallace (dwallace@rti.org)
Cc: Higgins, Rosemary (NIH/NICHD)
Subject: Changes to Sodium Diuretic Proposal

Based on the discussions at the meeting, I'm proposing the following changes to the proposal before sending it out to the rest of the steering committee:

1) Change the respiratory support criterion for beginning study diuretic from 6 to 48 continuous hours.
2) Change the creatinine exclusion criterion to a creatinine of 1.5, use furosemide/diuretic instead of thiazide/diuretic for enrolled infants whose creatinine is >1.5
3) Add a suggestion for a secondary PK study
4) I also thought we need to change the GA inclusion criterion so that it's consistently < 29 wks. In some parts of the proposal it say 22 – 28 6/7 weeks but lower GA infants who survive would be eligible because they would meet the weight criterion of <1000g so mentioning a lower GA is just confusing.
5) Mention that we intend to pre-specify the criteria for reporting main effects vs subgroup findings (no plan to try to do that before sending it out)

Wally and Ambal, I looked at what DailyMed http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=1004 and http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=3940 has to say about furosemide because I was considering using 2 mg/kg/dose PO for babies who had elevated creatinine and were on feedings. That sight warns against giving more than 1 mg/kg/day IV for preterm infants. I know it's commonly done, but are you concerned about going against these recommendations in the study?

I've discussed most of these with some of you, but I wanted to give everyone a chance to weigh in before sending it out. If you have any suggestions, comments, objections, please send them to me by **Wed 1/25** so we can get the revision out by the end of the week. The newly changed parts in the attached proposal are in blue.

Thanks to everyone for your help with this.

Kathleen A. Kennedy, MD, MPH
Richard W. Mithoff Professor of Pediatrics
Director, Division of Neonatal-Perinatal Medicine
Director, MS in Clinical Research Degree Program
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From: Kennedy, Kathleen A
Sent: Monday, April 18, 2011 3:45 PM
To: Higgins, Rosemary (NIH/NICHD)
Subject: Na Supplementation Diuretic Factorial Design Proposal

I didn't want to miss the deadline so I'm attaching the latest revision of this proposal that we'd like to submit to the Protocol Review Committee. As discussed in the April Steering Committee, a copy of the previous Concept Proposal votes and comments, with responses, has also been provided.

Kathleen A. Kennedy, MD, MPH
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Journal of Perinatology (2011) 31, 633–634

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EDITORIAL

Routine use of diuretics in very-low birth-weight infants in the absence of supporting evidence

Journal of Perinatology (2011) **31**, 633–634; doi:10.1038/jp.2011.44

In this issue of Journal of Perinatology, Hagadorn *et al.*[1] confirm the known variability of therapeutic approach among neonatologists and demonstrate the willingness of some neonatologists to routinely prescribe diuretics to very-low birth-weight infants in the first 28 days of life. They also show that some neonatologists overestimate the benefits (eg, sustained improvement in pulmonary mechanics, decreased ventilator days and decreased length of stay) of diuretic administration during the first 4 weeks of life and underestimate potential risks (eg, patent ductus arteriosus, hearing loss or renal failure) of diuretic administration. This study adds to the growing body of literature suggesting that diuretics may be one of the most commonly abused drugs in the neonatal intensive care unit.[2–4]

The 39% response rate in this survey is within the range (23–85%; 52 ± 18% (mean ± s.d.)) observed in 13 surveys involving US neonatologists and preterm infants published in 2005 to 2010 (unpublished data, Stewart and Brion), and similar to that of academic studies in behavioral sciences (56 ± 20%).[5] However, a limitation of this study is lack of assessment for possible non-response bias and lack of any procedures to minimize such bias.

Lung edema occurs in respiratory distress syndrome as a result of delayed sodium channel (ENaC) expression and may occur in chronic lung disease because of increased capillary permeability resulting from lung injury and inflammation, congestive heart failure due to patent ductus arteriosus, and fluid overload.[6–10] Diuretics might improve lung function by improving fluid absorption, by reducing lung congestion and by reducing lung fibrosis.[6–12] However, diuretics have many potential complications: (A) electrolyte imbalance such as hyponatremia, hypomagnesemia, hyperuricemia and either hypokalemic alkalosis (thiazides, loop diuretics) or hyperkalemia and acidosis (potassium-sparing diuretics); (B) reduction in extracellular volume, dehydration, hypovolemia, hypotension and pre-renal failure; (C) intrinsic renal failure potentially increasing toxicity of other medications; (D) mineral changes including either (most diuretics) osteopenia, phosphaturia, hypercalciuria, nephrocalcinosis and nephrolithiasis (associated with reduced glomerular and tubular function in childhood); or (thiazides, metolazone and potassium-sparing diuretics other than spironolactone) hypocalciuria and hypercalcemia; (E) persistent patent ductus arteriosus due to increased formation of prostaglandin E (furosemide); (F) metabolic: cholelithiasis (loop diuretics) and glucose intolerance (thiazides); (G) reduction of alveolar fluid absorption (amiloride and spironolactone);[13] (H) binding to androgen receptors with anti-androgen effects, disturbed gonadal and adrenal steroidogenesis, estrogen-like side effects, elevated gonadotrophin levels, interference with newborn screening for congenital adrenal hyperplasia (spironolactone);[14,15] (I) hearing loss, associated with a potential synergism of loop diuretics and aminoglycosides;[16,17] (J) worse neurodevelopmental outcome (acetazolamide and furosemide for treating post hemorrhagic ventricular dilatation).[18]

There is very little evidence to support routine use of diuretics in very-low birth-weight infants with respiratory distress syndrome or developing or established chronic lung disease.[6–10] The three trials that addressed mostly infants with postnatal ages of 7 to 28 days[19–21] looked at short-term renal and/or pulmonary outcomes varying from 24 to 96 h post treatment and not at long-term outcomes. Most trials of diuretics in preterm infants have only shown short-term effects on lung mechanics or oxygen requirement; these effects disappear as soon as the diuretics are stopped and do not shorten the duration of oxygen administration, long-term lung function or length of stay. Only one trial showed that chronic diuretic administration improved important outcomes.[22] This trial showed that an 8-week administration of thiazide and spironolactone in intubated very-low birth-weight infants who were at least 1 month of age and requiring a minimum of 30% O_2 improved survival at discharge, but did not affect the duration of ventilator support and length of stay. The patients did not receive prenatal steroids or surfactant. In addition, aminophylline, corticosteroids and bronchodilators were not allowed.[18] Another trial showed that chronic addition of spironolactone to thiazide for 8 weeks did not affect lung mechanics, serum sodium and potassium nor FiO_2.[23]

It is surprising that neonatologists are willing to routinely prescribe diuretics during the first 4 weeks of life[1] or for a long duration after extubation,[4] despite lack evidence for benefit from randomized controlled trials and for lack of information about long-term complications. A large randomized trial is needed to assess important and long-term outcomes including risks and benefits of diuretic administration to very-low birth-weight infants using current standard of care including prenatal steroids, caffeine and vitamin A.[24]

Conflict of interest

The authors declare no conflict of interest.

AL Stewart and LP Brion

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E-mail: luc.brion@utsouthwestern.edu

References

1 Hagadorn JI, Sanders MR, Staves C, Herson VC, Daigle K. Diuretics for very low birth weight infants in the first 28 days: a Survey of US Neonatologists. *J Perinatol* 2011; **31**: 677–681.

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From: McGowan, Elisabeth C
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Testa, Veronika
Subject: RE: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)
Date: Monday, January 23, 2012 9:37:49 AM

Hi Rose,

My administrative assistant will be in mid-week, and we will send the SUPPORT documentation as well as all other renewals. Everything has been completed.

Who should I send to ?

Liz

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, January 20, 2012 3:28 PM
To: McGowan, Elisabeth C
Subject: Fw: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)

Liz
Can you send?
Thanks
Rose

From: Frantz, Ivan [mailto:Ivan.Frantz@childrens.harvard.edu]
Sent: Friday, January 20, 2012 03:24 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: McGowan, Elisabeth C <emcgowan@tuftsmedicalcenter.org>
Subject: RE: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)

Rose: I no longer have access, but Liz should be able to get the items to you.

Ivan

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, January 20, 2012 2:43 PM
To: Frantz, Ivan
Cc: Maddox, Yvonne (NIH/NICHD) [E]; Hirschfeld, Steven (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]
Subject: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)

Ivan
As you are aware the Neonatal Research Network (NRN) continues to support studies under common protocols, but which require individual institutional IRB review prior to the conduct of these studies at each of the NRN sites. This is to inform you that The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), which provided the Federal support to the NRN, has been requested by the Office of Human Subjects Protection, to provide to the Office the most current consent form approved by your IRB and the corresponding IRB

approval for the main SUPPORT Study, including any revisions, as soon as possible. As the NICHD Program Director of the NRN, I am requesting that the most recent consent form with IRB approval for your site for SUPPORT be submitted to me as soon as possible, but no later than January 26, 2012. Thank you for your cooperation.

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From: Luc Brion
To: D"Angio, Carl; Keszler, Martin; Kristi Watterberg; Wallace, Dennis; Higgins, Rosemary (NIH/NICHD) [E]
Subject: revised protocol
Date: Saturday, January 21, 2012 7:00:04 PM
Attachments: Secondary - predicting ext success - Protocol 01212012 rev.docx
SBT response 20Jan12.doc

Martin, Carl, Kristi, Dennis, Rose:

Thanks a lot for all the feedback at the meeting.

Here is the updated protocol, taking into account all the suggestions from the protocol review committee and a first draft of the revised sample size analysis (not seen by Dennis yet).

Please let me know your suggestions (if possible by January 27th) so I can I send the protocol to the review committee at least one week before the next protocol review standing committee call (February 7th).

Thanks and best regards,

Luc

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PREDICTING SUCCESS OF EXTUBATION DURING HYDROCORTISONE THERAPY IN PRETERM INFANTS < 30 WEEKS OF GESTATIONAL AGE~~AND THE EFFECT OF DIFFERENT MODES OF SYNCHRONIZED VENTILATION~~

Luc P Brion, UT Southwestern at Dallas

Martin Keszler, Brown University

Kristi Watterberg, University of New Mexico

Dennis Wallace, RTI

Carl d'Angio, University of Rochester

Rose Higgins, RTI

Protocol

Rev 01~~11~~/21~~15~~/12~~1~~

Proposed secondary study to

"A RANDOMIZED CONTROLLED TRIAL OF THE EFFECT OF HYDROCORTISONE ON SURVIVAL WITHOUT BRONCHOPULMONARY DYSPLASIA AND ON NEURODEVELOPMENTAL OUTCOMES AT 18 - 22 MONTHS OF AGE IN INTUBATED INFANTS <30 WEEKS GESTATIONAL AGE",

Referred to as "Main Hydrocortisone Study" in this protocol

Kristi Watterberg, PI

Thanks to: Diana Vasil, RN, Coordinator at UT Southwestern at Dallas, and Glenn Metoyer, RT, Parkland Memorial Hospital

1. ABSTRACT (SYNOPSIS)

This observational study is primarily designed to evaluate whether a short endotracheal continuous positive airway pressure (ET CPAP) test (also called spontaneous breathing test (SBT) may help predict the success of extubation of ~~very~~ premature infants <30 weeks estimated gestational age at birth who remain intubated at 14 - 28 days postnatal age. ~~-~~For this purpose, we will use the 3-minute ET CPAP test ("spontaneous breathing test" or SBT) described by Kamlin in a single center.[1] The primary aim of this study is evaluate the point estimates and confidence intervals of sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio of a positive test, and likelihood ratio of a negative test for the SBT. The large number of patients we plan to recruit will allow us to test the external validity of the SBT in different centers using different types of ventilators and different modes of ventilation.

~~We will also assess if ventilation modes that support every breath, i.e., assist control (AC), pressure regulated volume control (PRVC), pressure support ventilation (PSV) or synchronized intermittent mandatory ventilation (SIMV) with PSV, are associated with shorter duration of mechanical ventilation than SIMV. Since there are many center and individual differences in approach to therapy we will use multivariate analysis ventilation to attempt to account for possible confounder. Shorter intubation will in part depend on approaches to fluids, volumes, sodium administration and nutritional management, caffeine, etc.~~

2. STATEMENT OF PROBLEM

Prediction of successful extubation in preterm infants remains a challenge. This question has not been addressed by the NRN, and specific data were not collected during the SUPPORT trial. Previous single-site studies suggested that successful extubation can be predicted by the SBT in preterm infants during the first days of life. However, validity of this test has not been established in a multicenter study, using different types of ventilators and different modes of ventilation, in a population of infants of greater post-natal age than in the original study by Kamlin et al.[1].

~~There is limited information about the relative merits of SIMV vs. ventilation modes that support every breath as weaning modes of mechanical ventilation. There are important physiological considerations suggesting that SIMV, although widely used, may not provide optimal support in very premature infants during weaning.~~

3. HYPOTHESIS

~~Since this is an observational study there is no primary hypothesis.~~

~~The study is primarily designed to test the external validity of the SBT in a multicenter study, with multiple institutions, using different types of ventilators and different modes of ventilation, in a population of infants of greater post-natal age than in the original study by Kamlin et al.[1]~~ Previous studies suggest that the success of extubation may be higher in patients with a positive SBT.1 Therefore we hypothesize that the percentage of successful extubation among patients with positive SBT is greater than that in those extubated based on criteria established for extubation in the main hydrocortisone study.

The null hypothesis is that the percentage of successful extubation among patients with positive SBT is not different from that in those extubated based on criteria established for extubation in the main hydrocortisone study.

Secondary n~~Secondary n~~ull -hypotheses include :

1. The predictive value of the SBT is not affected by whether the baby is supported by a ventilator using a mode supporting all breaths or by SIMV
2. The predictive value of the SBT is not affected by whether the baby is randomized to hydrocortisone or placebo. Hydrocortisone may affect lung compliance and laryngeal edema and thus improve success rate of extubation compared with placebo.

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3. The predictive value of the SBT is not affected by the resistance of the endotracheal tube (ETT). While on CPAP small diameter and long length of the ETT may increase work of breathing and contribute to failing of the SBT while not affecting success of extubation.

4. The predictive value of the SBT is not affected by postnatal age (within the ranges expected in the hydrocortisone trial)

4.5. The predictive value of the SBT is not affected by the mode of respiratory support after extubation. We would expect that success of extubation will be greater on patients extubated to NIPPV than on CPAP or high-flow nasal cannula, and lowest on those extubated to low flow nasal cannula or room air.

~~5. Modes of ventilation supporting all breaths and SIMV are associated with a similar duration of mechanical ventilation.~~

4. SPECIFIC AIMS

Primary aim:

To compare the percentage of successful extubation among patients with positive SBT with that in those extubated based on criteria established for extubation in the main hydrocortisone study.

~~To evaluate the point estimates and confidence intervals of sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio of a positive test, and likelihood ratio of a negative test for the SBT.~~

~~1.~~ *Secondary aims:*

1. To evaluate the point estimates and confidence intervals of sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio of a positive test, and likelihood ratio of a negative test for the SBT.

2. To evaluate point estimates and confidence intervals of sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio of a positive test, and likelihood ratio of a negative test for the SBT in various ~~two~~ subgroups: ~~infants ventilated with SIMV and infants ventilated using modes supporting all breaths.~~

~~3. To determine if ventilation modes that support every breath are associated with shorter duration of mechanical ventilation than SIMV.~~

5. RATIONALE/JUSTIFICATION

Success of elective extubation is one of the quality measures in neonatal intensive care. This study is designed

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1. ~~t~~To assess the external validity of the SBT to predict successful extubation in very premature infants. This proposal is the first multicenter study that will assess whether the predictive value of the SBT is better (or not) than other information available to the clinician (Fi02, PIP, PEEP, rate, presence of atelectasis, physiologic stability) to predict successful extubation. ~~and~~

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2. ~~To add to the limited body of knowledge regarding relative merits of various forms of synchronized ventilation during weaning.~~ Very little additional coordinator time will be needed to collect information that will be used in multivariate analysis that could build the basis for a future randomized trial.

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6. BACKGROUND AND SIGNIFICANCE

Success of extubation is around 60-73% in extremely low birth weight infants.[2,3]. Higher success rates (80-86%) have been reported in series including all preterm infants[4,5]. Infants who require re-intubation, with its attendant risks, may experience deterioration of their respiratory status due to atelectasis. Intermittent hypoxemia and/or hypercapnia prior to re-intubation may expose them to additional risks. On the other hand, a relatively large number of infants who self-extubate and remain extubated subsequently.[6,5] Those infants may be exposed to mechanical ventilation and potential ventilator-induced lung injury for longer than necessary or for elective reasons such as to facilitate growth or to prepare for surgery.

Thus, a test that improves the clinician's ability to predict readiness for extubation is highly desirable. Kamlin et al[1] compared three tests to predict success of extubation (no reintubation within 72 hours) in 50 infants with birth weight < 1250 grams using a 3-minute ET CPAP trial: (a) expired minute ventilation (VE) during ET CPAP; (b) ratio of minute ventilation during ET CPAP to minute ventilation during mechanical ventilation (VE ratio); (c) the spontaneous breathing test (SBT). The infant passed the SBT if there was no hypoxia or bradycardia during ET CPAP. The median age at the time of the study was 4 and 5 days, , respectively, for successful extubations and for extubations followed by reintubation within 72 hours,.. Kamlin concluded that the SBT had the highest sensitivity (97%), specificity (73%), positive predictive value (93%), negative predictive value (89%), likelihood ratio of a positive test (3.6) and the smallest likelihood ratio of a negative test (0.04) among the three tests.[1] Success rate of extubation predicted by a positive SBT was 3/43 (93%), compared with a success rate of 39/50 (78%) in the total cohort. Limitations of this study included small sample size (n=50) and failure to separate infants ventilated by different synchronized modes. In that study infants were weaned by reducing the tidal volume to 3.5 ml/kg using AC or by reducing ventilator rates to 20–30 breaths/minute on SIMV.

A subsequent study (n=180) provided a degree of validation of the SBT, but compared this test to a historical cohort, which differed substantially from the practice at the time of the validation study. Once more, various modes of ventilation were used, and there was no subanalysis by mode.[7,6] Most babies in the validation cohort were on volume guarantee ventilation (94% vs 26% in the controls), and most of them were ventilated using AC at the time of extubation (81%, compared with 93% using SIMV in controls). The median age at extubation was 0 days (range 0-27) for babies undergoing the SBT and 0 days (range 0-11 days for controls. Compared with historical controls, infants were extubated at significantly higher ventilator rates and airway pressures using the SBT, but the success rate of extubation was not significant (78% with SBT versus 72% in historical controls). The sensitivity of the SBT was 83% (compared with 97% in the first study).

It is not known if the SBT is equally predictive in infants with evolving chronic lung disease and prolonged ventilator dependence. It is also not known if the SBT is equally predictive in infants on different modes of synchronized ventilation. It is possible that modes in which every breath is supported mask significant respiratory control center immaturity or afford less respiratory muscle training compared to SIMV. SIMV remains the most widely used mode of assisted ventilation in newborn infants,[7] despite its potential disadvantages related to high work

of breathing resulting from the high resistance of small endotracheal tubes (ETT) in extremely low birth weight (ELBW) infants.[8-10] This is especially true as the SIMV rate is decreased during the weaning process. In contrast, AC and PSV (when used as a sole mode of ventilation) support each patient breath, thereby resulting in more even tidal volume, less tachypnea, lower work of breathing and lower tidal volume compared to SIMV.[11-13]

There is no information in the literature describing the success of extubation from various modes of ventilation. A practice survey of NRN investigators conducted in July 2011 yielded data from 10 centers. Ventilators include Draeger 8000 (n=6), Maquet Servo I (n=5), Draeger Evita XL (n=2), Draeger VN500 (n=2), Avea (n=2), and Bird VIP (n=1). Pressure-controlled ventilation is predominantly used in 6 NRN centers, and volume-targeted ventilation in 3 centers, while both are used equally in 2 centers. Volume-targeted ventilation is used either often or most of the time in 7 centers, and is used both during the acute phase and during weaning; it is used during weaning by 5 of 10 centers. During weaning and for extubation SIMV is used predominantly by 5 centers and modes supporting all breaths are used predominantly by 5 centers. Extubation from high-frequency ventilation is either rarely or never used. Eight of 10 centers would be ready to perform a 3-min SBT in patients on high-frequency ventilation. In summary the survey showed substantial heterogeneity across centers, with approximate equal distribution of SIMV and modes supporting all breaths.

There are limited data regarding the relative efficacy of ventilation modes that support every breath vs. SIMV in weaning from mechanical ventilation and no large clinical trials to evaluate their effect on survival or the risk of bronchopulmonary dysplasia. Three small studies compared SIMV and AC during weaning. In two of these studies SIMV rate was reduced to10 breaths/min; these studies showed shorter duration of ventilation when using AC. In the third trial, SIMV rate was not reduced below 20 breaths/minute, and the authors showed no difference in duration of ventilation between the two modes.[14,15] These findings support the physiologic explanation that the narrow ETT of ELBW infants increases work of breathing and impairs weaning from mechanical ventilation. Reyes et al showed faster weaning from mechanical ventilation in ELBW infants using SIMV+ PSV, compared to SIMV alone, suggesting that PSV may obviate this problem to some extent.[16] However, this option is not available on all ventilators and may not be widely used. One larger randomized trial enrolled 212 VLBW infants (birth weight 500-1249 g) from initiation of mechanical ventilation through extubation on AC or SIMV.[17] The study showed no differences between the groups in survival, BPD, age at extubation, or length of ventilation in survivors. This study used pressure regulated volume control using the Siemens Servo 300 ventilator, in which the volume targeted mode uses tidal volume measurement at the ventilator end of the circuit, in contrast with ventilator adjusting volume closer to the endotracheal tube. Cross-over for failure occurred in 33% of the infants receiving SIMV and 20% of those who received PRVC.

~~A practice survey of NRN investigators conducted in July 2011 yielded data from 10 centers. Ventilators include Draeger 8000 (n=6), Maquet Servo I (n=5), Draeger Evita XL (n=2), Draeger VN500 (n=2), Avea (n=2), and Bird VIP (n=1). Pressure-controlled ventilation is predominantly used in 6 NRN centers, and volume-targeted ventilation in 3 centers, while both are used equally in 2 centers. Volume-targeted ventilation is used either often or most of the time in 7 centers, and is used both during the acute phase and during weaning; it is used during weaning by 5 of 10 centers. During weaning and for extubation SIMV is used predominantly by 5 centers and modes supporting all breaths are used predominantly by 5 centers. Extubation from high-frequency ventilation is either rarely or never used. Eight of 10 centers would be ready to perform a 3-min SBT in patients on high-frequency ventilation. In summary the survey showed substantial heterogeneity across centers, with approximate equal distribution of SIMV and modes supporting all breaths.~~

7. METHODS AND PROCEDURES

a) Study design

This is an observational study (prospective cohort) ~~with prospective data collection~~in a selected group of patients enrolled in a randomized trial (the main hydrocortisone study).
The study will involve analysis of the operational characteristics of a diagnostic test (SBT) ~~and retrospective analysis of a cohort study (using two cohorts: babies ventilated using SIMV and babies ventilated using modes supporting all breaths)~~.
The spontaneous breathing test (SBT) will be performed by the study team just before elective extubation decided by the clinicians according to the protocol of the main hydrocortisone trial. Clinicians will remain blinded to the results.

b) Study population

We will use the same population as that for the ~~main study~~main hydrocortisone study. All patients enrolled in the ~~main study~~main hydrocortisone study will be approached for informed consent. It is up to each center to decide whether to use a separate consent for the substudy, or ~~an optional consent, indicated by~~ a check on the consent to the ~~main study~~main hydrocortisone study

c) Inclusion and exclusion criteria

Inclusion criteria:

These will be the same as for the ~~main study~~main hydrocortisone study, i.e:
Patients eligible for this study will be infants between 14 – 28 postnatal days who:
(a) are <30 weeks estimated gestational age, to be randomized in two strata: $\leq 26^{6/7}$ and $27^{0/7} - 29^{6/7}$ weeks);
(b) were inborn at an NRN site or were admitted to an NRN site before 72 hours postnatal age;
(c) have received ≥ 7days of mechanical ventilation;
(d) are receiving mechanical ventilation through an endotracheal tube .

We anticipate a starting time at the earliest 6/1/2012.

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Exclusion criteria:

Same as for the ~~main study~~main hydrocortisone study, i.e.:

(a) Major congenital anomalies
(b) Decision to limit support
(c) Indomethacin or ibuprofen treatment within 48 hours of study drug
(d) Previous corticosteroid treatment for BPD
(e) Hydrocortisone treatment for hypotension in the first week of life is common (35) and will not be an exclusion; however, infants will be excluded if they have received hydrocortisone:
    (i) for ≥ 14 cumulative days OR
    (ii) within 7 days of study entry.

In addition, we will exclude for this secondary study patients who have at the time of extubation an ETT size <2.5.

d) Enrollment centers and PIs

Case Western	Michele Walsh
Dallas	Luc P Brion
Wayne State	Seetha Shankaran
Emory	Barbara Stoll
Cincinnati	Kurt Schibler

Indiana	Brenda Poindexter
Brown	Martin Keszler
Stanford	Krisa Van Meurs
Alabama	Waldemar Carlo
Houston	Kathleen Kennedy
Duke	Ronald Goldberg
Iowa	Edward Bell
New Mexico	Kristi Watterberg
Pennsylvania	Barbara Schmidt
Rochester	Carl D'Angio
UCLA	Uday Devaskar
Ohio State	Leif Nelin
Missouri	William Truog

e) Study intervention and procedures

We will perform a maximum of 2 SBTs per patient: one at the time of the first elective extubation and one at the time of the second elective extubation, if any. Spontaneous unplanned extubations will not be analyzed since SBT will not be performed.

Extubation criteria in the main hydrocortisone study are as follows: "Extubation must be attempted within 72 hours of starting study drug and within 24 hours after meeting the following criteria: the FiO2 is <0.40 to maintain a saturation of 88%, the mean airway pressure is < 8, and the infant is hemodynamically stable (as defined for the SUPPORT trial: "clinically acceptable blood pressure and perfusion in the opinion of the clinical team")."

We will request that the clinical team inform the coordinator of a pending extubation after the baby has been enrolled to this study.

The intervention (SBT) will be similar to that described by Kamlin et al.[1] Specifically, when the clinicians decide a baby is ready to be extubated, the investigator will perform the SBT within 4 hours of the planned extubation. This intervention will be masked in order to prevent bias that would occur if the clinical provider knew the result of the SBT. We propose that the SBT be conducted after rounds in centers that review the monitoring tracing during rounds.

The infant's ETT will be suctioned prior to the SBT if suctioning is clinically indicated. The SBT will be done no less than 10 minutes after suctioning.

The researcher will silence any alarms and will place screens around the bedside before initiating the test to minimize the chance of unblinding. After ensuring that the clinical care team, including the patient's nurse, is away from be bedside (to maintain blinding) the investigator (respiratory therapist, fellow, nurse practitioner or attending), who must not be involved with the patient's clinical care, will switch the ventilator to CPAP for 3 minutes at the same pressure as the positive end-expiratory pressure setting. ~~The infant's ETT will be suctioned prior to the SBT if clinically indicated.~~ T~~and~~ the intervention will be done when the infant is in a quiet state, taking care to minimize stimulation and disturbance during the study.

The baby succeeds the SBT if he or she requires no more than a 15% increase in FiO2 for isolated hypoxemia. After 3 minutes on CPAP the study will be stopped, and ventilation will be restarted.

The baby fails the SBT if he or she develops a bradycardia (HR <100) for more than 15 seconds and/or a fall in SpO2 below 85% despite a 15% increase in FIO2. If isolated hypoxemia develops, FiO2 will be increased according to unit protocol. If hypoxemia does not respond to a 15% increase in FiO2, or if bradycardia develops, manual breaths are given through the ventilator and mechanical ventilation is restarted at the previous settings.

~~because of bradycardia or desaturation, this will be considered a failed test. At this point the study will be stopped, and ventilation will be restarted. If manual breaths are given through the ventilator because of bradycardia or desaturation, this will be considered a failed test. Data on the mode of ventilation, success and time of extubation will be collected for subsequent analysis.~~

The baby will be placed back on previous ventilatory settings forto 30 minutes, to limit the risk of derecruitment that could have resulted from performing the SBT. The investigator will document in the chart and communicate to the clinical team that the SBT was performed, the exact time of the procedure and the earliest time of extubation (30 min after the SBT). The results of the SBT will not be disclosed to the clinician or documented into the chart unless additional therapy is required as indicated below.

In rare circumstances, the baby may not respond well to the intervention described above. In that case, manual bagging is initiated for 30 seconds, and the clinical team is informed. If the baby responds well, mechanical ventilation is restarted; otherwise appropriate treatment is initiated.

f) Required follow-up

None beyond 72 hours after the second extubation

g) Primary and secondary outcomes

Primary outcomes:

Comparison of the ~~Point estimates and confidence intervals of sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio of a positive test, and likelihood ratio of a negative test to predict successful (defined as no reintubation within 72 hours) extubation using SBT~~ percentage of successful extubation among patients with positive SBT with that in those extubated based on criteria established for extubation in the main hydrocortisone study

Secondary outcomes:

1. Point estimates and confidence intervals of sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio of a positive test, and likelihood ratio of a negative test to predict successful (defined as no reintubation within 72 hours) extubation using SBT

1.2. Point estimates and confidence intervals of sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio of a positive test, and likelihood ratio of a negative test to predict successful extubation using SBT in two subgroups: infants ventilated with SIMV and infants ventilated using modes supporting all breaths at the time of the SBT

~~2.~~3. Point estimates and confidence intervals of sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio of a positive test, and likelihood ratio of a negative test to predict successful extubation using SBT by primary study group.

~~3.~~4. Point estimates and confidence intervals of sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio of a positive test, and likelihood ratio of a negative test to predict successful extubation using SBT according to ETT resistance calculated according to the formula:

$$R \propto L / r^4,$$

where L is the length of the tube and r is its radius

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5. Point estimates and confidence intervals of sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio of a positive test, and likelihood ratio of a negative test to predict successful extubation using SBT according to postnatal age

6. Point estimates and confidence intervals of sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio of a positive test, and likelihood ratio of a negative test to predict successful extubation using SBT according to the mode of respiratory support used after extubation: NIPPV, CPAP, high-flow nasal cannula, low flow nasal cannula or room air.

7. Point estimates and confidence intervals of sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio of a positive test, and likelihood ratio of a negative test to predict successful extubation using SBT using different definitions of failed extubation (at 12, 24 and 48 hours instead of 72 hours after extubation)

~~4.~~8. Odds ratio of successful extubation taking into account the SBT and multiple possible confounders

~~5. Duration of mechanical ventilation in two subgroups: infants ventilated with SIMV and infants ventilated using modes supporting all breaths for the majority of the time on the ventilator starting at the time of randomization~~

~~1.~~ Data to collect for this study beyond those in the main trial (see Appendix B):

~~2.~~ Information about the situation before the SBT: ~~At the time of randomization we will obtain the respiratory severity score, which will be calculated as mean airway pressure X FiO2.[18]~~

~~3.~~ Mode of ventilation, ventilatory settings, vital signs, m~~between the time of randomization and the SBT~~,

1. Most recent blood gas, ~~ventilatory settings and~~ ETT size
2. Response to SBT
3. Repiratory support after the second extubation

~~4. just before SBT~~

h) Sample size estimate

~~h)~~

Criteria used for elective extubation in the main hydrocortisone trial were targeted toward the lower end of the criteria in the SUPPORT trial. The percentage of successful elective extubation in the main hydrocortisone trial was estimated from data in the surfactant arm of the SUPPORT trial. In Kamlin's original study,[1] 86% of the infants had a positive SBT, and the success rate of extubation predicted by a positive SBT was 93%, compared with a success rate of 78% in the total cohort. Therefore sample size was determined assuming 65% success rate using extubation criteria used for the main hydrocortisone trial and 75% for patients with a positive SBT. Using two-sided chi-square analysis, a p value of 0.05, and a power of 80% we would need 320 patients in each group; using a power of 90% we would need 430 patients in each group. Since not all patients will have a positive SBT, the denominator will not be identical in the 2 groups.

Power was calculated using two-tailed chi-square analysis and an alpha error of 0.05. The following grid shows the estimated power using the estimated number of patients we will have available for the analysis (see next section). The table assume that 420 patients will undergo elective extubation, that 70-80% will have a positive SBT, that the success of extubation will be 60-75% in the whole group, and 10-15% higher among those with a positive SBT. We will have at least 79% power to detect a 10% difference success rate of extubation using clinical criteria and patients with a positive SBT.

% successful extubation if SBT is positive	Sample size with positive SBT (%)	% successful extubation using criteria using in the	Sample size undergoing elective extubation	Power

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		main hydrocortisone study		
70%	336 (80%)	60%	420	82%
75%	336 (80%)	60%	420	99%
70%	294 (70%)	60%	420	79%
75%	294 (70%)	60%	420	99%
75%	336 (80%)	65%	420	85%
80%	336 (80%)	65%	420	100%
75%	294 (70%)	65%	420	82%
80%	294 (70%)	65%	420	99%
80%	336 (80%)	70%	420	89%
85%	336 (80%)	70%	420	100%
80%	294 (70%)	70%	420	86%
85%	294 (70%)	70%	420	100%
85%	336 (80%)	75%	420	93%
90%	336 (80%)	75%	420	100%
85%	294 (70%)	75%	420	91%
90%	294 (70%)	75%	420	100%

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The Kamlin study,[1] which compared three tests, had a sample size of 50. This study was powered to detect a difference of one standard deviation in mean VE in the group failing extubation but not to detect differences in dichotomous outcomes between the three tests. This was a single-center study with a relatively uniform approach to ventilation. The high degree of variability of clinical practice within the NRN will impact the outcome measures in this proposed multicenter trial, thus clearly requiring a much larger sample size to detect a comparable effect size.

~~The Reyes study,[36] which was also a single center study, focused on a similar population demonstrated no significant difference in duration of mechanical ventilation (median [interquartile range] 22 [10-52] vs 34 d [19-59]). This study was powered to detect a 30% difference in the duration of oxygen dependency between groups at an alpha of 0.05 with a power of 90%; it did not reach statistical significance with n=107.~~

To the extent possible, we will use all available subjects from the total sample size of 800 available in the main trial. At the current date of this proposal, 40 of 800 patients have been enrolled into the main trial. Patients who self extubate before the SBT and remain off mechanical ventilation will not be available for this analysis. Those who are reintubated will have another SBT performed before attempting elective extubation. We estimate that about 670% of the total sample size available in the main trial will be available for the analysis of this secondary study; thus sample size is estimated at 373~~550~~.

The primary aim ~~goal~~ of this study is to generate estimates of the operating characteristics (sensitivity [Se], specificity [Sp], positive predictive value [PPV] and negative predictive value [NPV]) of the 3-minute ET CPAP test ("spontaneous breathing test" or SBT) for predicting successful extubation in this population of infants. Each of the operating characteristics of interest is a conditional probability (where the calculation is conditioned on a either success or failure of the extubation or the positive or negative value for the SBT), and the primary sample size consideration for the study is the precision with which these probabilities can be estimated with the available sample sizes. Based on information provided earlier that suggests that 60% to 80% of the extubations are likely to be successful, we assume that between 20% and 80% of the 550 subjects will be used in the denominator of each of the calculations. Furthermore, operating characteristics in the range of 0.7 to 1 are of greatest interest. Given those assumptions the available sample sizes are sufficient to provide confidence intervals with half widths, where a 95% confidence interval is typically computed as the estimate of the sensitivity ± the half width, shown in the table below.

Estimates of Confidence Interval Half Width for Different Levels of True Measure Prevalence and Conditional Denominator							
Se, Sp, PPV, NPV Value	Half Interval Width for Available Denominator						
	110	165	220	275	330	385	440
0.70	0.084	0.069	0.059	0.053	0.048	0.045	0.042
0.72	0.082	0.067	0.058	0.052	0.047	0.044	0.041
0.74	0.082	0.067	0.058	0.052	0.047	0.044	0.041
0.76	0.080	0.065	0.056	0.050	0.046	0.043	0.040
0.78	0.077	0.063	0.055	0.049	0.045	0.041	0.039
0.80	0.075	0.061	0.053	0.047	0.043	0.040	0.037
0.82	0.072	0.059	0.051	0.045	0.041	0.038	0.036
0.84	0.069	0.056	0.048	0.043	0.040	0.037	0.034
0.86	0.065	0.053	0.046	0.041	0.037	0.035	0.032
0.88	0.061	0.050	0.043	0.038	0.035	0.032	0.030
0.90	0.056	0.046	0.040	0.035	0.032	0.030	0.028
0.92	0.051	0.041	0.036	0.032	0.029	0.027	0.025
0.94	0.044	0.036	0.031	0.028	0.026	0.024	0.022
0.96	0.037	0.030	0.026	0.023	0.021	0.020	0.018
0.98	0.026	0.021	0.019	0.017	0.015	0.014	0.013

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i) Available population/compatibility with other ongoing protocols

Same as for the ~~main study~~main hydrocortisone study: Based on GDB data 06-07, and assuming 60% consent rate, 800 infants could be recruited to the ~~main study~~main hydrocortisone study over 3 years. Since the secondary study will start at the earliest 6/1/2012 we estimate 100 infants will have been recruited already in the main hydrocortisone study. Since some centers may use a separate consent form for the current study while other centers may use an embedded consent w~~W~~e estimate that about 70% of the total sample size available in the main trial will be available for the analysis of this secondary study; thus sample size is estimated at 420~~550~~.

~~Since the secondary study will start after the beginning of the main study, the total number of patients in this secondary study will be probably 10% smaller, i.e. 500 patients.~~

j) Projected recruitment time

The projected recruitment time for the ~~main study~~main hydrocortisone study was~~is~~ 30 months. However, as of November 2011, only 16 had been randomized per month (versus an original main trial estimate of 27 recruited per month). Initiation of the secondary study could be expected within 6 months (i.e., by 6/1/2012). ~~Therefore, projected recruitment time for the main study is estimated to be 24 months.~~Since recruitment into the main hydrocortisone study is slower than expected, recruitment may last longer than initially expected.

k) Data Analysis Plan

We will use chi-square analysis to compare the success of extubation in patients who will successively pass the SBT with that among all patients who are electively extubated and undergoing the SBT.

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~~1. We will determine the point estimates and 95% confidence intervals for the operating characteristics (sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio of a positive test, and likelihood ratio of a negative test) of successful extubation using the SBT.~~

We will ~~We will~~ determine the point estimates and 95% confidence intervals for the operating characteristics (sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio of a positive test, and likelihood ratio of a negative test) of successful extubation using the SBT in all patients undergoing SBT.

We

~~use the same~~ determine the same point estimates and 95% confidence intervals for the operating characteristics tests in the following subgroups:

1,

~~2, infants ventilated with SIMV versus infants ventilated using modes supporting all breaths at the time of the SBT.~~

infants with gestational age $\leq 26^{6/7}$ versus those with gestational age $27^{0/7}$ – $29^{6/7}$ weeks

2, primary study group

3, infants ventilated with SIMV and infants ventilated using modes supporting all breaths at the time of the SBT

4, according to the mode of respiratory support used after extubation: NIPPV, CPAP, high-flow nasal cannula, low flow nasal cannula or room air

~~3.~~ 5, using different definitions of failed extubation (at 12, 24 and 48 hours instead of 72 hours after extubation)

We will use Receiving operator characteristic curve (ROC) to analyze whether the operating characteristics of the SBT vary according to ETT resistance and to postnatal age.

~~Duration of mechanical ventilation will be compared in the two subgroups using non-parametric tests (two-sided Mann-Whitney test, alpha < 0.05) because this variable has a non-normal distribution. We will use multiple regression analysis of the duration of ventilation using as factors the gestational age, the center, the respiratory severity score at the time of randomization, the randomization arm (hydrocortisone versus control), and the mode of ventilation. Additional factors that differ by p < 0.10 on univariate analysis will be tested for significance in the multiple regression analysis.~~

The likelihood of success of extubation may depend on multiple factors other than SBT, including patient characteristics, mode of ventilation, individual clinician and center. For this purpose we will use multivariate logistic analysis using as predictors:[1] gestational age, weight for age at birth, postnatal age, PEEP, mode of ventilation and ventilation settings at the time of SBT (SIMV vs. ventilation supporting every breath), SBT, hydrocortisone (vs placebo), caffeine, symptomatic patent ductus arteriosus, center, and mode of respiratory support after extubation (NIPPV, CPAP, high flow nasal cannula, low flow nasal cannula, room air) .Additional factors that differ by $p \leq 0.10$ on univariate analysis will be tested for significance in the multiple regression analysis.

l) Data safety monitoring plan:

Eight interim blocks are planned in the ~~main study~~main hydrocortisone study. The DSMC will review data from the main trial and from this secondary study at the same time. For this secondary study, the DSMC will review the

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frequency of required treatment (bagging, resuscitation) related to the SBT. Serious adverse events to be reported to NICHD within 24 hours include death that would occur after a code related to the SBT.

m) Stopping limits for protocol termination:

The DSMC may decide to stop the main trial or this secondary study.

8. RISK, BENEFITS, LIMITATIONS

Ethical issues

Benefit: There is no direct benefit to participating in this secondary study.

Risks: Some babies may develop bradycardia or desaturation and may require increase in FiO2 or manual breaths on the ventilator ~~bagging~~ at the time of SBT. It is possible that an occasional infant may require additional interventions. However, nNo case of resuscitation related to the SBT has been described in the two published studies. Any baby requiring resuscitation will be reported to the IRB as an adverse event.

Blinding: SBT failure may be fairly predictive of failure of extubation. However, it is not part of standard practice in centers in the NRN. If the results of the SBT were provided to the clinical care team, it would result in bias in decision of extubation time. The SBT has been reported in more than Since reported infants undergoing the SBT had an uneventful course even if failing the SBT, ~~therefore~~ blinding the clinical care team to the results of this test is defensible, except in the rare circumstance of .

~~A consent form will be obtained for participation in this study. There is a slight possibility that asking for permission for this secondary study would affect enrollment rate in the primary study. We think it is unlikely with the opt-in checkbox.~~

Consent form: A consent form will be obtained for participation in this study. There is a slight possibility that asking for permission for this secondary study would affect enrollment rate in the primary study. Each center PI will decide whether to use a separate ~~This~~ consent for this secondary study or to ~~could be~~ embedded it in the consent form for the ~~main study~~main hydrocortisone study.

Limitations

Since this is an observational rather than a randomized study, success of extubation ~~the duration of mechanical ventilation~~ may be affected by multiple factors, biases and confounders, some of which we may not be able to quantify. Based on our survey, it appears that selection of the ventilation mode depends in large part on center and care provider/attending choice than on patient characteristics. For this purpose we will conduct multivariate analysis using patient characteristics (GA, prenatal steroids, disease severity), and information about individual patients. ~~NICU and providers' practices (fluid and salt administration, therapy for PDA, diuretics, caffeine, type of ventilator, choice of ventilator mode, blood gases at the time of extubation).~~

There may be inter-institutional and inter-individual variability in the decision about when to extubate. Variability will be limited by criteria set by Kristi Watterberg in the main trial protocol: "Extubation must be attempted within 72 hours of starting study drug and within 24 hours after meeting the following criteria: the FiO2 is <0.40 to maintain a saturation of 88%, the mean airway pressure is < 8, and the infant is hemodynamically stable (as defined for the SUPPORT trial: "clinically acceptable blood pressure and perfusion in the opinion of the clinical team"). The infant may be extubated from higher settings at the discretion of the attending physician. If the infant does not meet

these criteria within 72 hours, he/she will be reassessed every 24 hours during the intervention period and extubation will be attempted within 24 hours of those criteria being met."

Success of extubation depends on absence of apnea. Apnea may not be detected during the 3 minutes during which the SBT will be performed. We expect that majority but not all patients in the current trial may be on caffeine at the time of extubation, since a large multicenter randomized trial has shown it reduces the rate of bronchopulmonary dysplasia (oxygen requirement at 36 weeks postmenstrual age)[20] and improves the rate of survival without neurodevelopmental disability at 18 to 21 months but not in early childhood in infants with very low birth weight infants.[21,22]

Success of extubation will be limited in case of laryngeal edema, which may be more prevalent in the control arm. Hydrocortisone may limit this risk. We will record documentation of stridor and failure of successful extubation related to stridor.

We will not use VE as a predictor for extubation because the tidal volume cannot reliably be measured when the leak around the endotracheal tube is ≥ 30%. In spontaneously breathing infants, the tidal volume is not stable and the number of r breaths over which the VE is averaged varies among different types of ventilators.

SIMV with PS will be classified as a mode modes supporting all breaths; however this mode supports some breaths fully (SIMV) and other breaths to a lower extent (PS), in contrast with AC or PS.

~~Since subgroups for duration of mechanical ventilation will be based on the mode of respiratory support for the majority of the time on the ventilator from the time randomization, there will be possible overlap between the two groups, since some babies may be exposed to more than one mode. However, most changes in mode occur between the acute phase and beginning of weaning. Starting the count at the time of primary study entry (at least 14 d) will minimize this overlap.~~

We did consider alternatives to Kamlin's SBT.

1. During the SBT the baby will need to breathe against the resistance of the endotracheal tube. The resistance of the tube is proportional to L / r^4, where L is the length of the tube and r is its radius. We will record length and radius to assess whether the predictive value of the SBT decreases with increased resistance of the tube. An alternative to the SBT would be to design a modified SBT using PSV with minimal pressure instead of CPAP. Since no complications have been described with the SBT, this may not be necessary. Since this has not been tested in the past, we will not use this option.

2. Wilson et al[2122] described a minute ventilation test (MVT) of 10 minutes duration instead of the 3-minute test described by Kamlin. In a single institution, a spontaneous minute ventilation ≥ 50% of the ventilator-generated minute ventilation correctly predicted successful extubation in 86% of preterm infants with birth weight < 2 kg and requiring mechanical ventilation for > 24 hours.[22] In a subsequent randomized trial[2223] (mean GA 30 weeks), babies undergoing the MVT were extubated sooner than those in the control group. The positive predictive value of the MVT for extubation was 76% (95% CI, 55 to 89%) and the success of extubation was similar to the control group.[2122] Kamlin's SBT is more appropriate for our study for several reasons: his studies only included smaller babies; the SBT only uses 3 minutes and does not require minute ventilation measurement and thus could be used in multicenter setting with various ventilators, and appears at least as good as the 10 minute MVT.

3. Dimitriou et al[5] have described composite indices such as the diaphragmatic pressure–time index and the noninvasive respiratory muscle pressure–time index to predict success of extubation in preterm with mean gestatational age of 30 weeks and mean birthweight of 1.36 kg. The test had 86% positive predictive value

of successful extubation in the validation group. Kamlin's SBT is more appropriate for our study for the same reasons as described for the 10 minute MVT.

~~There is a slight possibility that asking for permission for this secondary study would affect enrollment rate in the primary study. We think it is unlikely with the opt-in checkbox.~~

9. BUDGET

Direct Costs

Cost per patient: $ 190~~113~~

Respiratory therapist: 30~~15~~ minutes x $5~~30~~ per hour = $ -50~~8~~

Coordinator time: 4~~3~~ hours x $35 per hour = $ 140~~105~~

Consent: ~~assuming consent for this secondary study is embedded in the consent for the main trial:~~ -- 30~~10~~ minutes

Screening for subjects who qualify for extubation: 60~~20~~ minutes

SBT: 60~~60~~ minutes

Data collection/entry/transmission: 90 minutes

Total Capitation ~~Direct~~ Cost for 436~~533~~ patients: $8259,840~~963~~

Training session at NRN steering committee $ 2,000

Total direct costs $84,840

Indirect costs (52.6%): $44,626

Total costs: $129,466

Note: there is no CPT code for the SBT test

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Appendix A: Authorship Plan:

We will follow the Policies and Procedures of the NICHD Neonatal Research Network

For abstracts, Authors of the Secondary Study with be the authors followed by "for the NICHD Neonatal Research Network.

For publications, authors will include Authors of the Protocol Subcommittee, Remaining participating Center PIs (those not serving on the Protocol Subcommittee), listed in order by the Center's combined ranking of the number of infants enrolled and the percent of eligible infants enrolled in the study by the Center, Followed by the phrase "for the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network."

Appendix B1: Data sample sheet

Data obtained for the ~~main study~~main hydrocortisone study and location on GDB or main hydrocortisone study form~~s~~:

Center: HCO2

Gestational age~~,~~ HCO1

B~~b~~irth weight~~,~~ GDB

Date of birth HCO1

~~date and time of birth, prenatal steroids,~~ Ddate of ~~and time of~~ randomization~~,~~ HCO2

R~~r~~andomization ~~arm~~code ~~,~~ HCO2

Information about first extubation~~center~~ HCO5

Appendix B2: Data sample sheet

~~1.~~ Data obtained for the secondary study: first elective extubation:

~~2. Exclusion criterion: ETT size < 2.5~~

~~3. At the time of randomization: FiO2 ___ Mean airway pressure: ___~~

~~4. Ventilation mode and duration:~~

~~From~~	~~Until~~	~~SIMV~~	~~PS/SIMV +PS/AC/PRVC~~

~~SBT~~ Planned extubation date and time: _____ ETT diameter: ___ total length: ___

Symptomatic PDA: Yes ___ No ___

Caffeine: yes ___ No ___

~~5.~~

~~6.~~ SBT: ~~(when quiet, change to CPAP at same pressure as prior PEEP for 3 min):~~ date and time

~~Planned extubation date and time:~~

Immediately before SBT	During SBT
~~PS/SIMV +PS/AC/PRVC~~ ~~SIMV~~ Ventilation mode: PS ___ SIMV ___ SIMV with PS ___ AC ___ Volume mode ___ Pressure control ___	Date: ___ From ___ until ___
ETT diameter: ___ length at lips: ___	

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Latest pH: ___ pCO2: ___ BE: ____	
PIP: ____ MAP: ____ Ventilator rate: ____ PEEP: ____ cm FiO2: ____ Sat: ____	CPAP: ____ cm
HR > 100: yes ____ no ____	Min HR < 100 for > 15 sec: Yes _____ No _____
FiO2: ___ Sat: ____	Fall < 85% despite 15% increase in FiO2: Yes _____ No _____
	Max FiO2 Manual breaths through ventilator: number: ___ Resuscitation needed: _bagging ___ minutes: ___ _chest compressions: ____ minutes: _epinephrine: ____

Stridor: ____ Racemic epinephrine: ____

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Appendix B3: Data sample sheet

Data obtained for the secondary study: second elective extubation:

Planned extubation date and time: _____ ETT diameter: ____ total length: ____

Symptomatic PDA: Yes ____ No ____

Caffeine: yes ____ No ____

SBT: date and time

Immediately before SBT	During SBT
Ventilation mode: PS ____ SIMV ____ SIMV with PS ____ AC ____ Volume mode ____ Pressure control ____	Date: ____ From ____ until ____
ETT diameter: ____ length at lips: ____	
Latest pH: ____ pCO2: ____ BE: ____	
PIP: ____ MAP: ____ Ventilator rate: ____ PEEP: ____ cm FiO2: ____ Sat: ____	CPAP: ____ cm
HR > 100: yes ____ no ____	Min HR < 100 for > 15 sec: Yes ____ No ____
FiO2: ____ Sat: ____	Fall < 85% despite 15% increase in FiO2: Yes ____ No ____
	Max FiO2 Manual breaths through ventilator: number: ____ Resuscitation needed: bagging ____ minutes: ____ chest compressions: ____ minutes: ____ epinephrine: ____

Stridor: ____ Racemic epinephrine: ____

HCO5: same data form as for first extubation in the main trial

~~7. Reintubation within 72 hours after extubation: no ____ yes: ____~~

~~If yes: date and time: _____~~

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DATE: January 19, 2012

TO: Brenda Poindexter
Chair, Protocol Review Subcommittee

FROM: Luc Brion

RE: Itemized response to the Protocol Review Subcommittee re: "Predicting Success of Extubation During Hydrocortisone Therapy and the Effect of Different Modes of Synchronized Ventilation"

We thank the protocol review subcommittee for a careful review of our proposal. We added itemized responses to each comment required a response or a change in the protocol. We modified the protocol considerably along the guidelines provided by the committee.

The Protocol Review Subcommittee reviewed this protocol during its conference call on January 3, 2012. Written comments were provided by Kurt Schibler, Brenda Poindexter, and Stephanie Archer and are included below.

The Subcommittee discussed differences between the population of infants studied in the Melbourne trial of spontaneous breathing versus those that will be in the hydrocortisone trial. It was noted that the investigators in Melbourne who described this test were using it every day on rounds, the purpose being to extubate VLBW infants as soon as possible (median age 4-5 days). On the other hand, infants in the hydrocortisone trial are a unique subgroup of babies who are stuck on the ventilator. The investigators need to explain how the results of the spontaneous breathing test (SBT) in the hydrocortisone cohort will be generalizable in the typical NICU setting.

We agree that the postnatal age of patients in the hydrocortisone study is different from those in the Melbourne study. We also agree data in the proposed study will not be generalizable to all patients in the NICU. The proposed study is specifically designed to address the current knowledge gap in the literature, i.e., vailidity of the SBT at later postnatal age. We have clarified the protocol to indicate dand expanded the rationale for the study.

The specific aim related to modes of ventilation was discussed at length by the Subcommittee. Given center differences in the use of assisted modes of ventilation, the consensus of the Subcommittee is that this aim is not feasible. In addition, only a limited amount of data is currently being collected for the Hydrocortisone trial (see HCO4 respiratory data collection form); in order to address the aim related to assisted ventilation, a significant increase in data collection would need to be incorporated into the study design.

We have removed the specific aim related to duration of ventilation based on different modes of ventilation.

Finally, the Subcommittee discussed the potential confounding of post-extubation management. In the current protocol, it is not clear how differences in clinical management following extubation will be handled (many which could significantly impact the success of extubation).

This may actually be a strength of the proposed study, which is aimed at finding out if the SBT is better or not to clinical decision about readiness to extubation across multiple centers and multiple approaches to post-extubation therapy (CPAP, high-flow nasal cannula, NIPPV). We will collect this information and analyze it by secondary subgroup analysis and by multivariate analysis.

As currently written, the Subcommittee had low enthusiasm for the proposed secondary. However, the Subcommittee would be willing to review a revised version of the protocol which addresses the concerns outlined below.

Comments submitted by Kurt Schibler:

This observational study is primarily designed to evaluate whether a short endotracheal continuous positive airway pressure (ET CPAP) test may help predict the success of extubation of very premature infants.

1) The primary aim of this study is evaluate the point estimates and confidence intervals of sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio of a positive test, and likelihood ratio of a negative test for the spontaneous breathing test (SBT).

2) Secondary aims are 1) To evaluate point estimates and confidence intervals of sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio of a positive test, and likelihood ratio of a negative test for the SBT in two subgroups: infants ventilated with SIMV and infants ventilated using modes supporting all breaths and 2) To determine if ventilation modes that support every breath are associated with shorter duration of mechanical ventilation than SIMV.

Methods

Study design - This is an observational study with prospective data collection.

The study will involve analysis of the operational characteristics of a diagnostic test (SBT) and retrospective analysis of a cohort study (using two cohorts: babies ventilated using SIMV and babies ventilated using modes supporting all breaths).

The spontaneous breathing test (SBT) will be performed by the study team just before extubation decided by the clinicians. Clinicians will remain blinded to the results.

Study population - We will use the same population as that for the main study. All patients enrolled in the main study will be approached for an optional consent, indicated by a check on the consent to the main study

Study intervention - when the clinicians decide a baby is ready to be extubated, the investigator will perform the SBT within 4 hours of the planned extubation.

The researcher will silence any alarms and will place screens around the bedside before initiating the test to minimize the chance of unblinding. After ensuring that the clinical care team, including the patient's nurse, is away from be bedside (to maintain blinding) the investigator (respiratory therapist, fellow, nurse practitioner or attending), who must not be involved with the patient's clinical care, will switch the ventilator to CPAP for 3 minutes at the same pressure as the positive end-expiratory pressure setting. The infant's ETT will be suctioned prior to the SBT if clinically indicated, and the intervention will be done when the infant is in a quiet state, taking care to minimize stimulation and disturbance during the study. The baby fails the SBT if he or she develops a bradycardia (HR <100) for more than 15 seconds and/or a fall in SpO2 below 85% despite a 15% increase in FIO2. At this point the study will be stopped, and ventilation will be restarted. If manual breaths are given through the ventilator because of bradycardia or desaturation, this will be considered a failed test. Data on the mode of ventilation, success and time of extubation will be collected for subsequent analysis.

The baby will be placed back on previous ventilatory settings to 30 minutes, to limit the risk of derecruitment that could have resulted from performing the SBT.

Sample size

The investigators estimate that about 70% of the total sample size available in the main trial will be available for the analysis of this secondary study; thus sample size is estimated at 550. Since the secondary study will start after the beginning of the main study, the total number of patients in this secondary study will be probably 10% smaller, i.e. 500 patients.

Analysis plan

The investigators will determine the point estimates and 95% confidence intervals for the operating characteristics (sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio of a positive test, and likelihood ratio of a negative test) of successful extubation using the SBT.

Investigators will use the same tests in subgroups:

1. infants ventilated with SIMV versus infants ventilated using modes supporting all breaths at the time of the SBT.
2. infants with gestational age ≤ $26^{6/7}$ versus those with gestational age $27^{0/7} - 29^{6/7}$ weeks

Receiving operator characteristic curve (ROC) will be used to analyze whether the operating characteristics of the SBT vary according to ETT resistance and to postnatal age.

Comments

1. Allowing time after suctioning and after the SBT for potential re-recruitment of alveoli is important particularly in the lower gestational age strata. – We added a minimum of 10 minutes between suctioning and the SBT.

2. The reasons for failure to remain extubated for 72 hours are multifactorial including individual infant associate factors and factors related to providers or center. – This fact is acknowledged in the protocol and in the limitations. We will use multivariate analysis for this purpose; however we wil not control for individual providers. We may actually consider this as one of the strength of this study: external validation of the SBT test, which so far has been tested in single-center studies.

3. It may not be possible to have SBT performed by someone not involved in clinical care of the study infant. Webelieve it is important to maintain blinding of SBT. It would be up to each center to decide whether the study PI, coordinator, respiratory therapist, fellow, attending, or NNP would be involved in theSBT. Centers who are not able to perform blinding SBT should not participate.

4. The effects of the study medication in the main trial may influence the utility of the SBT to predict extubation success. The study is designed to determine this as one of the secondary outcomes and by using multivariate analysis.

5. The study forms and additional data to be collected should be included with the protocol in order to determine how time intensive the secondary study will be. Appendix B includes all the additional information required for the study, and was edited to include all the comments and suggestions from the reviewer. Further development of the forms will be done in the manual.

6. The respiratory support variable collected around the time of the test may have little bearing on modes of support and their influence on extubation success or failure. We agree with the reviewer that this variable may not affect the validity of the SBT. This will be one among many variables we will test.

7. Whether consent should be imbedded or not should be at the discretion of the centers. We changed the protocol accordingly.

Comments submitted by Brenda Poindexter:

SUMMARY: The proposed study is a secondary study to the hydrocortisone trial to assess the sensitivity, specificity, positive and negative predictive value of the spontaneous breathing test (SBT) in predicting successful extubation in ELBW infants.

~~1.~~ The authors state that because this is an observational study, there is no primary hypothesis. This needs to be revised to reflect the analyses that will be done (hypothesis could be that the SBT will be more useful than clinical information alone). Thank you for this suggestion. The null hypothesis is that the percentage of successful extubation among patients with positive SBT is not different from

that in those extubated based on criteria established for extubation in the main hydrocortisone study.

~~2.~~1. In the methods and procedures section of the protocol the authors state that the study will involve analysis of the operational characteristics of the SBT and retrospective analysis of a cohort study. The retrospective analysis is not mentioned anywhere else in the protocol. As currently written, it seems that all infants enrolled as part of the hydrocortisone for extubation main trial will all receive the SBT, so it is is not clear where the retrospective cohort will come from. Thank you for this comment; we agree with you. We have removed this sentence from the study design. If the primary question is whether the SBT has better predictive ability than typical clinical information (such as FiO2, PIP, PEEP, etc.) as stated in the rationale/justification, then wouldn't there need to be a control group of infants who are subjected to the SBT? The primary question is not to determine whether SBT is better predictive than clinical information; this would be best studied by a randomized trial.

~~3.~~2. Secondary aim – the second secondary aim is to determine if ventilation modes that support every breath are associated with shorter duration of mechanical ventilation than SIMV. Although data will be collected related to mode of ventilation at time of extubation, it would seem that detailed data related to respiratory support prior to the time of extubation would be required. The HC04 respiratory form collects only very limited information related to type of ventilator support on study days 1, 3, 5, 7, 10, and 14 and collects no information related to assist control or pressure support. If modes of assisted ventilation shorten the duration of mechanical ventilation, wouldn't the duration of being on an assisted mode also contribute to the outcome? In other words, I would think there would be a difference between infants whose entire course on the ventilator is in SIMV versus those who are only changed to SIMV during the final stages of weaning (for 12-24 hrs) prior to extubation. In the data analysis plan, the subgroups are only divided by mode of ventilation at the time of the SBT. How will duration of time in assisted ventilation mode be dealt with in the analyses? The investigators state that "very little additional coordinator time will be needed to collect information that will be used in multivariate analysis that could build the basis for a future randomized trial" but have not provided a draft of the proposed data collection forms to be utilized in the secondary study. The wide range of practice variation in modes of ventilator management at NRN centers provided by the survery results in the protocol highlight the likelihood that center differences will bias the ability to evaluate this secondary aim (this concern was also raised in the concept comments). We agree with the reviewer's concerns and eliminated this part of the study.

~~4.~~3. Unplanned extubations – the investigators have not taken into account unplanned extubations (some of which are likely to be successful). How will these infants be handled in the analyses? These events will be excluded from the analysis, since SBT is not performed.

~~5.~~4. Post-extubation management – the role of post-extubation management is not addressed in the protocol as a potential confounder to prediction of extubation success. What type of data will be collected during the immediate post-extubation period and what variables (such as extubation to

CPAP versus HFNC or SiPAP, use of racemic epinephrine, etc.) will be considered in the analytic plan. This information was added to the protocol and to appendix B.

~~6.~~5. Treatment group – one of the secondary null hypotheses is that the predictive value of the SBT is not affected by whether the baby is randomized to hydrocortisone or placebo. This hypothesis needs to be justified as hydrocortisone, if efficacious as defined by the primary outcome measure of the main trial, could significantly confound the primary outcome of likelihood of extubation success (in addition to the other potential confounders mentioned in the protocol including fluid management, caffeine, etc.). We agree with the reviewer's comments. In this protocol we describe null hypotheses. We hypothesize that hydrocortisone might improve lung compliance and reduce laryngeal edema, thereby improving the success rate of extubation in comparison to the control group. We will analyze potential confounders by using multivariate analysis, which is now listed in the secondary outcome.

~~7.~~6. Masking – the protocol states that the individual performing the SBT should not be involved in the clinical care of the infant. Clarification is needed regarding the duration of time that this individual cannot be involved in the clinical care (before and after performance of the SBT). Regardless of who performs the test, it may be impossible to avoid having this person involved in the clinical care of the infant. It would be helpful to specify the period of time that the person administering the SBT should not be involved in the clinical care of the infant. The issue of clinical documentation and masking also needs to be addressed in the protocol. If an infant has significant hypoxia and/or bradycardia during the SBT, how will the documentation in the medical record be addressed? Given that data from our monitors in the NICU is recorded and reviewed on rounds on a daily basis, significant episodes of desaturation and/or bradycardia will be difficult to not relay to the clinical team; in addition, if the infant does require PPV or other intervention following a failed SBT, the clinical team will need to be informed. I would think that the IRB would question the plan to not inform the clinical team of a significant desaturation or bradycardia event knowing that an extubation attempt is being planned by the clinical team in the immediate future. In this regard, I disagree with the investigators that blinding the clinical team of a failed SBT (at least in the case of significant bradycardia or need for resuscitation) is "defensible". Thank you for your comments. The study cannot be done without masking the clinical team. If the caregivers know whether the baby has passed or failed the SBT, they will be biased by the study, and therefore it will be impossible to determine the outcomes described for the study. The large majority of the babies undergoing an SBT tolerate the procedure well and those who fail the SBT respond rapidly to manual breaths on the ventilator. If an occasional infant requires more than this, e.g., bag and mask ventilation or additional resuscitation. We have modified the protocol accordingly. We propose that the SBT be conducted after rounds in centers that review the monitoring tracing during rounds.

~~8.~~7. Budget – Two areas of the proposed budget warrant further consideration – first, there is a budget for a respiratory therapist for 15 minutes – does this mean that the SBT must be performed by a study respiratory therapist? I would assume that the majority of centers do not have respiratory therapists on their paid research team. For other NRN studies requiring support from respiratory

therapists (such as SUPPORT, Benchmarking, and the iNO studies), we have always relied on respiratory therapists at the centers providing their time without reimbursement. The protocol leaves to each center the choice of who will be involved in performing the SBT; in some centers only respiratory therapists are allowed to change ventilator settings. The second point that requires clarification is the 20 minutes of coordinator time for screening for subject who qualify for extubation. This would not be a one-time event, but rather would require daily screening until the infant met criteria for consideration of extubation. In addition, the decision to extubate is often made during morning rounds – therefore, this protocol will require that the clinical team inform the research coordinator of the intent to extubate in a timely manner (within the required 4 hours) or the opportunity to perform the SBT may be missed. In addition, for infants who require reintubation, the protocol states that a second SBT will be performed prior to the next extubation attempt; this effort for continuing to follow the infant after the first reintubation is not accounted for in the budget (nor is it required for the main RCT); the protocol is also inconsistent in this regard as the required follow-up is listed as being none beyond 72 hours after extubation (First extubation? Second if first one fails?). -Finally, the budget needs to be adjusted to reflect the additional data collection for type of respiratory support (as mentioned above, HC04 does not record whether infant is on assist control, SIMV, or pressure support). Thus, the time estimate for coordinator effort for this secondary study is markedly underestimated in the current budget. We now indicate in the protocol that we will use only the first 2 elective extubations after randomization. The coordinator time was increased to 4 hours based on your recommendations. We increased the time by only one hour because we have eliminated the collection of ventilator mode and support between randomization and the day of the SBT. We further revised the budget to follow Stephanie Archer's recommendations. We propose to leave the respiratory therapist. At Parkland, the plan is that one of the 2 respiratory therapists assigned to the NICU will perform the SBT. Each center will decide who could do the SBT; some centers may use the coordinator, the PI, the alternate PI, another attending, fellow or NNP for this purpose. Alternatively, we may further revise the budget if we decide that respiratory therapists will not be involved in the study.

~~9.~~8. Consent – the authors state that they do not feel that the imbedded consent will affect enrollment in the main trial because of the opt-out ability, but I do think that this issue will need to be prospectively monitored to ensure that enrollment in the main trial is not compromised. I am not in favor of imbedding consent for this secondary into the main trial; I would suggest that the decision of whether or not to imbed consent be left to the individual centers. We changed the protocol accordingly and will let each center choose whether to use a separate consent from or to imbed it into the consent for the main trial.

~~10.~~9. Data collection forms – drafts of the proposed data collection forms need to be included in the protocol; without these, it is impossible to ascertain whether the time estimates in the budget are appropriate or not. The data collection form is included in Appendix B and was updated based on all the comments from the review subcommittee.

Comments submitted by Stephanie Archer:

Questions:

- Estimated Start Date. I'm assuming no earlier than 6/1/12. Obviously, the later this is, the smaller the sample size, and the cheaper the cost. We modified the protocol accordingly.
- Consent rate. Not sure how you can say you will capture 70% of the original study population with only a 60% consent rate. I've used 70% in this estimate. We selected 70% because some centers may select centers may select a separate consent form for the secondary study while other centers may select an embedded consent.
- Sample size. This will depend on the start date, consent rate, and the rate of recruitment for the Main trial. As of November 2011, only 16 randomized (versus an original main trial estimate of 27 recruited per month). We changed the protocol accordingly.
- Respiratory therapist. This rate is too low. For IPGE, we used $100/hour, which is probably still too low. We changed the budget accordingly.
- Training costs. Assuming no need for extensive training for this secondary – with any training done at a Steering Committee meeting or via teleconference. We changed the budget accordingly.

Comments submitted during Concept Presentation (17 yes, 3 no votes):

Comments with yes votes

- This study can add critical information to the steroid tria.
- AC vs SIMV length of ventilation comparison is unlikely to yield useful results.
- Simple, inexpensive, important study.
- We'd enthusiastically test this hypothesis.
- Validation of SBT particularly among subgroups would be very valuable. Comparison of ventilator modes will b e hopelessly biased by center difference. It might be worth looking at multiple definitions of failure at 12, 24 and even 48 hours. Comparison of duration of ventilation support by ventilator modes was eliminated from the protocol. We will add various definitions of failure to secondary outcomes.
- Will PDA influence SBT? This will be one of the variables assessed in the multivariate analysis.
- Where is ref 4 cited? All references are cited.
- Good use of the HC extubation main trial to gain additional information.
- Consent should not be embedded as it may decrease consent into main trial. This was changed.
- Coordinator and RTI seemed to be an under-estimate. The budget was revised accordingly.
- SBT validation more worthwhile than trying to get at length of ventilation. Focus on SBT component. The length of ventilation was removed from the protocol.

Comments with no votes

- Not easy to predict by ~ 3 minute of CPAP. Previous studies have shown that the SBT is superior to clinical parameters to predict successful extubation in preterm infants. Issues with upper airway obstruction and apnea despite caffeine. This information is being collected in this study.
- Post extubation variation HFNC/CPAP ;this information will be collected

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "ronald.goldberg@duke.edu"
Subject: Re: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)
Date: Saturday, January 21, 2012 1:27:46 PM

Ron -
This was discussed at the steering committee meeting - mike can fill you in or we can discuss by phone

Rose

From: Ronald Goldberg, M.D. [mailto:ronald.goldberg@duke.edu]
Sent: Friday, January 20, 2012 09:09 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)

Will do.
What happened? Did we do something wrong? Seems serious.
Ron

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, January 20, 2012 02:47 PM
To: Ronald Goldberg, M.D.
Cc: Maddox, Yvonne (NIH/NICHD) [E] <maddoxy@exchange.nih.gov>; Spong, Catherine (NIH/NICHD) [E] <spongc@dir49.nichd.nih.gov>; Hirschfeld, Steven (NIH/NICHD) [E] <hirschfs@mail.nih.gov>
Subject: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)

Ron

As you are aware the Neonatal Research Network (NRN) continues to support studies under common protocols, but which require individual institutional IRB review prior to the conduct of these studies at each of the NRN sites. This is to inform you that The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), which provided the Federal support to the NRN, has been requested by the Office of Human Subjects Protection, to provide to the Office the most current consent form approved by your IRB and the corresponding IRB approval for the main SUPPORT Study, including any revisions, as soon as possible. As the NICHD Program Director of the NRN, I am requesting that the most recent consent form with IRB approval for your site for SUPPORT be submitted to me as soon as possible, but no later than January 26, 2012. Thank you for your cooperation.

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892

For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Maddox, Yvonne (NIH/NICHD) [E]
Subject: Re: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)
Date: Friday, January 20, 2012 5:45:34 PM

I already have 4 of the 20- one investigator asked about getting some (b)(5)
(b)(5)
(b)(5) Let me know if you have any advice to offer on that point.

Thanks for all your help

Rose

From: Maddox, Yvonne (NIH/NICHD) [E]
Sent: Friday, January 20, 2012 05:19 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)

I meant to copy you on this.

From: Maddox, Yvonne (NIH/NICHD) [E]
Sent: Friday, January 20, 2012 5:18 PM
To: 'Bradley Yoder'
Subject: RE: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)

Thank you for your quick attention to our request. We appreciate it.

From: Bradley Yoder [mailto:Bradley.Yoder@hsc.utah.edu]
Sent: Friday, January 20, 2012 4:55 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Roger Faix
Cc: Maddox, Yvonne (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Hirschfeld, Steven (NIH/NICHD) [E]; Karen Osborne RN
Subject: RE: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)

Rose, please see attached forms.
We had to get our parental consent approved in 2011 at the U due to one follow-up pt we needed to track down.
Please let me know if you need anything else.

Brad Yoder
Division of Neonatology
University of Utah SOM

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, January 20, 2012 12:42 PM
To: Roger Faix; Bradley Yoder
Cc: Maddox, Yvonne (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Hirschfeld, Steven (NIH/NICHD) [E]
Subject: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)

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301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Bradley Yoder
To: Higgins, Rosemary (NIH/NICHD) [E]; Roger Faix
Cc: Maddox, Yvonne (NIH/NIMHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Hirschfeld, Steven (NIH/NICHD) [E]; Karen Osborne RN
Subject: RE: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)
Date: Friday, January 20, 2012 4:55:13 PM
Attachments: IHC IRB SUPPORT approval letter Sep2011.pdf
IHC IRB SUPPORT parental consent English Feb2009.pdf
IHC IRB SUPPORT parental consnet Spanish Feb2009.pdf
UofU SUPPORT approval renewal 2011.doc
UofU SUPPORT parental consent English IRB stamped Jun2011.doc
UofU SUPPORT parental consent Spanish IRB stamped Jun2011.doc

Rose, please see attached forms.
We had to get our parental consent approved in 2011 at the U due to one follow-up pt we needed to track down.
Please let me know if you need anything else.

Brad Yoder
Division of Neonatology
University of Utah SOM

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, January 20, 2012 12:42 PM
To: Roger Faix; Bradley Yoder
Cc: Maddox, Yvonne (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Hirschfeld, Steven (NIH/NICHD) [E]
Subject: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)

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higginsr@mail.nih.gov

Intermountain Healthcare
Office of Research

8th Avenue and C Street
Salt Lake City, Utah 84143
801.408.1991
800.321.2107
801.408.6783 Fax
officeofresearch@imail.org

September 3, 2011

Bradley Yoder, M.D.
PO Box 581289
Salt Lake City, UT 84158-1289

RE: IRB # 1008869 - SUPPORT
Protocol Title: *The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely low Birth Weight Infants (formerly IRB # 06.2103)*
Meeting Date: 10/13/2011 (to be reported to the Committee)
On Agenda For: Continuing Review of Research – Expedited Review
Approved: 9/1/2011
Expiration Date: 8/31/2012

Dear Dr. Yoder:

The above referenced project has been reviewed by a member of the Intermountain Healthcare Institutional Review Board and continuing approval was recommended.

The FDA requires that research projects be reviewed annually, or more often at the discretion of the IRB. You will be notified when it is time for renewal of this study. It is your responsibility to respond to this notification. If you do not respond, approval of this study will be terminated. In the meantime, if there are any administrative, procedural or clinical changes you will need to submit them to the IRB for approval prior to making them effective.

It is your responsibility to notify DHHS and/or the FDA, and the Chairperson of the IRB Committee of any occurrence or emergency that seriously increases the risk to or affects the welfare of subjects.

If you have questions regarding this decision, please contact Anita Pascoe in the IRB Office at 801-408-6782.

Approved Items:

- Continuing review of research application dated 7/11/2011.

Sincerely,

Anthony G. Musci, MD
Chairperson
Intermountain Healthcare
Urban Central Region
Institutional Review Board

cc: Karen Osborne

INTERMOUNTAIN HEALTH CARE

PARENTAL PERMISSION and AUTHORIZATION DOCUMENT IHC INSITUTIONAL REVIEW BOARD

TITLE: The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weigh Infants (SUPPORT Trial)

PRINCIPAL INVESTIGATOR: Bradley A. Yoder, MD (801) 581-7052

CO-INVESTIGATOR(S): Roger Faix, MD (801) 581-7052
Susan Wiedmeier, MD (801) 408-3435

LOCATION: Intermountain Medical Center and Primary Children's Medical Center

BACKGROUND:

You are being asked to allow your baby to be in this research study because there is a possibility he/she will be born between 24 and 27 weeks gestation. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, and relatives if you wish. Ask us if there is anything that is not clear or if you would like more information. Please take time to decide whether or not you volunteer your baby to take part in this research study.

Our hospital is conducting this study in cooperation with the National Institutes for Child Health and Human Development (NICHD) Neonatal Research Network to try to determine the best way to manage early breathing support in the extremely premature infant and to determine the most appropriate level of oxygen in the blood of extremely premature babies.

STUDY PROCEDURES:

Prior to delivery, and after your permission, your baby will be randomized (chosen by chance, like a flip of a coin) to one of four treatment strategies as shown below. There are two breathing support strategies: 1) early CPAP (giving pressurized gas by small plastic tubes in the nose) and 2) Intubation/Surfactant (placing a breathing tube and giving a medicine through the tube to try to help the lungs work better). Both treatments are currently used immediately after delivery at this hospital. The decision as which to use is currently made by the physician attending the delivery. There are also two oxygen support strategies: 1) a low normal range (85-89%) and 2) a high normal range (91-95%). The box on the following page indicates the four possible treatment combinations your infant can be randomized to. There is an equal chance (1 in 4) for randomization to each treatment group.

CPAP and Higher oxygen saturation	CPAP and Lower oxygen saturation
Breathing tube + Surfactant and Higher oxygen saturation	Breathing tube + Surfactant and Lower oxygen saturation

Your baby will remain on a specially modified oxygen saturation monitor (measures oxygen levels in the blood through the skin without needle sticks) until he/she reaches 36 weeks corrected age (example: 24 weeks gestation plus 12 weeks of age = 36 weeks corrected age) or until the monitor is no longer needed because your baby is in room air. Because of the design of these monitors none of the nurses, doctors, or study personnel taking care of your baby will know if he/she is in the lower or higher oxygen saturation group.

Other care will continue as normal during his/her participation in the study.

A secondary purpose to this study is to determine the longer term effect of different approaches to breathing and oxygen support in the very premature baby. In that regard, this study includes three planned follow-up evaluations of all study baby's during the first two years of life including:

a. follow-up for subsequent lung problems

b. follow-up of neurodevelopmental function (a complete exam of their muscles, nerves, mental and coordinated movement skills) at 18-22 months age

c. a comparison of currently applied radiology studies (MRI and Ultrasound) obtained at 36-42 weeks corrected gestation for predicting later neurodevelopmental function

Some of these follow-ups may be by phone and some may be in our special follow-up clinic for very premature infants routinely provided at 6, 12 and 18-22 months age.

Our study coordinator will keep track of how your baby is doing up to 40 weeks gestational age (the babies original due date) or until discharge. Once your baby reaches 36 weeks gestational age we will record if he/she is still being treated with oxygen and/or a ventilator. If your baby is still on nasal cannula oxygen we will try to wean him/her off the oxygen using a standard protocol. If he/she successfully weans off oxygen, your baby's medical team may decide to take him/her completely off oxygen.

RISKS:

Because all treatments proposed in this study are currently accepted standard of care, there is no predictable increase in risk to your baby. Infants randomized to the CPAP group may, at some point in their care, require intubation and assisted breathing. This will be determined by your baby's attending physician and participating in this study will not effect this decision.

BENEFITS:

We cannot promise any direct benefits to your baby from being in this study. However, possible benefits to your child may include decrease in chronic lung disease (need for extra oxygen at discharge) and decrease in the need for eye surgery as a result of exposure to oxygen. The information we learn from this study may help us treat premature babies in the future.

ALTERNATIVE PROCEDURES:

As an alternative to participation in this study you may decide to have your baby's doctor decide which treatment your baby will receive. If you decide not to include your baby in this study, none of his/her medical information will be included in the study data. Participation in research is entirely voluntary. You may refuse to participate or withdraw at any time without jeopardy to the medical care your baby will receive at this institution. Data collection for this study will stop at that time.

PERSON TO CONTACT:

If you have concerns or questions about this research or any related matter, you can contact the primary investigator, Dr. Bradley Yoder @ 801-581-7052 (pager 801-339-0092) or co-investigator, Dr. Roger Faix@ 801-587-7500 (pager 338-2228), in the Department of Pediatrics/Neonatology, University of Utah School of Medicine.

INSTITUTIONAL REVIEW BOARD:

If you have questions regarding your child's rights as a research subject, or if problems arise which you do not feel you can discuss with the Investigator, please contact the Institutional Review Board Office at the LDS Hospital @ 801-408-6781.

INJURY NON-COMPENSATION STATEMENT:

In the event your child sustains an injury resulting from your participation in the research project, Intermountain Medical Center can provide to him/her, emergency and temporary medical treatment and will bill your insurance company. Since this is a research study, payment for any injury resulting from participation in this research study may not be covered by some health insurance plans. If you believe that your child sustained an injury as a result of your participation in this research program, please contact the Institutional Review Board Office at the LDS Hospital @ 801-408-6781.

VOLUNTARY PARTICIPATION:

It is up to you to decide whether or not your baby will take part in this study. If you do decide to have him/her take part you will be asked to sign this consent form. You are free at any time to withdraw from this study without giving a reason. Whether your baby joins this study or not, your baby will receive the same medical and nursing care as needed and it will not affect your relationship with the investigator or other medical staff.

UNFORESEEABLE RISKS:

A particular treatment may involve risks to the baby that are currently unforeseeable. However, because all of the treatments proposed in this study are currently accepted as standard of care, there is no unpredictable increase expected. Unknown risks may be learned during the study, and is so you will be informed by the study personnel. The only other risk of this study is a risk to confidentiality. Every effort will be made to keep your baby's medical information confidential.

RIGHT OF INVESTIGATOR TO WITHDRAW:

You may withdraw your baby from this study at any time without penalty. Dr. Bradley Yoder or his associate investigators can withdraw your baby without your approval. Possible reasons for withdrawal include a need to transfer care to a different hospital not involved in this study or early termination of this study for safety considerations.

COSTS TO SUBJECTS AND COMPENSATION:

There is no cost to parents nor is there any compensation for participating in this study.

NEW INFORMATION:

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, your research doctor will tell you about it and discuss with you whether you want your baby to continue in the study. If you decide to continue your baby in the study, you will be asked to sign an updated permission form. Also, on receiving new information your research doctor might consider it to be in the best interest of your baby to withdraw him/her from the study. They will explain the reasons and arrange your baby's care to continue.

INTERMOUNTAIN HEALTH CARE
URBAN CENTRAL REGION
IRB

FEB 3 2009 — APPROVED

DEC 11 2009 — EXPIRATION DATE

NUMBER OF SUBJECTS:

We expect to include about 1300 babies in the study from the sixteen NICHD Neonatal Research Network hospitals over a two-year period. Intermountain Medical Center, Primary Children's Medical Center, and the University of Utah Hospital will enroll around 80 babies over the two year period.

CONFIDENTIALITY/ APPROVAL TO USE YOUR CHILD'S PROTECTED HEALTH INFORMATION

IHC has a commitment to protect your child's confidentiality. Federal regulations require that you understand how your child's protected health information (PHI) is used for this study.
Signing this document means you allow us, the researchers in this study, and others working with us to use information about your baby's health for this research study. You can choose whether or not to participate in this research study. However, in order to participate you have to sign this consent and authorization form.

This is the information we will use:
Name
Address
Telephone number
Current and past medications or therapies
Information from a physical examination, such as blood pressure, heart rate, breathing rate, and temperature
Information related to the use of any device for support of lung function such as ventilator pressures, oxygen concentration and blood oxygen levels; any pertinent x-ray studies including head ultrasounds and MRI's; and information related to other neonatal diagnoses.

In records and information disclosed outside of IHC to the NICHD Neonatal Network Data Collection center at Research Triangle Park, North Carolina, your child's information will be assigned a unique code number. We will keep the key to the code in a secure file maintained in the Division of Neonatology, University of Utah School of Medicine.

Others who will have access to your child's protected health information for this research project include IHC's Institutional Review Board (the committee that oversees research studying people) and authorized members of the IHC's workforce who need the information to perform their duties (for example: provide treatment, to ensure integrity of the research, and for accounting or billing matters), the Food and Drug Administration, and others as required by law.

You may revoke this authorization at any time. **This must be done in writing.** You must either give your revocation in person to the Principal Investigator or the Principal Investigator's staff, or mail it to Dr. Bradley A. Yoder, Department of Pediatrics/Neonatology, University of Utah School of Medicine, and PO Box 581289, Salt lake City, UT 84158-1289. If you revoke this authorization, we will not be able to collect new information about your baby, and will be withdrawn from the research study. However, we can continue to use information we have already started to use in our research, as needed to maintain the integrity of the research.
You have a right to information used to make decisions about your baby's health care. However, your baby's information from this study will not be available during the study; it will be available after the study is finished. This authorization lasts until this study is finished.

For more information about rights to your child's protected health information, how to revoke this authorization, and how IHC uses your child's health information, you may ask to see or obtain a copy of the IHC Notice of Privacy Practices.

I hereby acknowledge that I have received or been offered a copy of IHC's Notice of Privacy Practices.

INTERMOUNTAIN HEALTH CARE
URBAN CENTRAL REGION
IRB

FEB 3 2009 — APPROVED
DEC 11 2009 — EXPIRATION DATE

CONSENT:

I confirm that I have read and understand this consent and authorization document and have had the opportunity to ask questions. I understand that my child's participation is voluntary and that I am free to withdraw my child at any time, without giving any reason, without his/her medical care or legal rights being affected. I will be given a signed copy of the consent and authorization form to keep.

INTERMOUNTAIN HEALTH CARE
URBAN CENTRAL REGION
IRB

FEB 3 2009 APPROVED

DEC 11 2009 EXPIRATION DATE

I agree to allow my child to participate in this research study and permit you to use and disclose health information about my child for this study, as you have explained in this document.

_____
Child's Name

(Please Note: Both parents must give their permission unless one parent is deceased, unknown, incompetent, not reasonably available, or when only one parent has legal responsibility for the care and custody of the child. If both parents are not able to sign, please list the name of the parent and the reason why they are not able to sign in the signature line.

Parent/ Guardian Name	Parent/ Guardian Signature	Title	Date

_____
Name of Person Obtaining Authorization and Consent

_____ _____
Signature of Person Obtaining Authorization and Consent Date

_____
Name of Witness

_____ _____
Signature of Witness Date

INTERMOUNTAIN HEALTH CARE

IHC

PERMISO DE LOS PADRES y DOCUMENTO DE AUTORIZACIÓN COMITÉ DE REVISIÓN INSTITUCIONAL DE IHC

TÍTULO: La Prueba de Surfactante Positivo en las Vías Respiratorias y Oximetría del Pulso en Bebés Nacidos con Peso Extremadamente Bajo (Prueba de SOPORTE)

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LUGAR: Centro Médico Intermountain y Centro Médico Infantil de la Primaria

ANTECEDENTES:

Debido a que hay una posibilidad que el nacimiento de su bebé se produzca entre las 24 y 27 semanas de gestación, le pedimos que permita la participación de su bebé en este estudio investigativo. Antes de decidir, es importante que entienda la razón por la que se hace esta investigación y qué es lo que incluirá. Por favor, tome tiempo para leer cuidadosamente le información siguiente y discutirla con amigos y familiares si así lo desea. Si hay algo que no está claro o desea recibir más información, pregúntenos a nosotros. Por favor dedique tiempo para decidir si su bebé participará o no en este estudio investigativo.

Nuestro hospital está llevando a cabo este estudio en cooperación con el Instituto Nacional de Salud Infantil y Desarrollo Humano (NICHD por sus siglas en inglés) y la Red de Investigación del Recién Nacido, para tratar de determinar los medios óptimos para administrar soporte respiratorio temprano en bebés extremadamente prematuros y para determinar el nivel de oxígeno más adecuado en la sangre de bebés extremadamente prematuros.

PROCEDIMIENTOS DEL ESTUDIO:

Previo al nacimiento y después de su permiso, su bebé será elegido al azar (por sorteo, tal como escoger un lado de la moneda) para una de cuatro estrategias de tratamiento como las que se muestran debajo. Hay dos estrategias de soporte respiratorio: 1) CPAP temprano (dando gas presurizado a través de pequeños tubos de plástico en la nariz) y 2) Intubación de Surfactante (colocando un tubo para respirar y dando una medicina a través del tubo para ayudar a que los pulmones funcionen mejor). Ambos tratamientos son usados actualmente en este hospital inmediatamente después del parto. La decisión sobre cuál de ellos se usa es hecha actualmente por el médico que asiste el parto. También hay dos estrategias de soporte de oxígeno: 1) un nivel normal bajo (85-89%) y 2) un nivel normal alto (91-95%). En el cuadro de la página siguiente indica las cuatro combinaciones posibles de tratamiento a las que será sorteado al azar su bebé. Cada grupo de tratamiento tiene las mismas posibilidades (1 en 4) en el sorteo.

CPAP y Saturación alta de Oxígeno	CPAP y Saturación baja de Oxígeno
Tubo de respiración + Surfactante y Saturación alta de oxígeno	Tubo de respiración + Surfactante y Saturación baja de Oxígeno

Su bebé permanecerá en un monitor de saturación de oxígeno especialmente modificado (mide los niveles de oxígeno en la sangre a través de la piel sin necesidad de agujas) hasta que alcanza las 36 semanas de edad ajustada (por ejemplo: 24 semanas de gestación + 12 semanas de vida= 36 semanas de edad ajustada) o hasta que el monitor ya no sea necesario debido a que su bebé respira el aire común de la habitación.

Otros tipos de atención médica continuarán como es normal durante su participación en el estudio.

Un propósito secundario para este estudio es el de determinar el efecto a largo plazo de diferentes opciones para respirar y el soporte de oxígeno en bebés muy prematuros. En tal respecto, este estudio incluye varias otras evaluaciones de seguimiento de todos los estudios hechos al bebé durante los primeros dos años de vida, tales como:
a. Seguimiento por problemas pulmonares subsiguientes.
b. A los 18-22 meses de edad seguimiento de las funciones de desarrollo neural (un examen completo de sus músculos, nervios, y habilidad de coordinación mental y movimiento.
c. Una comparación de estudios radiológicos actuales (Imagen por resonancia magnética (MRI) y Ultrasonido) obtenidos a las 36-42 semanas de gestación ajustada para pronosticar función de desarrollo neural posterior.

Algunos de esos seguimientos pueden ser hechos por teléfono y algunos podrán ser en nuestra clínica de seguimiento especial para bebés extremadamente prematuros, los que se proveen rutinariamente a los 6, 12 y 18 a 22 meses de vida.

Nuestro coordinador del estudio llevará la cuenta acerca cómo está su bebé hasta las 40 semanas de edad gestacional (la fecha probable de parto original), o hasta que sea dado de alta. Una vez que su bebé alcance las 36 semanas de edad gestacional se registrará si aún continua recibiendo tratamiento con oxígeno o con un ventilador. Si su bebé está aún con oxígeno a través de una cánula nasal, trataremos de quitarla usando un protocolo estándar. Si su bebé es desconectado exitosamente del oxígeno, el equipo médico de su bebé puede decidir quitarle el oxígeno por completo.

RIESGOS:
Debido a que todos los tratamientos propuestos en este estudio son aceptados actualmente como estándar de atención, no hay aumento predecible en riesgo para su bebé. Los bebés seleccionados al azar para el grupo de CPAP pueden, en alguna instancia de su atención, requerir intubación y respiración asistida. Esto será determinado por el médico a cargo de su bebé y su participación en el estudio no tendrá efecto en esta decisión. Algunos riesgos desconocidos pueden conocerse durante el estudio. Si esto ocurre, usted será informado por el personal del estudio. El único otro riesgo en este estudio es el riesgo de la confidencialidad. Se harán todos los esfuerzos para mantener confidencial la historia médica de su hijo/a. No habrá nombres u otra identificación del paciente en ningún informe del estudio que pueda ser publicado una vez que el estudio ha sido completado. Las medidas que se tomarán para proteger su identidad y la del bebé son descriptas en la sección confidencialidad.

BENEFICIOS:
No podemos prometer ningún beneficio directo para su bebé por estar en este estudio. Sin embargo, posibles beneficios para su hijo/a puede incluir la disminución de enfermedades pulmonares crónicas (la necesidad de oxígeno extra en el momento que es dado de alta) y disminución de la necesidad de cirugía de ojos como resultado de su exposición al oxígeno. La información que se obtenga por este estudio puede ayudarnos en el tratamiento futuro de bebés prematuros.

PROCEDIMIENTOS ALTERNATIVOS:
Como una alternativa a la participación en este estudio, usted puede decidir que el doctor de su bebé decida cuál tratamiento recibirá su bebé. Si usted decide que su bebé no sea incluido en este estudio, no se procesará información médica de sus hijo/a en los datos del estudio. La participación en la investigación es completamente voluntaria. Usted puede negarse a participar o retirarse en cualquier momento sin perjudicar la atención médica que recibirá su bebé en esta institución. La recopilación de información para este estudio sera detenida en ese momento.

PERSONAS A CONTACTAR:
Si tiene preguntas acerca de esta investigación o relacionada con ella, puede contactar al investigador primario, el Dr. Bradley Yoder en el 801-581-7052 (o al buscapersonas 801-339-0092) o al co-investigador, Dr. Roger Faix en el 801-587-7500 (buscapersonas 338-2228), en el Departamento de Neonatología Pediátrica en la Escuela de Medicina de la Universidad de Utah.

COMITÉ DE REVISIÓN INSTITUCIONAL:
Si tiene preguntas con respecto a los derechos de su hijo/a como participante de la investigación, o si surgen problemas que cree no poder discutirlos con el Investigador, sírvase contactar a la Oficina de Investigación de Intermountain en el 1-800-321-2107.

DECLARACIÓN DE NO COMPENSACIÓN POR HERIDAS:
En caso que usted resulte herido como resultado de su participación en el proyecto investigativo, el Centro Médico Intermountain puede proveerle tratamiento médico de emergencia y circunstancial, y facturar a su compañía de seguros. Siendo que este es un estudio de investigación, el pago por cualquier herida resultante por su participación en este estudio investigativo puede que no sea cubierta por algunos planes de seguro de salud. Si usted cree que ha resultado herido a causa de su participación en este programa de investigación, sírvase contactar a la Oficina de Investigación de Intermountain, en el 1-800-321-2107.

PARTICIPACIÓN VOLUNTARIA:

INTERMOUNTAIN HEALTH CARE
URBAN CENTRAL REGION
IRB

FEB 3 2009 APPROVED

DEC 11 2009 EXPIRATION DATE

Usted es quien decide si su hijo/a participa o no en este estudio. Si usted decide que participe, le será pedido que firme este formulario de Consentimiento. Usted es libre de retirarlo en cualquier momento de este estudio sin dar ninguna explicación. Si su hijo/a participa o no en este estudio, igualmente recibirá el mismo cuidado médico y de enfermería que sea necesario y no afectará su relación con el investigador u otro personal médico.

RIESGOS IMPREVISTOS:
Un tratamiento particular puede incluir riesgos para el bebé que actualmente son imprevisibles. Sin embargo, debido a que todos los tratamientos propuestos en este estudio están aceptados actualmente como estándar de cuidado médico, y no se espera que se registre un aumento de riesgos imprevisibles. Sin embargo, debido a todos los tratamientos propuestos en este estudio están aceptados como estándar en la atención médica actual y no se espera un aumento imprevisible. Riesgos desconocidos actualmente pueden descubrirse durante el estudio, y si ello ocurre, usted será informado por empleados de la investigación. El único otro riesgo es el riesgo a la confidencialidad. Se harán todos los esfuerzos para mantener confidencial la historia médica de su bebé.

DERECHO DEL INVESTIGADOR PARA RETIRARLO DEL ESTUDIO:
Usted puede retirar a su bebé de este estudio en cualquier momento y sin sufrir ninguna penalidad. El Dr. Bradley Yoder o sus investigadores asociados pueden retirar a su bebé sin necesidad que usted lo apruebe. Las razones probables para ser retirado incluye la necesidad de transferir su cuidado a otro hospital que no participe en el estudio o la necesidad de dar anticipar la terminación del estudio por razones de seguridad.

COSTOS Y COMPENSACIÓN PARA LOS PARTICIPANTES:
No hay ningún costo para los padres ni hay ninguna compensación por participar en este estudio.

INFORMACIÓN NUEVA:
Algunas veces durante el transcurso de un proyecto investigativo, se hace disponible información nueva sobre el tratamiento que está siendo estudiado. Si esto sucede, su doctor investigador le informará al respecto, y discutirá con usted sobre si usted quiere que su bebé continúe en el estudio. Si usted decide que su bebé continúe, se le pedirá que firme un formulario actualizado de autorización. También, al recibir información nueva puede que el doctor investigador considere que es conveniente para su bebé el retirarlo del estudio, Los investigadores le explicarán las razones y harán los arreglos necesarios para continuar la atención médica de su bebé.

NÚMERO DE PARTICIPANTES:
Esperamos incluir en el estudio durante un período de dos años a alrededor de 1300 bebés de los dieciséis hospitales de la Red de Investigación de Recién Nacidos del NICHD. El Centro Médico Intermountain, el Centro Médico Infantil de la Primaria y el Hospital de la Universidad de Utah enrolarán alrededor de 80 bebés durante dicho período de dos años.

CONFIDENCIALIDAD – APROBACIÓN PARA USAR LA INFORMACIÓN PROTEGIDA DE LA SALUD DE SU HIJO/A
IHC tiene un compromiso para proteger la confidencialidad de su bebé. Las reglamentaciones del Gobierno Federal requieren que usted entienda cómo proteger la información sobre la salud (PHI) de su hijo/a usada en este estudio. Al firmar este documento, usted significa que usted nos autoriza a nosotros, los investigadores en este estudio y a otros que trabajan con nosotros a utilizar para este estudio investigativo información sobre la salud de su bebé. Usted puede escoger el participar o no

en este estudio. Sin embargo, para poder participar tiene que firmar este formulario de consentimiento y autorización.

Esta es la información que utilizaremos:
Nombre
Dirección
Número de Teléfono
Medicamentos y terapias actuales y anteriores
Información de un examen físico, tales como presión arterial, pulso, ritmo respiratorio y temperatura. Información relacionada con el uso de algún aparato para apoyo de las funciones pulmonares tales como ventilación presurizada, niveles de concentración de oxígeno, información relacionada con el uso de un aparato de soporte de las funciones pulmonares; cualquier radiografía pertinente a los estudios, incluyendo ultrasonidos de la cabeza e imágenes de resonancia magnética (MRI), información relacionada con otros diagnósticos de recién nacidos y cualquier estudio pertinente de radiografías incluyendo radiografías y ultrasonido de la cabeza.

En registros e información divulgada fuera de IHC al Centro de Recolección de Información de Recién Nacidos del NICHD en Research Triangle Park, North Carolina, a la información de su hijo/a le será asignado un número codificado único. Nosotros guardaremos la clave codificada en un archivo seguro, el que será mantenido en la División de Neonatología de la Escuela de Medicina de la Universidad de Utah.

Otras personas que tendrán acceso a la información protegida de la salud de su hijo/a para este estudio investigativo incluyen al comité de Revisión Institucional de IHC (el Comité que supervisa las investigaciones de seres humanos) y personal de IHC que necesita la información para desempeñar sus tareas (por ejemplo proveer tratamiento, o para asegurar la integridad de la investigación, y por asuntos relacionados con contabilidad y facturación), la Administración de Medicinas y Alimentos, y otros según sea requerido por ley.

Usted puede revocar esta autorización en cualquier momento. **Lo que debe ser hecho por escrito.** Usted puede entregar su nota de revocación en persona al Investigador Principal o a su personal, o enviarla por correo al Dr. Bradley A. Yoder, Department of Pediatrics/Neonatology, University of Utah School of Medicine, PO Box 581289, Salt lake City, UT 84158-1289. Si usted revoca esta autorización, no podremos reunir información nueva sobre su bebé, quien será retirado del estudio investigativo. Sin embargo, podremos continuar utilizando la información que ya hayamos comenzado a utilizar, según sea necesario para mantener la integridad de la investigación.

Usted tiene derecho a la información utilizada para tomar decisiones sobre la atención médica de su bebé. Sin embargo, la información de su bebé para este estudio no estará disponible durante el estudio hasta tanto el mismo haya sido finalizado. Esta autorización continua vigente hasta que finalice este estudio.

Para mayor información sobre sus derechos en cuanto a la información protegida sobre la salud de su hijo/a, cómo revocar esta autorización, y cómo IHC utiliza la información sobre la salud de su hijo/a, usted puede solicitar una copia de la Información sobre Prácticas de Privacidad de IHC.
Por la presente reconozco que he recibido o me ha sido ofrecida una copia de la Información sobre Prácticas de Privacidad de IHC.

CONSENTIMIENTO:

Confirmo que he leído y entiendo este documento de consentimiento y autorización y que he tenido oportunidad de hacer preguntas. Entiendo que la participación de mi bebé es voluntaria y que soy libre de retirarlo en cualquier momento y sin dar ninguna explicación, si que mi atención médica o derechos legales sean afectados. Me será dada una copia firmada del formulario de consentimiento y autorización para guardar en mi poder.

Estoy de acuerdo en permitir que mi hijo/a participe en este estudio investigativo y permitir a ustedes usar y divulgar información sobre la salud de mi hijo/a para este estudio, tal como ustedes han explicado en este documento.

Nombre del niño/a

(Por favor, tome nota: Ambos padres deberán dar su permiso a menos que uno de ellos haya fallecido, sea desconocido, es incompetente, no está razonablemente disponible, o cuando uno de los padres tiene la responsabilidad legal por la atención médica y tenencia del niño/a. Si ambos padres nos pueden firmar, sírvase apuntar el nombre de uno de los padres y la razón por la que no pueden firmar en el lugar correspondiente.

Nombre de uno de los Padres/Tutor	Firma de uno de los Padres/Tutor	Titulo	Fecha

Nombre de la Persona que obtiene el consentimiento y autorización

Firma de la Persona que obtiene el consentimiento y autorización Fecha

[La sección con la firma del testigo puede ser incluida si el patrocinador o la fuente de financiación o usted requiere que se incluye. Sin embargo, este no es un requisito del Comité de Revisión Institucional.]

Nombre del Testigo

Firma del Testigo Fecha

INTERMOUNTAIN HEALTH CARE
URBAN CENTRAL REGION
IRB

FEB 3 2009 APPROVED

DEC 11 2009 EXPIRATION DATE

INSTITUTIONAL REVIEW BOARD
THE UNIVERSITY OF UTAH

IRB_00017893

PI: Bradley Yoder

Title: The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Exremely Low Birth Weight Infants (SUPPORT Trial)

This Continuing Review Application has been reviewed and approved by a University of Utah IRB convened board. The convened board approved your study on 1/18/2012 . Federal regulations and University of Utah IRB policy require this research protocol to be re-reviewed and re-approved prior to the expiration date, as determined by the convened board.

Your study will expire on 1/17/2013 11:59 PM.
Any changes to this study must be submitted to the IRB prior to initiation via an amendment form.

Click CR_00009821 to view the application and access the approved documents.

The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

Background

You are being asked to allow your baby to be in the study because there is a possibility he/she will be born between 24 and 27 weeks gestation. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, and relatives if you wish. Ask us if there is anything that is not clear or if you would like more information. Please take time to decide whether or not you volunteer your baby to take part in this research study.

Our hospital is conducting this study in cooperation with the National Institutes for Child Health and Human Development (NICHD) Neonatal Research Network to try to determine the optimal means for managing early breathing support in the extremely premature infant (CPAP or a breathing tube) and to determine the appropriate level of oxygen saturation (oxygen levels in the blood) in extremely premature babies. CPAP stands for Continuous Positive Airway Pressure. The pressure is provided by the flow of oxygen and air through prongs or a tube in the nose, and the purpose of the pressure is help keep the lungs inflated making it easier for the baby to breathe and to get adequate oxygen into the blood.

Study Procedures

Prior to delivery, and after your permission, your baby will be randomized (chosen by chance, like a flip of a coin) to one of two lung treatment strategies. The use of early CPAP and Intubation/Surfactant are both treatments currently used immediately after delivery at this hospital. The decision as which to use is currently made by the physician attending the delivery. The randomized treatments are as follows:

1) CPAP immediately after delivery continuing in the neonatal intensive care unit (NICU), or
2) The placement of a breathing tube (ETT) in the airway immediately after delivery followed by surfactant administration and assisted ventilation (breathing for the baby using a machine)
And,
3) Oxygen saturation levels (O2-SAT's) maintained between 85-89% (low range), or
4) Oxygen saturation levels (O2-SAT's) maintained between 91-95% (high range)
The box below indicates the 4 possible treatment combinations your infant can be randomized to.

CPAP and Higher range oxygen saturation	CPAP and Lower range oxygen saturation
Breathing tube + Surfactant and Higher range oxygen saturation	Breathing tube + Surfactant and Lower range oxygen saturation

The physician or nurse caring for your baby will not know which oxygen saturation group the baby is randomized to.

Your baby will remain on the specially modified O2-SAT monitor until he/she reaches 36 weeks corrected age (example: 24 weeks gestation plus 12 weeks of age = 36 weeks adjusted age) or until the monitor is no longer needed because your baby is in room air.

Other care will continue as normal during his/her participation in the study.

A secondary purpose to this study is to determine the longer term effect of different approaches to breathing and oxygen support in the very premature baby. In that regard, this study includes several other planned follow-up evaluations of all study baby's during the first two years of life including:

a. follow up at 6 and 12 months in our high-risk infant follow-up clinic
b. follow-up for subsequent lung problems
c. follow-up at 18-22 months of age for neurodevelopmental function (a complete exam of their muscles, nerves, mental and coordinated movement skills)
d. a comparison of currently applied radiology studies (MRI and Ultrasound) obtained at 36-42 weeks corrected gestation for predicting later neurodevelopmental function

Some of these follow-ups may be by phone and some may be in our special follow-up clinic for very premature infants. The costs of all follow-up evaluations and the MRI examination are covered by the NIH Neonatal Research Network.

Our study coordinator will keep track of how your baby is doing up to 40 weeks gestational age (the babies original due date) or until discharge. Once your baby reaches 36 weeks gestational age we will record if he/she is still being treated with oxygen and/or a ventilator. If your baby is still on nasal cannula oxygen we will try to wean him/her off the oxygen using a standard protocol. If he/she successfully weans off oxygen, your baby's medical team may decide to take him/her completely off oxygen. All information will have a code number and, after discharge, this information will be sent to the NICHD Neonatal Network's Data Collection center at Research Triangle Park, North Carolina.

A further planned follow-up will occur when your baby is about 6 – 7 years old. This will involve neurological, developmental and intelligence testing at a Follow-Up clinic appointment. With your permission we will maintain contact with you in order for your baby to attend the Follow Up appointment when he/she is in grade school.

Risks

All treatments proposed in this study are currently accepted standard of care. All of these treatment options may have risks but there is no known predictable increase in risk to your baby from any one approach. We don't know which approach to treatment is better or safer – that is why we are doing this study. Infants randomized to the CPAP group may, at some point in their care, require intubation and assisted ventilation. If the attending physician deems necessary, participating in this study will not effect this decision. Some unknown risks may be learned during the study. If this occurs, you will be informed by the study personnel. The only other risk in this study is the risk to confidentiality. Every effort will be made to keep your child's medical

record confidential. There will be no names or other patient identification in any study report that may be published after the study is complete. Measures taken to protect you and your baby's identity are described in the confidentiality.

Benefits

There may be benefits to your child directly, including a possible decrease in chronic lung disease (need for extra oxygen at discharge) and decrease in the need for eye surgery as a result of exposure to oxygen. However, we cannot promise any benefits to your baby from being in this study. The knowledge learned from this study may help us treat babies in the future.

Confidentiality

As an alternative to participation in this study you may decide to have your baby's doctor decide which treatment your baby will receive. If you decide not to include your baby in this study, none of his/her medical information will be included in the study data. Participation in research is entirely voluntary. You may refuse to participate or withdraw at any time without jeopardy to the medical care your baby will receive at this institution. Data collection for this study will stop at that time.

Person to Contact

If you have concerns or questions about this research or any related matter, you can contact the primary investigator, Dr. Bradley Yoder @ 801-581-7052 or co-investigator, Dr. Roger Faix@ 801-587-7500, in the Department of Pediatrics/Neonatology, University of Utah School of Medicine. After hours, please call the NICU directly (University Hospital: 801-581-2775; or Primary Children's Medical Center: 801-588-3800) and ask for the doctor on call. They will be able to answer your questions or contact the above investigators. If you believe your child has been harmed as a result of participation, or if you have any complaints or concerns, please contact the study team.

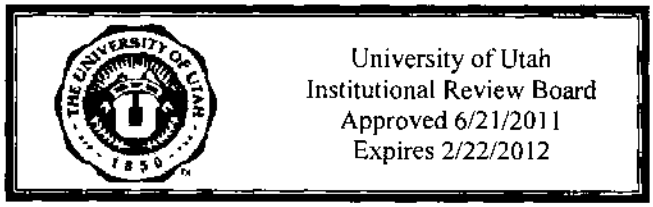
Institutional Review Board

Contact the Institutional Review Board (IRB) if you have questions regarding your child's rights as a research participant. Also, contact the IRB if you have questions, complaints or concerns which you do not feel you can discuss with the investigator. The University of Utah IRB may be reached by phone at (801) 581-3655 or by e-mail at irb@hsc.utah.edu.

Research Participant Advocate: You may also contact the Research Participant Advocate (RPA) by phone at (801) 581-3803 or by email at participant.advocate@hsc.utah.edu.

Research-Related Injury

If your infant is injured from being in this study, medical care is available at either the University of Utah Hospital or Primary Children's Medical Center, as it is to all sick or injured people. The University of Utah Hospital and Primary Children's Medical Center do not have a program to pay you if your infant is hurt or has other bad results from being in the study. The costs for any treatment or hospital care would be charged to you or your insurance company (if you have insurance), to the study sponsor or other third party (if applicable), to the extent those parties are responsible for paying for medical care you receive. Since this is a research study, some health insurance plans may not pay for the costs.



The University of Utah is a part of the government. If your child is injured in this study, and you want to sue the University or the doctors, nurses, students, or other people who work for the University, special laws may apply. The Utah Governmental Immunity Act is a law that controls when a person needs to bring a claim against the government, and limits the amount of money a person may recover. See Section 63G-7-101 to -904 of the Utah Code. .

Voluntary Participation
It is up to you to decide whether or not your baby will take part in this study. If you do decide to have him/her take part you will be asked to sign this consent form. You are free at any time to withdraw from this study without giving a reason. Whether your baby joins this study or not, your baby will receive the same medical and nursing care as needed and it will not affect the relationship you have with the investigator or other medical staff.

Unforeseeable Risks
The particular treatment or procedure may involve risks to the baby that are currently unforeseeable but because all of the treatments proposed in this study are standard of care, there is no unpredictable increase. If unknown risks are learned during the study, you will be informed by the study personnel. The only other risk of this study is a risk to confidentiality. Every effort will be made to keep your baby's medical record confidential.

Right of Investigator to Withdraw
Your baby may withdraw from the study at any time without penalty. Dr. Bradley Yoder or his associate investigators can withdraw your baby without your approval. Possible reasons for withdrawal include a need to transfer care to a different hospital not involved in this study or early termination of this study for safety considerations.

Costs to Subjects and Compensation
There is no cost to parents nor is there any compensation for participating in this study. Standard costs for care will be billed to you and your insurance company in the usual manner. The exception to this is that the cost of the MRI scan to be obtained at 36 weeks corrected age will be covered by study funds obtained from the NIH Neonatal Research Network and will not be billed to you.

New Information
Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, your research doctor will tell you about it and discuss with you whether you want to continue in the study. If you decide to continue your baby in the study, you will be asked to sign an updated permission form. Also, on receiving new information your research doctor might consider it to be in your baby's best interest to withdraw him/her from the study. They will explain the reasons and arrange your baby's care to continue.

Number of Subjects
We expect to include about 1310 babies in the study from the fifteen NICHD Neonatal Research Network hospitals over a two- year period. The University of Utah and LDS Hospital will enroll around 60 babies over the two year period.

Approval to Use Your Child's Protected Health Information

University of Utah
Institutional Review Board
Approved 6/21/2011
Expires 2/22/2012

Signing this document means you allow us, the researchers in this study, and others working with us to use information about your baby's health for this research study. You can choose whether or not to will participate in this research study. However, in order to participate you have to sign this consent and authorization form.

This is the information we will use:

- Name
- Address
- Telephone number
- Current and past medications or therapies
- Information from a physical examination, such as blood pressure reading, heart rate, breathing rate, and temperature
- Information related to the use of any device for support of lung function such as ventilator pressures, oxygen concentration and blood oxygen levels; any pertinent x-ray studies including head ultrasounds; information related to other neonatal diagnoses.

Others who will have access to your child's information for this research project are the University's Institutional Review Board (the committee that oversees research studying people) and authorized members of the University's and/or Primary Children's Medical Center workforce who need the information to perform their duties (for example: to provide treatment, to ensure integrity of the research, and for accounting or billing matters). The sponsor of the study does not have the right to inspect patient records.

If we share your child's information with anyone outside the University of Utah Health Sciences Center and/or Primary Children's Medical Center, your child will not be identified by name, social security number, address, telephone number, or any other information that would directly identify him/her, unless required by law. In records and information disclosed outside of the University of Utah Health Sciences Center and/or Primary Children's Medical Center, your child's information will be assigned a unique code number. We will keep the key to the code in a password protected computer. We will destroy the key to the code at the end of the research study.

You may revoke this authorization at any time. **This must be done in writing.** You must either give your revocation in person to the Principal Investigator or the Principal Investigator's staff, or mail it to Dr. Bradley A. Yoder, Department of Pediatrics/Neonatology, University of Utah School of Medicine, and PO Box 581289, Salt lake City, UT 84158-1289. If you revoke this authorization, we will not be able to collect new information about your child and they will be withdrawn from the research study. However, we can continue to use information we have already started to use in our research, as needed to maintain the integrity of the research. You have a right to information used to make decisions about your baby's health care. However, your baby's information from this study will not be available during the study; it will be available after the study is finished. This authorization lasts until this study is finished.

Consent

I confirm that I have read and understand this consent and authorization document and have had the opportunity to ask questions. I understand that my child's participation is voluntary and that I am free to withdraw my child at any time, without giving any reason, without my medical care or legal rights being affected. I will be given a signed copy of the consent and authorization form to keep.

I agree to allow my child to participate in this research study and permit you to use and disclose health information about my child for this study, as you have explained in this document.

_____
Child's Name

_____
1st Parent/Guardian's Name

_____ _____
1st Parent/Guardian's Signature Date

_____
Relationship to Child for 1st Parent/Guardian

_____
2nd Parent/Guardian's Name

_____ _____
2nd Parent/Guardian's Signature Date

_____
Relationship to Child for 2nd Parent/Guardian

Permission cannot be obtained from 2nd parent/guardian because *(please check which one applies to the situation. 45 CFR 46.408):*

____ The parent/guardian is deceased.
____ The parent/guardian is unknown.
____ The parent/guardian is incompetent.
____ The parent/guardian is not reasonably available.
____ Only one parent/guardian has legal responsibility for the care and custody of the child.

_____
Name of Person Obtaining Authorization and Consent

_____ _____
Name of Person Obtaining Authorization and Consent Date

La Prueba de Surfactante Positivo en las Vías Respiratorias y Oximetría del Pulso en Bebés de Peso Extremadamente Bajo al Nacer

Antecedentes

Siendo que hay una posibilidad que el nacimiento de su bebé se produzca entre las 24 y 27 semanas de gestación, le pedimos que permita la participación de su bebé en el estudio. Antes de decidir, es importante que entienda la razón por la que se hace esta investigación y qué es lo que incluirá. Por favor, tome tiempo para leer y discutir la información con amigos y familiares si así lo desea. Si hay algo que no está claro o desea recibir más información, pregúntenos a nosotros. Por favor, dedique tiempo para decidir voluntariamente si su bebé participará o no en este estudio investigativo.

Nuestro hospital está llevando a cabo este estudio en cooperación con el Instituto Nacional de Salud Infantil y Desarrollo Humano (NICHD por sus siglas en inglés), y la red de investigación del Recién Nacido, para tratar de determinar los medios óptimos para administrar soporte respiratorio temprano en bebés extremadamente prematuros (con el uso de CPAP o tubo de respiración) y así determinar el nivel de saturación de oxígeno adecuado (niveles de oxígeno en la sangre) en bebés extremadamente prematuros.

Procedimientos del Estudio

Previo al nacimiento, y después de su permiso, su bebé será elegido al azar (por sorteo, tal como escoger un lado de la moneda) para una de dos estrategias de tratamiento. El uso temprano de CPAP e intubación son tratamientos usados actualmente en este hospital después del parto. La decisión sobre cuál usar es hecha actualmente por el medico que atiende el parto. Los tratamientos al azar son los siguientes:

1) CPAP inmediatamente después del nacimiento, continuando en la Unidad Neonatal de Cuidado Intensivo (NICU), o
2) La inserción de un tubo de respiración (ETT) en las vías respiratorias inmediatamente después del parto seguido por la administración de surfactante y ventilación asistida (el bebé usando una máquina para respirar).
Y,
3) Oxígeno con niveles de saturación (O2-SAT's) mantenidos entre 85-89% (nivel bajo), o
4) Oxígeno con niveles de saturación (O2-SAT's) mantenidos entre 91-95% (nivel alto)
El cuadro de abajo indica las 4 combinaciones de tratamiento posibles que podría recibir al azar su bebé.

CPAP y Nivel Alto de Saturación de Oxígeno	CPAP y Nivel Bajo de Saturación de Oxígeno
Tubo de Respiración + Surfactante y Nivel Alto de Saturación de Oxígeno	Tubo de Respiración + Surfactante y Nivel Bajo de Saturación de Oxígeno

El médico o enfermera que atiendan a su bebé no sabrán cuál es el grupo de saturación de oxígeno al que su bebé ha sido sorteado al azar.

Su bebé permanecerá en el monitor especialmente modificado de O2-SAT hasta que alcance las 36 semanas de edad ajustada (por ejemplo: 24 semanas de gestación más 12 semanas de vida = 36 semanas de edad ajustada) o hasta que ya no sea necesario el monitor debido a que su bebé ya respira el aire común de la habitación..

Otros tipos de atención médica continuarán como es normal durante su participación en el estudio.

Un propósito secundario para este estudio es el de determinar el efecto a largo plazo de diferentes opciones para respirar y el soporte de oxigeno en bebés muy prematuros. En tal respecto, este estudio incluye varias otras evaluaciones de seguimiento de todos los estudios hechos al bebé durante los primeros dos años de vida, tales como:
a. Seguimiento a los 6 y 12 meses en nuestra clínica de bebés de alto riesgo.
b. Seguimiento por problemas pulmonares subsiguientes.
c. Seguimiento a los 18-22 meses de edad para las funciones de desarrollo neural (un examen completo de sus músculos, nervios, y habilidades de coordinación mental y movimientos)
d. Una comparación de estudios radiológicos actuales (Imagen por resonancia magnética (MRI) y Ultrasonido) obtenidos a las 36-42 semanas de gestación ajustada para predecir función de desarrollo neural posterior.

Algunos de esos seguimientos pueden ser por teléfono y algunos podrán ser en nuestra clínica de seguimiento especial para bebés extremadamente prematuros. Los costos de todas las

evaluaciones de seguimiento y el examen de MRI son cubiertos por la NIH Red investigativa del Recién Nacido.

Nuestro coordinador del estudio llevará la cuenta de cómo está su bebé hasta las 40 semanas de edad gestacional (la fecha probable de parto original) o hasta que sea dado de alta. Una vez que su bebé alcance las 36 semanas de edad gestacional se registrará si aún continua recibiendo tratamiento con oxígeno o con un ventilador. Si su bebé continúa con oxígeno a través de una cánula nasal, trataremos de quitarla usando un protocolo estándar. Si su bebé es desconectado exitosamente del oxígeno, el equipo medico puede decidir quitarle el oxígeno por completo. Toda la información tendrá un número codificado y, después de dar el alta, esta información será enviada al Centro de Recopilación de Información del Research Triangle Park, North Carolina.

Una continuación planeada adicional ocurrirá cuando su bebé es aproximadamente 6 – 7 años. Este implicará neurológico, del desarrollo y pruebas de inteligencia en una cita de clínica de Continuación. Con su permiso mantendremos el contacto con usted para su bebé para asistir a Seguir cita cuando él/ella está en la escuela primaria.

Riesgos
Todos los tratamientos propuestos en este estudio están actualmente aceptados como estándar de atención. Todas esas opciones de tratamientos pueden tener riesgos pero se desconoce un aumento predecible de riesgo para su bebé desde cualquier enfoque. No sabemos cuál de los enfoques de tratamiento es mejor o más seguro, ésa es la razón por la que estamos haciendo este estudio. Los bebés seleccionados al azar en el grupo de CPAP pueden, en alguna instancia de su atención, requerir intubación y ventilación asistida. Si el medico a cargo lo estima necesario, el participar en este estudio no afectará esta decisión. Algunos riesgos desconocidos pueden conocerse durante el estudio. Si esto ocurre, usted será informado por el personal del estudio. El único otro riesgo en este estudio es el riesgo a la confidencialidad. Se harán todos los esfuerzos para mantener confidencial la historia médica de su hijo/a. No habrá nombres u otra identificación del paciente en ningún informe del estudio que pueda ser publicado una vez que se ha completado el estudio. Las medidas que se tomarán para proteger su identidad y la del bebé son descriptas en la sección confidencialidad.

Beneficios
Pueden haber beneficios directos para su hijo/a, incluyendo la posibilidad de disminución de enfermedad pulmonar crónica (necesidad de oxígeno adicional al ser dado de alta) y disminución de la necesidad de cirugía de ojos como resultado de su exposición al oxígeno. Sin embargo, no podemos prometer ningún beneficio a su bebé por participar en este estudio. El conocimiento obtenido de este estudio puede ayudarnos en el tratamiento futuro de los bebés.

ConfidencialidadComo una alternativa a la participación en este estudio, usted puede decidir que el médico de su bebé que decida cuál tratamiento recibirá su bebé. Si usted decide que su

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bebé no sea incluido en este estudio, no se procesará información médica de su hijo/a en los datos del estudio. La participación en esta investigación es completamente voluntaria. Usted puede negarse a participar o retirarse en cualquier momento sin perjudicar la atención médica que recibirá su bebé en esta institución. La recopilación de información para este estudio será detenida en ese momento.

Persona a Contactar
Si tiene preguntas o preocupaciones acerca de esta investigación o relacionada con ella, usted puede contactar al investigador primario, el Dr. Bradley Yoder en el 801-581-7052 o al co-investigador, Dr. Roger Faix en el 801-587-7500, en el Departamento de Pediatría/Neonatología de la Escuela de Medicina de la Universidad de Utah. Fuera de hora, sírvase llamar directamente a la NICU (Hospital de la Universidad: 801-581-2775; o al Centro Médico Infantil de la Primaria: 801-588-3800) y pregunte por el doctor de guardia. Allí podrán responder a sus preguntas o contactar a alguno de los investigadores mencionados arriba.

Comité de Revisión Institucional
Si tiene preguntas con respecto a los derechos de su hijo/a como participante de la investigación, o si surgen problemas que cree no poder discutirlos con el Investigador, sírvase contactar a la Oficina del Comité de Revisión Institucional en el (801) 581-3655.

Abogado Participante en Investigación: Usted podría también contactar al Abogado Participante en Investigación (API) por teléfono al (801) 581-3803 o por correo electrónico a participant.advocate@hsc.utah.edu

Declaración de Responsabilidad de la Universidad
Si su hijo/a resulta herido por estar en este estudio, la Universidad de Utah puede darle atención médica a su hijo/a. Esta atención médica será dada inmediatamente por problemas de emergencia. La Universidad no le facturará por esta atención médica, pero podremos facturar al compañía de seguro médico si usted tiene seguro. Si usted firma este documento no está renunciando a su derecho de entablar acción legal contra la Universidad u otras compañías involucradas con esta investigación.
La Universidad de Utah es una parte del gobierno. Si su hijo/a resulta herido en este estudio, y usted quiere demandar a la Universidad o los doctores, enfermeras, estudiantes u otras personas que trabajan para la Universidad, pueden aplicarse leyes especiales. La ley de Inmunidad Gubernamental de Utah es una ley que controla cuando una persona necesita presentar una queja contra el gobierno, y limita el monto de dinero que puede recuperar una persona. Vea la Sección 63G -7-101 a la 63G-7-904 del Código de Utah. .

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Participación Voluntaria
Usted es quien decide si su bebé participa o no en este estudio. Si usted decide que participe, le será pedido que firme este formulario de consentimiento. Usted es libre de retirarlo de este estudio en cualquier momento y sin dar ninguna razón. Participe o no su bebé en este estudio,

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Expires 3/16/2011

recibirá la misma atención médica y de enfermería necesaria y no afectará la relación que tenga con el investigador u otro personal médico.

Riesgos Imprevisibles
El tratamiento o procedimiento particular puede involucrar riesgos al bebé que son imprevistos en este momento pero debido a que todos los tratamientos propuestos en este estudio son estándar en la atención médica, y no hay ningún aumento impredecible. Si riesgos desconocidos son descubiertos durante el estudio, usted será informado por empleados de la investigación. El único otro riesgo de este estudio es el de la confidencialidad. Se harán todos los esfuerzos necesarios para mantener confidencial la historia médica de su bebé.

Derecho del Investigador para Retirarle del Estudio
Su bebé puede retirarse del estudio en cualquier momento y sin penalidad alguna. El Dr. Bradley Yoder o sus investigadores asociados pueden retirar a su bebé sin necesidad que usted lo apruebe. Las razones probables para retirarle incluyen la necesidad de transferir su atención médica a otro hospital no involucrado en este estudio o por terminación anticipada de este estudio debido a consideraciones de seguridad.

Costos y Compensación para los Participantes
No hay ningún costo ni compensación para los padres por participar en este estudio. La Red Investigativa del Recién Nacido NIH cubrirá los costos por la participación de su bebé en este estudio.

Información Nueva
Algunas veces durante el curso de un proyecto de investigación surge información nueva sobre el tratamiento que está siendo estudiado. Si esto sucede, su doctor investigador le informará acerca de ello y discutirá con usted si aún desea continuar en el estudio. Si usted decide que su bebé continúe, se le pedirá que firme un formulario de permiso actualizado. También, al recibir información nueva el doctor investigador podría considerar que para su mejor interés haya que retirarlo/a del estudio. Ellos explicarán las razones y harán los arreglos para que continúe la atención médica de su bebé.

Número de Participantes
Durante el período de dos años esperamos incluir en el estudio alrededor de1300 bebés de los quince hospitales de la Red Investigativa del Recién Nacido NICHD. La Universidad de Utah y el Hospital LDS enrolarán alrededor de 60 bebés durante el mismo período de dos años.

Aprobación para usar la Información Protegida de la Salud de su Hijo/a.
Al firmar este documento significa que usted nos permite a nosotros, los investigadores en este estudio, y otros trabajando con nosotros el uso de la información sobre la salud de su bebé para este estudio investigativo. Usted puede escoger si participa o no en este estudio investigativo.

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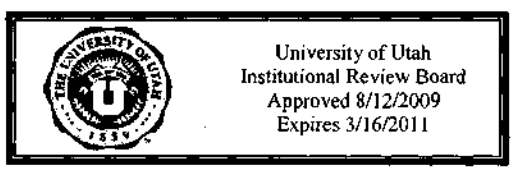

Sin embargo, para participar usted tiene que firmar este formulario de consentimiento y autorización.

Esta es la información que utilizaremos:
Nombre
Dirección
Número de teléfono.
Tratamientos y medicamentos actuales o anteriores.
Información sobre un examen físico, tale como lectura de la presión arterial, frecuencia cardíaca, frecuencia respiratoria, y temperatura.
La información relacionada con el uso de algún aparato para soporte de funcionamiento pulmonar tal como ventilador a presión, concentrador de oxígeno, y niveles de oxígeno en la sangre, y algún estudio radiológico pertinente incluyendo ultrasonidos de la cabeza, e información relacionada con otros diagnósticos del recién nacido.

Otros que tendrán acceso a la información de su hijo/a para este proyecto investigativo son el Comité de Revisión Institucional de la Universidad (el comité que supervisa los estudios investigativos sobre personas) y miembros autorizados y personal de la Universidad y/o del Centro Médico Infantil de la Primaria que necesitan la información para desempeñar sus tareas (por ejemplo: proveer tratamiento, asegurar la integridad de la investigación, y por asuntos de contabilidad o facturación). El patrocinador de este estudio no tiene el derecho a inspeccionar la historia médica de los pacientes.

Si compartimos la información de su hijo/a con alguien fuera del Centro de Ciencias de la Salud de la Universidad de Utah y/o del Centro Médico Infantil de la Primaria, su hijo/a no será identificado por su nombre, número de Seguridad Social, dirección, número de teléfono o cualquier otra información que podría identificarle directamente, a menos que sea requerido por ley. En los registros e información divulgada afuera del Centro de Ciencias de la Salud de la Universidad de Utah y/o Centro Médico Infantil de la Primaria, a la información de su hijo/a le será asignado un número codificado único. Nosotros guardaremos la clave al código en una computadora protegida por una contraseña. Al finalizar el estudio investigativo destruiremos la clave al número codificado.

Usted puede revocar esta autorización en cualquier momento. **Esto debe ser hecho por escrito.** Usted puede entregar su revocación ya sea en persona al Investigador Principal o a su personal, o enviarla por correo dirigida a: Bradley A. Yoder, Department of Pediatrics/Neonatology, University of Utah School of Medicine, y PO Box 581289, Salt lake City, UT 84158-1289. Si usted revoca esta autorización, no podremos reunir información nueva sobre su hijo/a y éste/a será retirado del estudio investigativo. Sin embargo, nosotros podemos continuar usando la información que ya hemos comenzado a usar en nuestra investigación, según sea necesario para mantener la integridad de la investigación.

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Institutional Review Board
Approved 8/12/2009
Expires 3/16/2011

Usted tiene el derecho a la información usada para hacer decisiones sobre la atención médica de su bebé. Sin embargo, la información de su bebé obtenida para este estudio no estará disponible durante el curso del mismo. Lo estará después que se haya finalizado con este estudio. Esta autorización dura hasta que el estudio haya sido finalizado.

Consentimiento
Confirmo que he leído y entendido este documento de consentimiento y autorización y que se me ha dado la oportunidad de hacer preguntas. Entiendo que la participación de mi hijo/a es voluntaria y que soy libre de retirarle en cualquier momento sin dar ninguna razón, y sin que mi atención médica o derechos legales sean afectados. Me será dada una copia firmada de este documento de consentimiento y autorización para guardar en mi poder.

Estoy de acuerdo en permitir a mi hijo que participe en este estudio investigativo yles permito usar y divulger la información sobre la salud de mi hijo/a para este estudio, así como ha sido explicado en este documento.

_____
Nombre del niño/a

_____
Nombre del 1er. Padre o tutor

_____ _____
Firma del 1er. Padre o tutor. Fecha

_____
Parentesco del niño/a con el 1er. Padre/tutor.

_____
Número del 2do. Padre/tutor

_____ _____
Firma del 2do. Padre o Tutor Fecha

_____
Parentesco del niño/a con el 2do. Padre/tutor

El permiso no se puede obtener del 2do. Padre/tutor
(Sírvase chequear cuál de ellos se aplica a la situación. 45 CFR 46.408):

____ El padre/tutor ha fallecido.

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University of Utah
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Approved 8/12/2009
Expires 3/16/2011

____ Se desconoce quién es el padre/tutor
____ El padre/tutor es incompetente.
____ El padre/tutor no está razonablemente disponible.
____ Sólo uno del padre/tutor tiene la responsabilidad legal de dar custodia al niño/a.

_____
Nombre de la persona que obtiene el Consentimiento y autorización.

_____ _____
Nombre de la persona que obtiene el Consentimiento y Autorización. Fecha

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From: Rich, Wade
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: Approved UCSD Consent (dated 5/1/08) scanned to PDF for project 080603
Date: Friday, January 20, 2012 4:21:59 PM
Attachments: 080603_2011_07_22_UCSD_Consent1.PDF
SUPPORT - Spanish Consent.pdf

English and Spanish copies of most current consent.

-----Original Message-----
From: hrpp@ucsd.edu [mailto:hrpp@ucsd.edu]
Sent: Friday, January 20, 2012 1:15 PM
To: Finer, Neil; Rich, Wade
Subject: Approved UCSD Consent (dated 5/1/08) scanned to PDF for project 080603

A letter with details is attached in PDF format.

DTF1200

PATIENT INFORMATION

University of California, San Diego

Parent Informed Consent

The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

The SUPPORT Trial of the NICHD Neonatal Research Network

This is a research study. Research studies include only subjects who choose to take part. You are being asked to to allow your child to be in the study because there is a possibility he/she will be born between 16 and 12 weeks early (24-28 weeks gestational age). Please take your time to make your decision. Discuss it with your family. Be sure to ask any questions that you may have.

STUDY INVESTIGATOR AND SPONSOR

Investigator(s): Neil Finer, MD
Sponsor: **Eunice Shriver National Institute of Child Health and Human Development**

WHY IS THIS STUDY BEING DONE?

This reasons this study is being done are:

1) To compare infants who receive delivery room CPAP (Continuous Positive Airway Pressure – a **commonly used method of keeping babies lungs expanded with increased airway pressure)** and who have strict guidelines for having a breathing tube placed with infants who have the tube placed and surfactant (a liquid which helps babies with immature lungs breath easier by helping keep their lungs from collapsing) given in the delivery room.
2) To compare low range (85-89%) oxygen saturation levels with high range (91-95%) levels to determine if a lower range results in decreased ROP (Retinopathy of Prematurity, an eye disease that may result in impairment of vision or even blindness, which may be

5-1-08
5-1-08
4-30-09
7 Pgs

4-12678

caused by excessive levels of oxygen.)

WHAT MAKES THIS DIFFERENT FROM THE USUAL TREATMENT?

The use of CPAP and Intubation/Surfactant are both treatments currently used in the delivery room at UCSD. The decision as to which to use is currently made by the physician attending the delivery.

The oxygen level currently used in the NICU at UCSD is between 85% and 95%. Both treatment groups (85-89% and 91-95%) fall within that range. The study will attempt to keep babies in one of these two smaller ranges.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

50 subjects will be in this study at UCSD, and a total of 1310 nationwide at 16 other academic medical centers.

HOW LONG WILL YOUR CHILD BE IN THE STUDY?

Your child will be in the study for 18-22 months. The part of the study which uses either CPAP or Intubation and Surfactant lasts for 14 days. The part which keeps your baby in one of two levels of oxygen continues until your baby no longer need oxygen, or reach 36 weeks adjusted age. (A baby who was born at 24 weeks gestation will reach 36 weeks adjusted age 12 weeks after birth.) The follow-up part of the study that will see how your baby is doing developmentally will take place at 18-22 months. The NICHD is currently considering following infants in the SUPPORT trial until school age (6-7 years). This consent will include your permission to contact you at that time to re-evaluate you child's development. Because this will occur for some children after 7 years of age, we would also ask your child for their assent at that time.

You can stop your child's participating at any time. However, if you decide to stop your child from participating in the study, we encourage you to talk to the research doctor.

WHAT IS INVOLVED IN THE STUDY?

This is what will happen if your child participates in this study:

Prior to delivery, and after your permission, your baby will be randomized (chosen by chance like the flip of a coin) to one of two lung treatment strategies. The treatments are as follows:
1) CPAP in the delivery room immediately after birth and continuing in the NICU, or
2) The placement of a tube in his/her trachea (windpipe) in the delivery room followed by

surfactant administration and ventilation (breathing for the baby using a machine)
And,
In addition to being randomly assigned to one of the two groups described above, your baby will be randomized to a High reading or Low reading oximeter [a monitor that displays how much oxygen is in the blood.] The oximeters (oxygen monitors) used in this trial are FDA approved oximeters which have been modified for research purposes. This modification makes the monitors show a value which is either slightly higher or slightly lower than the true oxygen level when values are between 85 and 95%. Outside those ranges, the oximeter works the same as the standard of care device.
Which group your baby is randomized to will not be known to the nurse taking care of your baby, or his/her physician. Only the study coordinator will know which group your baby is in. Within the range of oxygen which we normally keep babies in, your baby will either be on the high end of normal or the low end of normal. He/she will remain on this device until he/she reaches 36 weeks adjusted age. (e.g. 24 wks gestation plus 12 weeks of age = 36 weeks adjusted age.) Other care will be conducted as normal during his/her participation in the study.

Your baby will be followed in our Infant Follow-up clinic at 6 and 12 months as standard of care for small babies. At 18-22 months corrected age your baby will receive, at no charge to you, a complete exam of their muscles, nerves, and mental and coordinated movement skills.

We will continue to stay in touch with you and your infant by telephone or in person at one of your visits every 6 months over the next 18-22 months, a total of three times.

WHAT ARE THE RISKS OF THE STUDY?

Participation in this study may involve some added risks or discomforts. Because all of the treatments proposed in this study are standard of care, there is no predictable increase in risk for your baby. Infants randomized to the CPAP group may, at some point in their care, require intubation and assisted ventilation (methods to help them breathe). If the attending physician thinks this is necessary, participation in the study will not affect this decision. Some unknown risks may be learned during the study. If these occur, you will be informed by the study personnel. The only other risk of this study is the risk to confidentiality. Every effort will be made to keep your child's medical record confidential. There will be no name or other patient identification in any study report that may be published after the study is completed. Measures taken to protect you and your baby's identity are described in the confidentiality section of this document.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?
There may be benefits to your child directly, including a possible decrease in chronic lung disease (need for extra oxygen near discharge) and/or a decrease in the need for eye surgery as a result of exposure to oxygen. Because we do not know in advance the actual

strategies chosen for your child, or which of the treatment strategies is the most effective, it is also possible that your baby will receive no direct benefit. The knowledge learned from this study may help us treat babies in the future. However, as noted above, each of the 4 possible combinations of treatments is considered by some units to represent their desired approach.

WHAT OTHER OPTIONS ARE THERE?

As an alternative to participation in this study you may decide to have your baby's doctor decide which treatment your baby will receive. If you decide not to include your child in this study, none of his/her medical information will be included in the study data. Participation in research is entirely voluntary. You may refuse to participate or withdraw at any time without jeopardy to the medical care your child will receive at this institution of other loss of benefits to which your child is entitled. If you withdraw your child from the study, the attending physician will decide whether to maintain current treatment or change it, based on your child's needs at the time of the decision. Data collection for research purposes will stop at that time.

CAN YOUR CHILD BE REMOVED FROM THE STUDY WITHOUT YOUR CONSENT?

Your child's participation in this study may be ended without your consent by the investigator or your baby's doctor if it is in your child's best medical interest, there is a lack of effect, or for other reasons. If your newborn leaves the study early, he/she will continue with whichever treatment the doctor feels is best.

WHAT ABOUT CONFIDENTIALITY?

Every reasonable effort will be made to keep your child's records confidential. Clinical information will be collected from your baby's chart by study personnel at UCSD. Information will be labeled with a code number. Coded information will be sent to the NICHD Neonatal Network's Data Collection Center at Research Triangle Institute (RTI) in Research Triangle Park, North Carolina. The study log linking the code number with your baby's identity will be kept under lock and key at UCSD. Information directly identifying your baby will not leave UCSD. Research records will be kept confidential to the extent provided by law.Your child's records and information will not be released without your consent to the extent the law allows. If the study results are published or presented, your child will not be identified.

WHAT ARE THE COSTS?

There are no costs to participate in this trial.

WHAT IF YOUR CHILD IS INJURED IN THE STUDY?

If your child is injured as a direct result of participation in this research, the University of California will provide any medical care your child needs to treat those injuries. The University will not provide any other form of compensation to you if your child is injured. You may call the UCSD Human Research Protections Program office at (858) 455-5050 for more information about this, or to inquire about your rights as a research subject, or to report research-related problems.

_____ has explained this study to you and answered your questions. If you have other questions or research-related problems, you may reach Wade Rich, the Study Coordinator, or Renee Bridge, the Research Nurse, at 619-543-3759. You may contact the principal investigator Dr. Neil Finer at 619-543-3794

WILL YOU OR YOUR CHILD BE COMPENSATED?

Neither you nor your child will receive compensation for participation in this trial.

WHO DO YOU CALL IF YOU OR YOUR CHILD HAVE QUESTIONS OR PROBLEMS?

For questions about the study or a research-related injury, contact the researcher:

Neil Finer, MD
619-543-3794

WHAT ARE YOUR CHILD'S RIGHTS AS A RESEARCH SUBJECT?

Taking part in this study is voluntary. You may choose not to let your child take part or you or your child may choose to leave the study at any time. Your decision will not result in any penalty or loss of benefits to which your child is entitled. If you have questions about your child's rights you may call:

University of California, San Diego
Human Research Protections Program
(858) 455-5050

You will be told about any new information that may affect your child's health, welfare, or willingness to stay in this study.

SIGNATURE AND CONSENT TO BE IN THE STUDY:

Your signature below means that you have read the above information about the _____ study and have had a chance to ask questions to help you understand

what your child will do in this study and how your child's information will be used.

You or your child can change your minds later if you want to. You will be given a copy of this consent form and a copy of the Subject's Bill of Rights. By signing this consent form you are not giving up any of your or your child's legal rights.

NAME OF PARTICIPANT	AGE
SIGNATURE OF PARENT OR GUARDIAN	DATE
SIGNATURE OF 2nd PARENT OR GUARDIAN	DATE
SIGNATURE OF WITNESS (person explaining this form)	DATE

SUBJECT'S BILL OF RIGHTS

It is important that the purpose and procedures of the research study are fully understood and that consent is offered willingly. A subject in a research study or someone, who is asked to give consent on behalf of another person for such participation, has the right to:

1. Be informed of the nature and purpose of the research.

2. Be given an explanation of all procedures to be followed and of any drug or device to be used.

3. Be given a description of any risks or discomforts, which can be reasonably expected to result from this research study.

4. Be given an explanation of any benefits, which can be reasonably expected to the subject as a result of this research study.

5. Be informed of any appropriate alternative procedures, drugs, or devices that may be advantageous and of their relative risks and discomforts.

6. Be informed of any medical treatment, which will be made available to the subject if complications should arise from this research.

7. Be given an opportunity and encouraged to ask any questions concerning the study or the procedures involved in this research.

8. Be made aware that consent to participate in the research may be withdrawn and that participation may be discontinued at any time without affecting continuity or quality of medical care.

9. Be given a copy of the signed and dated written consent form if requested.

10. Not be subjected to any element of force, fraud, deceit, duress, coercion, or any influence in reaching the decision to consent or to not consent to participate in the research.

If you have any further questions or concerns about your child's rights as a research subject, please contact your research doctor, the Children's Hospital Office for Human Subjects Protection at (858) 966-4008 or the UCSD Human Research Protections Program.

DTF1200

INFORMACIÓN DEL

University of California, San Diego

Consentimiento con información de los padres

Estudio de investigación sobre el uso de surfactante para la presión positiva en las vías respiratorias y oximetría de pulso en bebés con peso extremadamente bajo al nacer

Estudio SUPPORT de la Red de Investigación Neonatal de NICHD

Éste es un estudio de investigación. Los estudios de investigación sólo incluyen a sujetos que eligen participar. Se le pide que permita la participación de su hijo(a) en el estudio porque existe la posibilidad de que éste nazca entre 16 y 12 semanas antes de la fecha prevista (entre las 24 y 28 semanas de edad gestacional). No se apresure en tomar una decisión, analícelo con su familia y asegúrese de hacer todas las preguntas que pueda tener.

PATROCINADOR E INVESTIGADOR DEL ESTUDIO

Investigadores: Dr. Neil Finer, (MD)
Patrocinador: **Eunice Shriver National Institute of Child Health and Human Development**

¿POR QUÉ SE REALIZA ESTE ESTUDIO?

Las razones por las que se realiza este estudio son:

1) Para comparar a bebés que reciben presión positiva continua en las vías respiratorias (CPAP, por sus sigas en inglés; **un método utilizado comúnmente para mantener los pulmones de los bebés expandidos con mayor presión de las vías respiratorias**), en la sala de partos y para quienes se tienen estrictas pautas sobre la colocación de un tubo para respirar, con los bebés a los que se les colocó el tubo y se les administró surfactante (un líquido que ayuda a los bebés, cuyos pulmones no están maduros, a respirar con mayor facilidad, al evitar que los pulmones se colapsen), en la sala de partos.

2) Para comparar los niveles de saturación de oxígeno de bajo rango (85 a 89%) con los niveles de saturación de oxígeno de alto rango (91 a 95%), a fin de determinar si un rango menor tiene como resultado una disminución de la retinopatía del prematuro o ROP, una enfermedad de la vista que puede tener como consecuencia vista defectuosa o incluso ceguera, la que puede ser causada por niveles excesivos de oxígeno.

¿QUÉ DISTINGUE A ESTE TRATAMIENTO DEL TRATAMIENTO HABITUAL?

En la actualidad, los tratamientos de CPAP e intubación y surfactante se usan en la sala de partos en UCSD, y es el médico que atiende el parto quien decide cuál usar.

El nivel de oxígeno usado actualmente en la UCIN (Unidad de cuidados intensivos neonatales) en UCSD es de entre un 85% y un 95%. Ambos grupos de tratamiento (85 a 89% y 91 a 95%) están dentro de ese rango. El estudio procurará mantener a los bebés en uno de estos dos rangos menores.

¿CUÁNTAS PERSONAS PARTICIPARÁN EN EL ESTUDIO?

En este estudio en UCSD participarán 50 sujetos, y un total de 1310 en todo el país en otros 16 centros médicos académicos.

¿CUÁNTO TIEMPO ESTARÁ SU HIJO(A) EN EL ESTUDIO?

Su hijo(a) participará en el estudio durante un período de 18 a 22 meses. La parte del estudio en que se usa CPAP o intubación y surfactante dura 14 días. La parte en que se mantiene a su bebé en uno de los dos niveles de oxígeno continúa hasta que éste ya no necesite oxígeno o cumpla la edad ajustada de 36 semanas (un bebé que nació a las 24 semanas de gestación cumplirá la edad ajustada de 36 semanas 12 semanas después del parto). La parte de seguimiento del estudio en que se observará cómo evoluciona el desarrollo de su bebé se realizará entre los 18 y 22 meses. El NICHD está considerando actualmente realizar el seguimiento de los bebés en el estudio SUPPORT hasta la edad escolar (6 a 7 años). Este consentimiento incluirá su permiso para comunicarse con usted en ese momento a fin de volver a evaluar el desarrollo de su hijo(a). Debido a que esto ocurrirá para algunos niños después de los 7 años, también le solicitaríamos a su hijo(a) su asentimiento en ese momento.

Puede suspender la participación de su hijo(a) en cualquier momento. Sin embargo, si decide hacerlo, le instamos a que hable con el médico de la investigación.

¿QUÉ IMPLICA EL ESTUDIO?

Esto es lo que sucederá si su hijo(a) participa en este estudio:

Antes del parto, y después de que usted lo autorice, se elegirá una de las dos estrategias de tratamiento pulmonar que recibirá su bebé en forma aleatoria (al azar, como cuando se arroja una moneda al aire). Los tratamientos son los siguientes:
1) CPAP en la sala de partos, inmediatamente después del nacimiento y continuación en la UCIN, o
2) Colocación de un tubo en la traquea (conducto por el cual pasa el aire hacia los pulmones) en la sala de parto, seguida de la administración de surfactante y ventilación (el bebé respirará usando una máquina).
Además,
Aparte de ser asignado en forma aleatoria a uno de los dos grupos descritos anteriormente, se asignará a su bebé en forma aleatoria a un oxímetro (un monitor que muestra la cantidad de oxígeno que hay en la sangre) de lectura alta o baja. Los oxímetros (monitores de oxígeno) usados en este estudio están aprobados por la FDA y se modificaron para fines de la investigación. Esta modificación hace que los monitores muestren un valor que es ligeramente más alto o más bajo que los verdaderos niveles de oxígeno cuando los valores están entre 85 y 95%. Fuera de esos rangos, el oxímetro funciona igual que el dispositivo que se usa para el estándar de atención.
La enfermera o el médico que atienden a su bebé no sabrán a qué grupo se asignó en forma aleatoria al bebé, esto sólo lo sabrá el coordinador del estudio. Dentro del rango de oxígeno en el que normalmente mantenemos a los bebés, su bebé estará, ya sea en el extremo alto o bien, en el extremo bajo de lo normal. El bebé permanecerá conectado a este dispositivo hasta que cumpla la edad ajustada de 36 semanas. (por ejemplo, 24 semanas de gestación más 12 semanas de edad = edad ajustada de 36 semanas). El resto de la atención se realizará en forma normal durante su participación en el estudio.

Se le hará un seguimiento a su bebé en nuestra Clínica de Seguimiento de Bebés a los 6 y 12 meses de acuerdo al estándar de atención para bebés de bajo peso. A la edad corregida de 18 a 22 meses su bebé recibirá, sin costo para usted, un examen completo de sus músculos, nervios y habilidades mentales y de movimiento coordinado.

Seguiremos comunicándonos con usted y su bebé por teléfono o personalmente en una de sus consultas cada 6 meses durante los siguientes 18 a 22 meses, un total de tres veces.

¿CUÁLES SON LOS RIESGOS DE ESTE ESTUDIO?

La participación en este estudio puede implicar algunos riesgos o molestias adicionales. Debido a que todos los tratamientos propuestos en este estudio son estándares de atención, no existe un aumento predecible en los riesgos para su bebé. Los bebés asignados en forma aleatoria al grupo CPAP pueden, en algún momento de su atención, requerir intubación o ventilación asistida (métodos para ayudarles a respirar). Si el médico adjunto considera que esto es necesario, la participación en el estudio no afectará esta decisión. Se pueden descubrir algunos riesgos desconocidos durante el estudio. Si sucede esto, el personal del estudio se lo informará. El único riesgo adicional de este estudio es el de confidencialidad. Se hará todo lo posible para mantener la

confidencialidad de la historia clínica de su hijo(a). No se colocará ningún nombre u otra identificación del paciente en ningún informe del estudio que pueda ser publicado después de terminar el estudio. En la sección de confidencialidad de este documento se describen las medidas tomadas para proteger su identidad y la del bebé.

¿HAY BENEFICIOS POR PARTICIPAR EN EL ESTUDIO?

Puede haber beneficios directos para su bebé, incluidos una posible disminución en la enfermedad pulmonar crónica (necesidad de oxígeno adicional cerca del alta hospitalaria) o la necesidad de cirugía ocular como resultado de la exposición al oxígeno. Debido a que no sabemos con anticipación las estrategias reales elegidas para su hijo(a), o cuál de las estrategias de tratamiento es la más eficaz, también es posible que su bebé no reciba ningún beneficio directo. La información que obtengamos de este estudio puede ayudarnos a tratar a los bebés en el futuro. Sin embargo, como se indica antes, algunas unidades consideran que cada una de las 4 combinaciones posibles de tratamientos representa el enfoque deseado.

¿EXISTE ALGUNA OTRA OPCIÓN?

Como una alternativa a su participación en este estudio usted puede determinar que sea el médico de su bebé quien decida el tratamiento que éste recibirá. Si decide no incluir a su hijo(a) en este estudio, no se incluirá su información médica en los datos del estudio. La participación en esta investigación es completamente voluntaria. Puede negarse a participar o retirarse del estudio en cualquier momento, sin que esto afecte la atención médica que su hijo(a) recibirá en esta institución o sin que pierda beneficios a los cuales tiene derecho. Si retira a su hijo(a) del estudio, el médico adjunto decidirá si mantener el tratamiento actual o cambiarlo, en base a las necesidades de su hijo(a) en el momento de tomar la decisión. La recopilación de datos con fines de investigación se suspenderá en ese momento.

¿SE PUEDE RETIRAR A SU HIJO(A) DEL ESTUDIO SIN SU CONSENTIMIENTO?

El investigador o el médico de su bebé pueden retirar a su hijo(a) de este estudio sin el consentimiento de usted, si es lo más conveniente para su hijo(a) desde el punto de vista médico, si no se obtiene el efecto deseado o por otras razones. Si su recién nacido deja el estudio antes, su tratamiento, cualquiera que sea, continuará si el médico considera que es lo mejor.

¿QUÉ SUCEDE CON LA CONFIDENCIALIDAD?

Se hará todo lo razonable para mantener los expedientes de su bebé con carácter de confidencial. El personal del estudio en UCSD recopilará la información clínica de la historia clínica de su bebé, la que se etiquetará con un número de código. La información codificada se enviará al Centro de Recopilación de Datos de la Red Neonatal de NICHD

en Research Triangle Institute (RTI), ubicado en Research Triangle Park, Carolina del Norte. El registro del estudio que vincula el número de código con la identidad de su bebé se mantendrá guardado con llave, bajo estricta reserva, en UCSD. La información que identifica directamente a su bebé no saldrá de UCSD. Los registros de la investigación se mantendrán con carácter de confidencial en la medida que lo permita la ley. Los registros y la información de su bebé no se divulgarán sin el consentimiento de usted, en la medida que lo permita la ley. Si se publican o presentan los resultados del estudio, su hijo(a) no será identificado(a).

¿CUÁLES SON LOS COSTOS?

No hay costos por participar en este estudio.

¿QUÉ PASA SI SU HIJO(A) SE LESIONA EN EL ESTUDIO?

Si su hijo(a) se lesiona como resultado directo de su participación en esta investigación, University of California le proporcionará la atención médica necesaria para tratar dichas lesiones. La Universidad no le proporcionará ninguna otra forma de indemnización si su hijo(a) resulta lastimado(a). Para obtener más información con respecto a esto, consultar sobre los derechos que tiene como sujeto de investigación o para informar sobre problemas relacionados con la investigación, puede llamar a la oficina del Programa de Protección para la Investigación en Seres Humanos de UCSD al (858) 455-5050.

_____ le explicó este estudio y respondió a sus preguntas. Si tiene otras preguntas o problemas relacionados con la investigación, puede comunicarse con el coordinador del estudio Wade Rich, o con la enfermera de la investigación Renee Bridge, al 619-543-3759. Puede comunicarse con el investigador principal, el Dr. Neil Finer al 619-543-3794.

¿RECIBIRÁ USTED O SU HIJO(A) UNA REMUNERACIÓN?

Ni usted ni su hijo(a) recibirán remuneración por la participación en este estudio.

¿A QUIÉN DEBE LLAMAR SI USTED O SU HIJO(A) TIENE PREGUNTAS O PROBLEMAS?

Si tiene preguntas sobre el estudio o las lesiones relacionadas con éste, comuníquese con el investigador:

Neil Finer, MD
619-543-3794

¿CUÁLES SON LOS DERECHOS DE SU HIJO(A) COMO SUJETO DE INVESTIGACIÓN?

La participación en este estudio es voluntaria. Puede decidir que su hijo(a) no participe en el estudio o usted o su hijo(a) puede elegir retirarse del mismo en cualquier momento. Su decisión no tendrá como consecuencia ninguna sanción ni pérdida de beneficios a los que su hijo(a) tenga derecho. Si tiene preguntas sobre los derechos de su hijo(a), puede llamar a:

University of California, San Diego
Programa de Protección para la Investigación en Seres Humanos
(858) 455-5050

Le daremos a conocer toda información nueva que pueda afectar la salud y el bienestar de su hijo(a) o la buena voluntad de permanecer en el estudio.

FIRMA Y CONSENTIMIENTO PARA PARTICIPAR EN EL ESTUDIO:

Su firma a continuación significa que usted leyó la información anterior acerca del estudio _____ y que tuvo la oportunidad de hacer preguntas para comprender qué es lo que hará su hijo(a) en el estudio y cómo se usará la información de su hijo(a).

Usted o su hijo(a) puede cambiar de opinión más adelante si lo desea. Se le entregará una copia de este formulario de consentimiento y una copia de la Declaración de derechos de los sujetos para que las guarde en su poder. Al firmar este formulario de consentimiento no renuncia a ninguno de sus derechos legales ni a los de su hijo(a).

_____	_____
NOMBRE DEL PARTICIPANTE	EDAD
_____	_____
FIRMA DEL PADRE, LA MADRE O EL TUTOR	FECHA
_____	_____
FIRMA DEL 2º PADRE O MADRE, O DEL TUTOR	FECHA
_____	_____
FIRMA DEL TESTIGO (persona que explica este formulario)	FECHA

DECLARACIÓN DE DERECHOS DE LOS SUJETOS

Es importante que el propósito y los procedimientos del estudio de investigación se entiendan completamente, y que el consentimiento se dé en forma voluntaria. El participante en un estudio de investigación, o a quien se le pide que dé su consentimiento en nombre de otra persona para dicha participación, tiene derecho a:

1. ser informado de la naturaleza y el propósito de la investigación;

2. recibir explicaciones de todos los procedimientos que se realizarán y de cualquier medicamento o dispositivo que se vaya a usar;

3. recibir una descripción de todos los riesgos o las molestias que se puedan esperar razonablemente como consecuencia de este estudio de investigación;

4. recibir una explicación sobre los beneficios que el sujeto puede esperar como resultado de este estudio de investigación;

5. recibir información sobre todos los procedimientos, medicamentos y dispositivos alternativos que resulten ventajosos, así como también de sus riesgos y molestias relativos;

6. recibir información sobre todos los tratamientos que el sujeto pueda tener a disposición si surgen complicaciones producto de esta investigación;

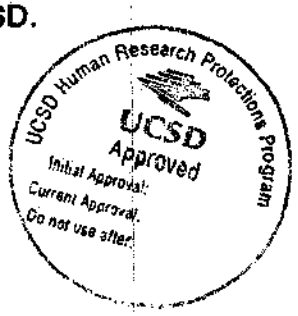
7. que se le dé una oportunidad para formular preguntas relacionadas con el estudio o con los procedimientos que implica esta investigación, además de que se le aliente a hacerlo;

8. saber que puede retirar en cualquier momento este consentimiento para participar en la investigación, y que también se puede interrumpir su participación sin afectar la continuidad ni la calidad de la atención médica;

9. recibir una copia del formulario de consentimiento escrito, firmado y fechado, si la solicita;

10. no estar sujeto a elementos de presión, fraude, engaño, coacción, coerción ni a ninguna influencia que le obligue a dar o a no dar el consentimiento para la participación en la investigación.

Si tiene cualquier otra pregunta o inquietud acerca de los derechos de su hijo(a) como sujeto de investigación, comuníquese con el médico de la investigación o con la Oficina para la Protección de Sujetos Humanos de Children's Hospital al (858) 966-4008 o al Programa de Protección para la Investigación en Seres Humanos de UCSD.



From: Rich, Wade
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)
Date: Friday, January 20, 2012 4:08:16 PM
Attachments: 080603_2011_02_04_approve.pdf

As we are not enrolling in support, the protocol is approved (see attached), but we no longer have an active consent.

wade

From: Finer, Neil
Sent: Friday, January 20, 2012 12:54 PM
To: Rich, Wade
Subject: FW: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)

Can you send this to Rose please?

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, January 20, 2012 11:42 AM
To: Finer, Neil
Cc: Maddox, Yvonne (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Hirschfeld, Steven (NIH/NICHD) [E]
Subject: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)

Neil-

As you are aware the Neonatal Research Network (NRN) continues to support studies under common protocols, but which require individual institutional IRB review prior to the conduct of these studies at each of the NRN sites. This is to inform you that The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), which provided the Federal support to the NRN, has been requested by the Office of Human Subjects Protection, to provide to the Office the most current consent form approved by your IRB and the corresponding IRB approval for the main SUPPORT Study, including any revisions, as soon as possible. As the NICHD Program Director of the NRN, I am requesting that the most recent consent form with IRB approval for your site for SUPPORT be submitted to me as soon as possible, but no later than January 26, 2012. Thank you for your cooperation.

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

080603

UNIVERSITY OF CALIFORNIA, SAN DIEGO
HUMAN RESEARCH PROTECTIONS PROGRAM

TO: Dr. Neil Finer Mailcode: 8774

RE: Project #080603
Project #041069 The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants The SUPPORT Trial of the NICHD Neonatal Research Network * Renewal - Previous Project # 041069

Dear Dr. Finer:

The above-referenced project was reviewed and approved by one of this institution's Institutional Review Boards in accordance with the requirements of the Code of Federal Regulations on the Protection of Human Subjects (45 CFR 46 and 21 CFR 50 and 56), including its relevant Subparts. This approval, based on the degree of risk, is for 365 days from the date of **IRB review and approval** unless otherwise stated in this letter. The regulations require that continuing review be conducted on or before the 1-year anniversary date of the IRB approval, even though the research activity may not begin until some time after the IRB has given approval.

The IRB has reviewed this protocol in accordance with the guidelines on research involving children as research subjects and has found that this project meets the requirements as stated in 45 CFR 46.406 in that: this research represents a minor increase over minimal risk; the procedure presents experiences to the child subjects that were reasonably commensurate with those inherent in their actual, or expected medical, dental, psychological, social, or educational situations; the procedure is likely to yield generalizable knowledge about the subject's disorder or condition which is of vital importance for the understanding or amelioration of the disorder or condition; and adequate provisions exist on seeking the assent of the children and permission of the parents or guardians, as set forth in HHS regulations at 45 CFR 46.408.

Since the study is closed to accrual, consent forms are not enclosed.

Date of IRB review and approval: **2/3/2011**

On behalf of the Institutional Review Board,

/cp

Michael Caligiuri, Ph.D.
Director, Human Research Protections Program
(858) 455-5050

Note: All Human Subject research conducted at the VA facility and/or utilizing VA/VMRF funds MUST BE APPROVED by the VA Research and Development Committee prior to commencing any research. In addition, please ensure that the clinical trial agreement or other funding is appropriately in place prior to conducting any research activities.

IRB approval does not constitute funding **or other institutional required approvals.** Should your studies involve other review committees such as Conflict of Interest (COI), Protocol Review Monitoring Committee (PRMC), and committees under Environmental Health & Safety (EH&S) such as Institutional Biosafety Committee (IBC), Human Exposure Committee (HERC), and RSSC (Radiation Safety and Surveillance Committee), it is the researchers responsibility to ensure that all approvals are in place prior to conducting research involving human subjects or their related specimens.

Approval release date: 2/4/2011

UCSD HUMAN RESEARCH PROTECTIONS PROGRAM

GENERAL APPROVAL INFORMATION

The information below does not encompass all human subjects protections requirements, however, is intended to highlight those of significance to ensure awareness by researchers engaged in research involving human subjects or their related specimens and data.

Approval Letters and Consent Documents

Unless otherwise stated, approval letters will be accompanied by stamped, approved consents. Should a study be closed to accrual and no consent released as a result, this information will be documented on the approval letter. Also, any waivers will be documented in the approval letter (such as waiver of documented consent or waiver of authorization for use of PHI).

All Human Subject research conducted at the VA facility and/or utilizing VA/VMRF funds MUST BE APPROVED by the VA Research and Development Committee prior to commencing any research. In addition, the PI must ensure approval is in place from other appropriate review boards (such as Radiation Safety, Institutional Biosafety Committee, Conflict of Interest, ESCRO, etc.)

If other institutions are involved, the PI must ensure that IRB approvals (or other administrative approvals) from those sites are secured and forwarded for the study file. In addition, PI's must ensure that the clinical trial agreement, as applicable, or other funding (such as a grant) is appropriately in place prior to conducting any research activities. IRB approval does not constitute funding approval.

Duration of IRB approval

The IRB may grant approval up to 365 days. (See 45 CFR 46.109(d) (DHHS) and 21 CFR 56.109(d) (FDA)). However, for some studies the committee may grant approval for a lesser period or a specific number of subjects to allow for more frequent monitoring. The approval letter or related documentation will indicate this information.

Because IRB review of research studies must be completed at least annually, investigators should plan ahead to meet required continuing review dates. **Please submit complete continuing review documentation at least 45 days prior to the expiration date to guard against a lapse in IRB approval.** The signed continuing review facepages and any other required hard copies must be received by the HRPP office before the continuing review process can begin.

As a courtesy, automated continuing review reminders can be set-up by PIs at various intervals (75 days, 45 days, 30 days, for example) on the website at https://irb.ucsd.edu. However, as these are automated electronic messages based on data entered, and the HRPP cannot anticipate which type of software programs (such as spam-blockers or anti-virus software) may block receipt of the messages, **PI's are required to not rely upon notification, but have internal mechanisms which track continuing review submission times**. Ultimately, it is the PI's responsibility to initiate a continuing review application, allowing sufficient time for the review and re-approval process to be completed before the current approval expires.

Continuing review is required even if no changes are made, or if the only study activity is participant follow-up, and even if the only study activity is data analysis.

What happens if there is a lapse in IRB approval?

If the IRB has not reviewed and approved a research study by the study expiration date, **all research activities must stop**. This includes the following:

All research-related interventions or interactions with currently enrolled subjects (unless the IRB finds that it is in the best interests of the individual subjects to continue participating in the research interventions or interactions;*) recruitment and informed consent procedures; and continued collection and/or analysis of data/information.

**Exception:* Research-related interventions or interactions with enrolled subjects may continue if the IRB determines that stopping the research would jeopardize the rights or welfare of current subjects. The IRB will decide which subjects should continue receiving the intervention during the lapse in approval. A request for such an exception must be submitted in writing to the attention of the IRB Chair by the Principal Investigator. If any project activity—even activity required for participant safety—occurs or continues after the expiration date, the investigator is out of compliance with both federal regulations and university policy. Retrospective approval for work done after the expiration date cannot be granted. For studies involving the VA, additional conditions apply. See VA Handbook 1200.5, Investigator Responsibilities, http://www1.va.gov/vhapublications/ViewPublication.asp?pub_ID=418.

Amendment/revision to an IRB approved study

IRB approval is required before implementing any changes in the approved research plan, consent documents, recruitment materials, or other study-related documents. Please see Amendment Fact Sheet at http://irb.ucsd.edu/amendmodchg.pdf for submission guidance.

Adverse Event and Unanticipated Problems Reporting

All problems having to do with subject safety must be reported to the IRB within ten working days. All deaths, whether or not they are directly related to study procedures, must be reported. For adverse events, please utilize the form found at http://irb.ucsd.edu/AE_biomedical_plain.doc. For deviations and other reports, a cover letter and any supplemental information appropriate to the review should be provided. Please see IRB Guidelines for more information at https://irb.ucsd.edu.

Changes in financial Interest or Conflict of Interest (COI) disclosure

Any changes in the financial relationship between the study sponsor and any of the investigators on the study and/or any new potential conflicts of interest must be reported immediately to the Independent Review Committee via the Conflict of Interest Office. If these changes affect the conduct of the study or result in a change in the required wording of the approved consent form, then these changes must also be submitted as an amendment request.

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "wrich@ucsd.edu"
Subject: Re: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)
Date: Friday, January 20, 2012 4:11:16 PM

Please send the most recent consent form from the main SUPPORT trial

Thanks
Rose

From: Rich, Wade [mailto:wrich@ucsd.edu]
Sent: Friday, January 20, 2012 04:08 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)

As we are not enrolling in support, the protocol is approved (see attached), but we no longer have an active consent.
wade

From: Finer, Neil
Sent: Friday, January 20, 2012 12:54 PM
To: Rich, Wade
Subject: FW: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)

Can you send this to Rose please?

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, January 20, 2012 11:42 AM
To: Finer, Neil
Cc: Maddox, Yvonne (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Hirschfeld, Steven (NIH/NICHD) [E]
Subject: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)

Neil-
As you are aware the Neonatal Research Network (NRN) continues to support studies under common protocols, but which require individual institutional IRB review prior to the conduct of these studies at each of the NRN sites. This is to inform you that The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), which provided the Federal support to the NRN, has been requested by the Office of Human Subjects Protection, to provide to the Office the most current consent form approved by your IRB and the corresponding IRB approval for the main SUPPORT Study, including any revisions, as soon as possible. As the NICHD Program Director of the NRN, I am requesting that the most recent consent form with IRB approval for your site for SUPPORT be submitted to me as soon as possible, but no later than January 26, 2012. Thank you for your cooperation.

Rosemary D. Higgins, MD
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301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Bell, Edward (Pediatrics)"
Cc: Maddox, Yvonne (NIH/NIMHD) [E]; Hirschfeld, Steven (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]
Subject: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)
Date: Friday, January 20, 2012 2:42:00 PM

Ed

As you are aware the Neonatal Research Network (NRN) continues to support studies under common protocols, but which require individual institutional IRB review prior to the conduct of these studies at each of the NRN sites. This is to inform you that The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), which provided the Federal support to the NRN, has been requested by the Office of Human Subjects Protection, to provide to the Office the most current consent form approved by your IRB and the corresponding IRB approval for the main SUPPORT Study, including any revisions, as soon as possible. As the NICHD Program Director of the NRN, I am requesting that the most recent consent form with IRB approval for your site for SUPPORT be submitted to me as soon as possible, but no later than January 26, 2012. Thank you for your cooperation.

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301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Michael O`Shea
Cc: Maddox, Yvonne (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Hirschfeld, Steven (NIH/NICHD) [E]
Subject: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)
Date: Friday, January 20, 2012 2:41:00 PM

Mike -

As you are aware the Neonatal Research Network (NRN) continues to support studies under common protocols, but which require individual institutional IRB review prior to the conduct of these studies at each of the NRN sites. This is to inform you that The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), which provided the Federal support to the NRN, has been requested by the Office of Human Subjects Protection, to provide to the Office the most current consent form approved by your IRB and the corresponding IRB approval for the main SUPPORT Study, including any revisions, as soon as possible. As the NICHD Program Director of the NRN, I am requesting that the most recent consent form with IRB approval for your site for SUPPORT be submitted to me as soon as possible, but no later than January 26, 2012. Thank you for your cooperation.

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Blansfield, Earl (NIH/NICHD) [E]

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Friday, January 20, 2012 2:41 PM
To: 'Kennedy, Kathleen A'; 'Tyson, Jon E'
Cc: Spong, Catherine (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NIMHD) [E]; Hirschfeld, Steven (NIH/NICHD) [E]
Subject: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)

Kathleen and Jon
As you are aware the Neonatal Research Network (NRN) continues to support studies under common protocols, but which require individual institutional IRB review prior to the conduct of these studies at each of the NRN sites. This is to inform you that The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), which provided the Federal support to the NRN, has been requested by the Office of Human Subjects Protection, to provide to the Office the most current consent form approved by your IRB and the corresponding IRB approval for the main SUPPORT Study, including any revisions, as soon as possible. As the NICHD Program Director of the NRN, I am requesting that the most recent consent form with IRB approval for your site for SUPPORT be submitted to me as soon as possible, but no later than January 26, 2012. Thank you for your cooperation.

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: mcw3@cwru.edu
Cc: Spong, Catherine (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]; Hirschfeld, Steven (NIH/NICHD) [E]
Subject: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)
Date: Friday, January 20, 2012 2:40:00 PM

Michele -

As you are aware the Neonatal Research Network (NRN) continues to support studies under common protocols, but which require individual institutional IRB review prior to the conduct of these studies at each of the NRN sites. This is to inform you that The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), which provided the Federal support to the NRN, has been requested by the Office of Human Subjects Protection, to provide to the Office the most current consent form approved by your IRB and the corresponding IRB approval for the main SUPPORT Study, including any revisions, as soon as possible. As the NICHD Program Director of the NRN, I am requesting that the most recent consent form with IRB approval for your site for SUPPORT be submitted to me as soon as possible, but no later than January 26, 2012. Thank you for your cooperation.

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Shankaran, Seetha"
Cc: Maddox, Yvonne (NIH/NIMHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Hirschfeld, Steven (NIH/NICHD) [E]
Subject: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)
Date: Friday, January 20, 2012 2:40:00 PM

Seetha

As you are aware the Neonatal Research Network (NRN) continues to support studies under common protocols, but which require individual institutional IRB review prior to the conduct of these studies at each of the NRN sites. This is to inform you that The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), which provided the Federal support to the NRN, has been requested by the Office of Human Subjects Protection, to provide to the Office the most current consent form approved by your IRB and the corresponding IRB approval for the main SUPPORT Study, including any revisions, as soon as possible. As the NICHD Program Director of the NRN, I am requesting that the most recent consent form with IRB approval for your site for SUPPORT be submitted to me as soon as possible, but no later than January 26, 2012. Thank you for your cooperation.

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higginsr@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Wally Carlo, M.D."
Cc: Maddox, Yvonne (NIH/NIMHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Hirschfeld, Steven (NIH/NICHD) [E]
Subject: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)
Date: Friday, January 20, 2012 2:40:00 PM

Wally-

As you are aware the Neonatal Research Network (NRN) continues to support studies under common protocols, but which require individual institutional IRB review prior to the conduct of these studies at each of the NRN sites. This is to inform you that The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), which provided the Federal support to the NRN, has been requested by the Office of Human Subjects Protection, to provide to the Office the most current consent form approved by your IRB and the corresponding IRB approval for the main SUPPORT Study, including any revisions, as soon as possible. As the NICHD Program Director of the NRN, I am requesting that the most recent consent form with IRB approval for your site for SUPPORT be submitted to me as soon as possible, but no later than January 26, 2012. Thank you for your cooperation.

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Pablo.Sanchez@UTSouthwestern.edu
Cc: Spong, Catherine (NIH/NICHD) [E]; Hirschfeld, Steven (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]
Subject: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)
Date: Friday, January 20, 2012 2:40:00 PM

Pablo-

As you are aware the Neonatal Research Network (NRN) continues to support studies under common protocols, but which require individual institutional IRB review prior to the conduct of these studies at each of the NRN sites. This is to inform you that The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), which provided the Federal support to the NRN, has been requested by the Office of Human Subjects Protection, to provide to the Office the most current consent form approved by your IRB and the corresponding IRB approval for the main SUPPORT Study, including any revisions, as soon as possible. As the NICHD Program Director of the NRN, I am requesting that the most recent consent form with IRB approval for your site for SUPPORT be submitted to me as soon as possible, but no later than January 26, 2012. Thank you for your cooperation.

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Barbara Stoll"
Cc: Maddox, Yvonne (NIH/NIMHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Hirschfeld, Steven (NIH/NICHD) [E]
Subject: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)
Date: Friday, January 20, 2012 2:39:00 PM

Barbara

As you are aware the Neonatal Research Network (NRN) continues to support studies under common protocols, but which require individual institutional IRB review prior to the conduct of these studies at each of the NRN sites. This is to inform you that The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), which provided the Federal support to the NRN, has been requested by the Office of Human Subjects Protection, to provide to the Office the most current consent form approved by your IRB and the corresponding IRB approval for the main SUPPORT Study, including any revisions, as soon as possible. As the NICHD Program Director of the NRN, I am requesting that the most recent consent form with IRB approval for your site for SUPPORT be submitted to me as soon as possible, but no later than January 26, 2012. Thank you for your cooperation.

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Duara, Shahnaz"
Cc: Maddox, Yvonne (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Hirschfeld, Steven (NIH/NICHD) [E]
Subject: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)
Date: Friday, January 20, 2012 2:39:00 PM

Shahnaz-

As you are aware the Neonatal Research Network (NRN) continues to support studies under common protocols, but which require individual institutional IRB review prior to the conduct of these studies at each of the NRN sites. This is to inform you that The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), which provided the Federal support to the NRN, has been requested by the Office of Human Subjects Protection, to provide to the Office the most current consent form approved by your IRB and the corresponding IRB approval for the main SUPPORT Study, including any revisions, as soon as possible. As the NICHD Program Director of the NRN, I am requesting that the most recent consent form with IRB approval for your site for SUPPORT be submitted to me as soon as possible, but no later than January 26, 2012. Thank you for your cooperation.

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Kurt Schibler"
Cc: Maddox, Yvonne (NIH/NIMHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Hirschfeld, Steven (NIH/NICHD) [E]
Subject: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)
Date: Friday, January 20, 2012 2:38:00 PM

Kurt-

As you are aware the Neonatal Research Network (NRN) continues to support studies under common protocols, but which require individual institutional IRB review prior to the conduct of these studies at each of the NRN sites. This is to inform you that The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), which provided the Federal support to the NRN, has been requested by the Office of Human Subjects Protection, to provide to the Office the most current consent form approved by your IRB and the corresponding IRB approval for the main SUPPORT Study, including any revisions, as soon as possible. As the NICHD Program Director of the NRN, I am requesting that the most recent consent form with IRB approval for your site for SUPPORT be submitted to me as soon as possible, but no later than January 26, 2012. Thank you for your cooperation.

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Ehrenkranz, Richard"
Cc: Maddox, Yvonne (NIH/NIMHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Hirschfeld, Steven (NIH/NICHD) [E]
Subject: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)
Date: Friday, January 20, 2012 2:38:00 PM

Richard-

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Kristi Watterberg"
Cc: Maddox, Yvonne (NIH/NIMHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Hirschfeld, Steven (NIH/NICHD) [E]
Subject: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)
Date: Friday, January 20, 2012 2:37:00 PM

Kristi-

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Krisa Van Meurs; dstevenson@stanford.edu
Cc: Maddox, Yvonne (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Hirschfeld, Steven (NIH/NICHD) [E]
Subject: SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)
Date: Friday, January 20, 2012 2:36:00 PM

Krisa and David -

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From: Pablo Sanchez
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: support consent form
Date: Friday, January 20, 2012 11:45:23 AM
Attachments: English%20-Add%20Luc%20Lijun%20LeVan-delete%20fellows%20-%20clean[1].docx

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The University of Texas Southwestern Medical Center at Dallas
Parkland Health & Hospital System and Children's Medical Center

CONSENT TO PARTICIPATE IN RESEARCH

Title of Research: The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

Sponsor: National Institute of Child Health and Human Development Neonatal Research Network

Investigators:	Telephone No. (regular office hours)	Telephone No. (other times)
Pablo J. Sánchez, MD	214-648-3753	972-(b)(6)
Luc P. Brion, MD	214-648-2060	972-
Lijun Chen, RN, PhDDiana Vasil,	214-648-3780	214-
RNC-NIC	214-648-3789	972-
Lizette Torres, RN	214-456-2585	972-
Roy Heyne, MD	214-648-3753	972-
Jaclyn LeVan, MD	214-648-2098	972-
Alicia Guzman	214-456-8041	972-

INVITATION: You/your newborn infant are invited to participate in this research because there is a possibility he/she will be born 12 to 16 weeks early and could possibly develop a lung problem called bronchopulmonary dysplasia (an abnormal formation of the lungs in premature infants leading to a need for oxygen treatment for a long time) and an eye problem called retinopathy of prematurity (an eye disease that may result in poor vision or loss of sight in premature infants), which may be caused by high oxygen treatment.

Medical research involves offering a plan of care to a group of patients, collecting and studying information about each patient's experience, and using that information to develop the best possible care for future patients.

NUMBER OF PARTICIPANTS: The sponsor plans to include 1300 newborn infants in the study from all the National Institute of Child Health and Human Development Neonatal Research Network hospitals over a two-year period.

PURPOSE: This study has three purposes and they are:
1) To compare newborn infants, in the delivery room, who receive breathing support through their nose with a cannula with newborn infants who have a tube placed in their windpipe (a process called intubation) and surfactant (a liquid which helps babies with immature lungs breathe easier by keeping their lungs from collapsing) given in the first hour of life.

2) To compare newborn infants, in the intensive care nursery, treated with low range (85-89%) oxygen saturation levels (a measure of the amount of oxygen in the blood) with newborn infants treated with high range oxygen saturation (91-95%) levels.

3) To measure the effects of the oxygen therapies used in the study on the growth of premature infants.

PROCEDURES
Breathing support through the nose with a cannula blowing air (also called nasal continuous positive airway pressure), or intubation with surfactant are both treatments currently used in the delivery room at Parkland Health and Hospital System. The decision to use one or the other on any newborn infant is made by the doctor who is in the delivery room.

Screening: The study doctor will ask you questions on whether you are admitted to the hospital in premature labor and

whether we can approach you to be in this study.

Randomization: If you agree for your newborn infant to be in this study, your infant will be randomized (chosen by chance like the flip of a coin) to one of two lung treatment groups:

1) Nasal continuous positive airway pressure through the nose or the mouth in the delivery room immediately after birth and continuing in the intensive care nursery, or
2) The placement of a tube in his/her windpipe in the delivery room followed by giving surfactant and mechanical ventilation (breathing for the baby using a machine).

After admission to the intensive care nursery, your newborn infant will also be randomized to a low or a high oxygen saturation group using a specially designed oximeter (a monitor that displays blood oxygen level).

Your infant will have a 1 in 4 chance of being in one of these groups:

Group 1: the nasal continuous positive airway pressure /low saturation,
Group 2: the nasal continuous positive airway pressure /high saturation,
Group 3: oral intubation with surfactant/low saturation, or
Group 4: oral intubation with surfactant/ high saturation.

Treatment:

Groups 1 and 2 (nasal continuous positive airway pressure):
Delivery Room Care: In the delivery room the doctor resuscitating your newborn infant will try using nasal continuous positive airway pressure on your baby. If your baby responds to nasal continuous positive airway pressure, he/she will continue on nasal continuous positive airway pressure and will be transferred to the intensive care nursery. If your baby does not improve with nasal continuous positive airway pressure, the doctor resuscitating your baby will intubate your baby in the delivery room. If intubated in the delivery room, your infant will receive one dose of surfactant within one hour of life. Your infant may receive more than one dose of surfactant in his/her first day of life, but your infant's doctor, based on your infant's condition, will decide this.

Care in the Neonatal Intensive Care Nursery: The doctor may intubate your infant if he/she believes your infant is not doing well on the nasal continuous positive airway pressure. The study sponsor has guidelines for your infant intubation or extubation (the process of removing the tube from the windpipe) to safeguard your infant. Your infant's doctor will follow the sponsor guidelines for intubating or extubating your infant in the first two weeks of life. However, if your infant requires intubation three times, he/she will be out of the study and further intubations or extubations will be decided solely by your infant's doctor. After two weeks of life all intubations and extubations are decided only by your infant's doctor.

Groups 3 and 4 (oral intubation with surfactant):
Delivery Room Care: In the delivery room, the doctor resuscitating your newborn infant will place a tube in his/her windpipe after delivery and will give a dose of surfactant in the first hour of life. Your infant will be transported to the intensive care nursery on a breathing machine.

Care in the Neonatal Intensive Care Nursery: Your newborn infant will be admitted to the intensive care nursery on a breathing machine. The study sponsor has specified guidelines for the first two weeks of life at which your infant will be taken off the breathing machine and your infant's doctor will follow those criteria to decide on extubating your infant. Once your infant is extubated for the first time, further intubations or extubations will be decided only by his/her doctor.

All study infants will be placed on the study oximeter within two hours of birth. (An oximeter is an object placed on the skin to measure oxygen in the blood). Which oxygen saturation group your infant is randomized to will not be known to the nurse taking care of your infant, or his/her doctor. Only the study coordinator will know which group your infant is in. However, your infant will either be on the high end or the low end of the normal oxygen saturation that we normally use in our intensive care nursery. Your infant will remain on the study oximeter until he/she reaches 36 weeks adjusted age (e.g. 24 wks gestation plus 12 wks of age = 36 wks adjusted age) or until he/she is discharged home.

We will measure your infant's weight, length, and head at birth, day of life 7, 14, 21, 28, and at 32 and 36 wks of age and at home discharge to evaluate the effects of the study procedures on his/her growth.

All other care will be conducted as normal during your infant's participation in the study. The studies to be done on your baby's blood will be performed on blood already drawn in the standard care and no additional blood draws will be done for the research. Your baby will be followed in our infant follow-up clinic at Children's Medical Center after discharge from the intensive care nursery as we usually do for all babies his/her size.

Follow-up after discharge from the Neonatal Intensive Care Nursery: At the time of a regular follow-up visit, following your infant's discharge from the NICU, our follow-up staff (Dr. Roy Heyne or his designee) will interview you (or your designee) to find out about your child's diet, breathing problems in the family, and things in the home that may increase your child's risk of breathing problems. This interview will take about 15 minutes and will include questions about the air quality at your home, your home location, your infant's exposure to infections, your family history of asthma and allergies, and any recent hospital or doctor office visits. You do not need to answer any questions that make you uncomfortable. The follow-up staff will be in touch with you and your infant, either by telephone or in person at one of your follow-up visits every 6 months for a total of three times. At these times, they will ask questions about your child's breathing (especially wheezing and coughing), medication use, and visits to a Doctor, Emergency Room, or Hospital for treatment of breathing problems. They will also ask you several questions about things in the home or day care setting that may affect your child's breathing. The entire call should take about 15 minutes of your time, less if your baby has had no breathing problems. If your infant is followed in the Low Birth Weight Clinic at Children's Medical Center, the follow-up staff will arrange to meet you during the clinic visit to ask you these questions. Otherwise, they will schedule the telephone calls at a time that is convenient for you. The telephone calls will occur when your infant is 6, 12, and 18 months after his/her expected delivery at full term. The results from your baby's questionnaire will be combined with those of other infants from around the country. However, your baby's name will not be used.

At 18-22 months of age your baby will receive, at no charge, a complete exam of their muscles, nerves, intelligence and motor function. We will also measure his/her weight, length, and head size. This exam is done at the Children's Medical Center Follow-up Clinic.

Evaluations during the Research: Dr. Sánchez and his research staff will closely monitor your infant's response to the study in the delivery room and in the intensive care nursery. Dr. Sánchez and his research staff will review your infant's medical record to gather information on your infant's date, time and place of birth, delivery room events, birth weight, length, head circumference, age at birth, gender, results of lab tests performed by your infant's doctor, results of the physical exam performed by your infant's doctor, type and name of medicines your infant receives during his hospitalization, duration and

type of respiratory support and mechanical ventilation, duration and degree of oxygen therapy, complications during hospitalization, amounts of milk and intravenous nutrition, duration of hospital stay, results of the head ultrasounds performed during the hospital stay (head ultrasounds, also called head sonograms, are pictures taken of the baby's brain by

a special machine that is brought to the baby's bedside), results of the eye exam performed during the hospital stay, results of the neurologic exams and the Bayley tests performed in the follow-up clinic(the neurologic and Bayley tests are a complete evaluation of your infant's muscles, nerves, intelligence, and motor function). Dr. Roy Heyne and his research staff will review the results of the interview to gather information on your infant breathing problems and conditions that may affect his/her breathing following the study.

Investigational Procedures: The oximeters (oxygen monitors) used in this trial are FDA approved oximeters, but have been modified for this study. The FDA is a government agency that oversees new drugs and medical equipment.

POSSIBLE RISKS

All the treatments in this study are currently used in the intensive care nursery and most infants born at the same age as your infant will receive all those treatments during their stay in the intensive care nursery.

The risk of intubation includes injury to your infant's throat and windpipe, but this is unusual. The risk of surfactant treatment includes bleeding in the lung but this is rare. Infants receiving nasal continuous positive airway pressure in the delivery room may have problems breathing and their heart-beat may abnormally slow down. If this happens to your infant, your infant's doctor in the delivery room will intubate your infant and place him/her on a breathing machine. Infants placed on nasal continuous positive airway pressure for a long time, may have damage to their nose; our nurses and doctors are very aware of this possible problem and are careful to prevent it. The weight, length, and head measurements of your infant are performed by experienced nurses and do not add any risk. Some unknown risks may be learned during the study. If these occur, you will be informed by the study personnel.

Following discharge from the NICU, you (or your designee) will be involved in a series of interviews about factors related to your child's breathing; and while answering interview questions you may experience some anxiety or emotional discomfort; but you do not have to answer questions you do not feel comfortable responding to.

Another risk of this study is the risk to confidentiality. Every effort will be made to keep your infant's medical record confidential. There will be no name or other patient identification in any study report that may be published after the study is completed. Measures taken to protect you and your infant's identity are described in the confidentiality section.

Blood samples: Your infant will have the same amount of blood collected whether your infant receives standard medical care for your infant's health problems or participates in this research. Therefore, your infant's risk of complications from collecting the blood is the same.

Your infant may experience discomfort, bleeding and/or bruising. On a rare occasion, an infection could develop at the site where the blood was collected.

Unforeseen risks: A previously unknown problem could result from your newborn infant's participation in this research. It is not possible to estimate the changes of such problems or how serious problems could be.

POSSIBLE BENEFITS

Benefit to your infant: Your study doctor cannot guarantee that your newborn infant will benefit from participation in this research.

Benefit to other premature infants: The information learned from this study may help us better treat premature infants in the future. However, your infant's study doctor will not know whether there are benefits to other premature infants until all of the information obtained from this research has been collected and analyzed.

ALTERNATIVES TO YOUR INFANT'S PARTICIPATION IN THIS RESEARCH: Your infant does not have to participate in this research to receive care for your infant's medical problem. If you decide not to participate in this research, your infant will receive the standard of care at Parkland Health and Hospital System and Children's Medical Center intensive care nurseries. The standard of care at the Parkland Health and Hospital System and Children's Medical Center neonatal intensive care nurseries varies with the attending doctor taking care of your infant and may be similar to any of the above 4 groups of therapies that the research is studying.

Please ask your infant's study doctor as many questions as you wish. The doctor's answers to your questions could help you decide whether your infant will participate in this research or receive the standard care that is currently available for your infant's medical problem.

If you decide now that your infant will participate in research, and later change your mind, your infant may stop participation in the research then and receive the standard of care.

THE STUDY DOCTOR'S DECISION TO STOP YOUR INFANT'S PARTICIPATION: Your infant's study doctor or the sponsor may stop your infant's participation in this research without your or your infant's permission under any one of the following conditions:

- Your infant's study doctor believes participation in the research is no longer safe for your infant.
- Your infant's study doctor believes that other treatments may be more helpful.
- The sponsor or the FDA stops the research for the safety of the participants.
- The sponsor cancels the research.

PROCEDURES AFTER STOPPING PARTICIPATION IN THIS RESEARCH: If you, the study doctor, or the sponsor stops your infant's participation in the research, it is your responsibility to do the following:

- Let the study doctor know immediately that you wish that your infant withdraw from the research.
- Return to the research center for tests that may be needed for your infant's safety.
- Discuss your infant's future medical care with the study doctor and/or your infant's regular doctor.

INCENTIVE TO TAKE PART IN THIS RESEARCH: You will not be paid for your infant's participation in this research.

COSTS TO YOU: The sponsor will pay the expenses for the neurodevelopmental testing (tests that evaluate the function of nerves, muscles and intelligence of your infant) which are part of the research.

Expenses related to standard medical care for prematurity are your responsibility (or the responsibility of your insurance provider or government program). Since nasal continuous positive airway pressure, intubation, mechanical ventilation, surfactant treatment, and the use of a pulse oximeter are all part of the routine care of preterm infants, the research will not pay for those therapies.

You, your insurance or your government program will be responsible for the cost of delivery room care, the costs of the day-to-day care in the intensive care nursery, the using cost of all respiratory equipments (mechanical ventilation machine, nasal continuous positive airway machine, pulse oximeter) used in the day-to-day care of your infant, and the costs of the daily physician care.

COMPENSATION FOR INJURY: Compensation for an injury resulting from your infant's participation in this research is not available from the University of Texas Southwestern Medical Center at Dallas, Children's Medical Center, or Parkland Health & Hospital System. You and your infant retain your legal rights during your infant's participation in this research.

VOLUNTARY PARTICIPATION IN RESEARCH: You and your infant have the right to agree to or refuse participation in this research. If you decide that your infant will participate and later change your mind, you are free to discontinue participation in the research at any time.

Your refusal to participate in this research will involve no penalty or loss of benefits to which you and your infant are otherwise entitled. Your refusal to participate in this research will not affect your legal rights or the quality of health care that you and your infant receive at this center.

NEW INFORMATION: Any new information which becomes available during your infant's participation in the research and may affect your infant's health and safety or your willingness for your infant to continue in the research will be given to you.

RECORDS OF YOUR INFANT'S PARTICIPATION IN THIS RESEARCH: You and your infant have the right to privacy. Any information about you or your infant that is collected for this research will remain confidential as required by law. In addition to this consent form, you will be asked to sign an "Authorization for Use and Disclosure of Protected Health Information for Research Purposes."

YOUR QUESTIONS: Your infant's study doctor, Dr. Pablo J. Sánchez and his research staff are available to answer your questions about this research; and Dr. Roy Heyne and his research nurse, Lizette Torres, RN, are available to answer questions about the breathing interview. The Chairman of the IRB is available to answer questions about your rights and your infant's rights as a participant in research or to answer your questions about an injury or other complication resulting from your infant's participation in this research. You may telephone the Chairman of the IRB during regular office hours at 214-648-3060.

YOU WILL HAVE A COPY OF THIS CONSENT FORM TO KEEP.

Your signature below certifies the following:

- You have read (or been read) the information provided above.
- You have received answers to all of your questions.
- You have freely decided that your infant may participate in this research.
- You understand that you and your infant are not giving up any of your legal rights.

_____
Participant's Name (printed)

_____
Legally authorized representative's name (printed)

_____ _____
Legally authorized representative's signature Date

_____
Name of person obtaining consent (printed)

_____ _____
Signature of person obtaining consent Date

From: Buchanan, Lisa (HHS/OASH)
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: "SUPPORT Trial" (HHS Protocol 2U10HD034216)
Date: Friday, January 20, 2012 8:59:23 AM

Thanks!

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, January 19, 2012 4:53 PM
To: Buchanan, Lisa (HHS/OASH)
Cc: Borror, Kristina C (HHS/OASH); Maddox, Yvonne (NIH/NICHD) [E]
Subject: RE: "SUPPORT Trial" (HHS Protocol 2U10HD034216)

HI
We are in the process of obtaining the requested consent forms and will forward them to you as requested. Let me know if you have other questions.

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Buchanan, Lisa (HHS/OASH)
Sent: Monday, January 09, 2012 11:40 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Borror, Kristina C (HHS/OASH)
Subject: "SUPPORT Trial" (HHS Protocol 2U10HD034216)

Good morning Dr. Higgins,

I am reviewing responses' to allegations of noncompliance with Department of Health and Human Services (HHS) regulations for the protection of human research subjects (45 CFR Part 46) involving the above-referenced research. OHRP has only opened its investigation with the University of Alabama. However, we would like to review the informed consent documents for all of the sites (~20). The data coordinating center, RTI, recommended that we contact you for this information. (See email below.) Would it be possible for you to provide copies of all the most recent IRB-approved informed consent documents from the different sites in the SUPPORT study?

Please feel free to contact me if you have any questions regarding this request.

Thanks,
Lisa

Lisa Buchanan, MAOM
Public Health Analyst, Division of Compliance Oversight
Office for Human Research Protections
Department of Health and Human Services
1101 Wootton Parkway, Suite 200
Rockville, MD 20852
Ph: 240-453-8298
Fax: 240-453-6909

From: Borasky, David [mailto:dborasky@rti.org]
Sent: Thursday, August 04, 2011 12:19 PM
To: Borror, Kristina C (HHS/OASH)
Cc: Caddell, Juesta M.
Subject: RE: clarification requested

Hi Kristina –

We had a chance to discuss your request with the RTI DCC folks this morning and how RTI may be able to help facilitate this for OHRP.

As I mentioned this morning, the RTI IRB does not require the DCC to provide RTI IRB with copies of the approved informed consent documents for each site. I did confirm that the DCC requires sites to submit copies of study approval notices to the DCC, but they do not require submission of copies of site-level informed consent documents to the DCC. Some site do include them with the approval notices, but this is not done consistently and may not be done every time a consent document is amended at the site level. Therefore, the DCC's records for site-level consent documents are incomplete.

The RTI IRB and the Neonatal Research Network DCC appreciate your desire to expeditiously obtain site-level informed consent documents for the SUPPORT Trial. We believe that the best way to facilitate this is to have OHRP submit a formal request to the Neonatal Research Network steering committee via the NICHD project officer Rosemary Higgins (contact information below) to have the RTI Data Coordinating Center collect copies of the final approved consent forms (as well as whether or not this is the initially approved documents or all versions that were used with participants for the duration of the study) for each of the SUPPORT Trial sites for transmittal to OHRP.

I hope this is a suitable approach.

Best,

Dave

Dr. Higgins contact information:

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
6100 Executive Blvd., Room 4B03
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Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

****

David Borasky, MPH, CIP
Office of Research Protection
RTI International
3040 Cornwallis Rd
RTP, NC 27709
USA

Phone: 919-316-3903
Fax: 919-316-3897
E-mail: dborasky@rti.org

From: Borror, Kristina C (HHS/OASH) [mailto:Kristina.Borror@hhs.gov]
Sent: Friday, July 29, 2011 4:23 PM
To: Borasky, David
Cc: Caddell, Juesta M.
Subject: RE: clarification requested

Dave,
We were wondering if you would be able to get us copies of all the most recent IRB-approved informed consent documents from the different sites in the SUPPRT study. Is that possible?
Thanks for your assistance.
Kristina

From: Borasky, David [mailto:dborasky@rti.org]
Sent: Monday, July 25, 2011 1:13 PM
To: Borror, Kristina C (HHS/OASH)
Cc: Caddell, Juesta M.
Subject: RE: clarification requested

Thank you for the quick response Kristina.

RTI was not engaged in the conduct of the SUPPORT clinical protocol nor would have been considered the IRB of record. RTI serves as the network data coordinating center for all sites, and in this role received coded data for analysis.

Therefore, as per your email, we will not submit a response to the letter dated July 18,

2011.

Regards,

Dave

****

David Borasky, MPH, CIP
Office of Research Protection
RTI International
3040 Cornwallis Rd
RTP, NC 27709
USA

Phone: 919-316-3903
Fax: 919-316-3897
E-mail: dborasky@rti.org

From: Borror, Kristina C (HHS/OASH) [mailto:Kristina.Borror@hhs.gov]
Sent: Monday, July 25, 2011 1:00 PM
To: Borasky, David
Cc: Caddell, Juesta M.
Subject: RE: clarification requested

Dave,
If RTI is not engaged in the research, we do not require any additional information at this time. We'll let you know if we need anything else.

Kristina C. Borror, Ph.D.
Director
Division of Compliance Oversight
Office for Human Research Protections
1101 Wootton Parkway, Suite 200
The Tower Building
Rockville, MD 20852
email: kristina.borror@hhs.gov
Phone: (240) 453-8132
Fax: (240) 453-6909

From: Borasky, David [mailto:dborasky@rti.org]
Sent: Monday, July 25, 2011 11:10 AM
To: Borror, Kristina C (HHS/OASH)
Cc: Caddell, Juesta M.
Subject: clarification requested

Good morning Kristina,

On Friday we (RTI) received a letter from you that was addressed to both our signatory official (Ward Sax) and the SO of UAB (Dr. Marchase) related to the SUPPORT trial. However, we noticed that the letter's salutation was only addressed to Dr. Marchase.

For the SUPPORT Trial (and for the entire Neonatal Research Network) RTI serves as the data coordinating center and we have no oversight of the clinical research. We receive

and analyze coded data, and do not have access to the code linking subjects to identifiers.

Given our role and that we are not in the salutation, we assume that OHRP does not expect a formal response from RTI. Would you please confirm if our assumption is correct, and if not, provide guidance on what OHRP would want RTI to provide given our role with the SUPPORT Trial? I leave on vacation tomorrow, so if you could reply to all I would appreciate it. Juesta Caddell is the Director of our IRB office and is the HPA on our FWA.

Thank you.

Dave

****

David Borasky, MPH, CIP
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RTI International
3040 Cornwallis Rd
RTP, NC 27709
USA

Phone: 919-316-3903
Fax: 919-316-3897
E-mail: dborasky@rti.org

From: Luc Brion
To: Keszler, Martin; D"Angio, Carl; Kristi Watterberg
Cc: Wallace, Dennis; Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: Protocol Review Summary of SBT Secondary
Date: Friday, January 20, 2012 12:02:48 AM
Attachments: Secondary - predicting ext success - Protocol 01192012 rev.docx
SBT response 19Jan12.doc
Watterberg, Hydrocortisone, 2012-01-19 rev.xlsx

Martin, Carl, Kristi,
Here are the revised documents: the protocol, the budget and the itemized responses.
Sorry again I missed the first email from Stephanie and thank you for your willing to meet tomorrow morning.
Looking forward for our discussion tomorrow
Best regards,

Luc P. Brion, MD
Professor of Pediatrics
Director, Fellowship Training Program in Neonatal-Perinatal Medicine The University of Texas Southwestern Medical Center at Dallas
5323 Harry Hines Boulevard, STOP 9063
Dallas, TX 75390-9063
Office: (214) 648-2835
Fax: (214) 648-2481
luc.brion@utsouthwestern.edu

From: Archer, Stephanie (NIH/NICHD) [E] [mailto:archerst@mail.nih.gov]
Sent: Thursday, January 19, 2012 8:21 AM
To: Luc Brion
Cc: Brenda Poindexter (bpoindex@iupui.edu); Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: Protocol Review Summary of SBT Secondary

Here it is again.

Stephanie Wilson Archer
The Eunice Kennedy Shriver

National Institute of Child Health and Human Development
Pregnancy & Perinatology Branch
6100 Executive Boulevard, Room 4B03
Rockville, MD 20852

Tel. 301-496-0430
Fax 301-496-3790
archerst@mail.nih.gov

From: Poindexter, Brenda B [mailto:bpoindex@iupui.edu]
Sent: Monday, January 09, 2012 3:58 PM
To: 'Luc.Brion@UTSouthwestern.edu'
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Archer, Stephanie (NIH/NICHD) [E]; Cunningham, Meg; Adas@rti.org; Wallace, Dennis (dwallace@rti.org); KWatterberg@salud.unm.edu
Subject: Protocol Review Summary of SBT Secondary

Luc,

Attached please find a summary of the discussion by the Protocol Review Subcommittee for the Spontaneous Breathing Test secondary protocol; please forward to your co-investigators. I am also attaching a budget estimate spreadsheet (separate tab linked to an updated version of the main Hydrocortisone study) prepared by Stephanie Archer. Since the Subcommittee is requesting a revision of the protocol, we will schedule another conference call once you have submitted your response to the review. We typically have the investigator participate at the beginning of the conference call to answer questions/summarize the revisions. If you have any questions about the summary or would like to discuss in person, just let me know.

Best regards,
Brenda

UT Southwestern Medical Center
The future of medicine, today.

PREDICTING SUCCESS OF EXTUBATION DURING HYDROCORTISONE THERAPY IN PRETERM INFANTS < 30 WEEKS OF GESTATIONAL AGE~~AND THE EFFECT OF DIFFERENT MODES OF SYNCHRONIZED VENTILATION~~

Luc P Brion, UT Southwestern at Dallas

Martin Keszler, Brown University

Kristi Watterberg, University of New Mexico

Dennis Wallace, RTI

Carl d'Angio, University of Rochester

Rose Higgins, RTI

Protocol

Rev 01~~11~~/19~~5~~/12~~1~~

Proposed secondary study to

"A RANDOMIZED CONTROLLED TRIAL OF THE EFFECT OF HYDROCORTISONE ON SURVIVAL WITHOUT BRONCHOPULMONARY DYSPLASIA AND ON NEURODEVELOPMENTAL OUTCOMES AT 18 – 22 MONTHS OF AGE IN INTUBATED INFANTS <30 WEEKS GESTATIONAL AGE",

Kristi Watterberg, PI

Thanks to: Diana Vasil, RN, Coordinator at UT Southwestern at Dallas, and Glenn Metoyer, RT, Parkland Memorial Hospital

1. ABSTRACT (SYNOPSIS)

This observational study is primarily designed to evaluate whether a short endotracheal continuous positive airway pressure (ET CPAP) test (also called spontaneous breathing test (SBT) may help predict the success of extubation of ~~very~~ premature infants ≤30 weeks estimated gestational age at birth who remain intubated at 14 - 28 days postnatal age. For this purpose, we will use the 3-minute ET CPAP test ("spontaneous breathing test" or SBT) described by Kamlin in a single center.[1] The primary aim of this study is evaluate the point estimates and confidence intervals of sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio of a positive test, and likelihood ratio of a negative test for the SBT. The large number of patients we plan to recruit will allow us to test the external validity of the SBT in different centers using different types of ventilators and different modes of ventilation.

~~We will also asseso if ventilation modes that support every breath, i.e., assist control (AC), pressure regulated volume control (PRVC), pressure support ventilation (PSV) or synchronized intermittent mandatory ventilation (SIMV) with PSV, are associated with shorter duration of mechanical ventilation than SIMV. Since there are many center and individual differences in approach to therapy we will use multivariate analysis ventilation to attempt to account for possible confounder. Shorter intubation will in part depend on approaches to fluids, volumes, sodium administration and nutritional management, caffeine, etc.~~

2. STATEMENT OF PROBLEM

Prediction of successful extubation in preterm infants remains a challenge. This question has not been addressed by the NRN, and specific data were not collected during the SUPPORT trial. Previous single-site studies suggested that successful extubation can be predicted by the SBT in preterm infants during the first days of life. However, validity of this test at later postnatal age and in multicenter settings has not been established.

~~There is limited information about the relative merits of SIMV vs. ventilation modes that support every breath as weaning modes of mechanical ventilation. There are important physiological considerations suggesting that SIMV, although widely used, may not provide optimal support in very premature infants during weaning.~~

3. HYPOTHESIS

~~Since this is an observational study there is no primary hypothesis.~~

The study is primarily designed to test the external validity of the SBT in a multicenter study, with multiple institutions, using different types of ventilators and different modes of ventilation, in a population of infants of greater post-natal age than in the original study by Kamlin et al.[1]

~~Secondary~~ Null hypotheses include :

1. The percentage of successful extubation among patients with positive SBT is not different from that in those extubated based on clinical information alone. Previous studies suggest that the success of extubation may be higher in patients with a positive SBT.

~~1.~~2. The predictive value of the SBT is not affected by whether the baby is supported by a ventilator using a mode supporting all breaths or by SIMV

~~2.~~3. The predictive value of the SBT is not affected by whether the baby is randomized to hydrocortisone or placebo. Hydrocortisone may affect lung compliance and laryngeal edema and thus improve success rate of extubation compared with placebo.

~~3.~~4. The predictive value of the SBT is not affected by the resistance of the endotracheal tube (ETT). While on CPAP small diameter and long length of the ETT may increase work of breathing and contribute to failing of the SBT while not affecting success of extubation.

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5. The predictive value of the SBT is not affected by postnatal age (within the ranges expected in the hydrocortisone trial)

~~4.~~6. The predictive value of the SBT is not affected by the mode of respiratory support after extubation. We would expect that success of extubation will be greater on patients extubated to NIPPV than on CPAP or high-flow nasal cannula, and lowest on those extubated to low flow nasal cannula or room air.

~~5. Modes of ventilation supporting all breaths and SIMV are associated with a similar duration of mechanical ventilation.~~

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4. SPECIFIC AIMS

Primary aim:
To evaluate the point estimates and confidence intervals of sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio of a positive test, and likelihood ratio of a negative test for the SBT.

~~1.~~ *Secondary aims:*

~~2.~~ To evaluate point estimates and confidence intervals of sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio of a positive test, and likelihood ratio of a negative test for the SBT in various ~~two~~ subgroups ~~infants ventilated with SIMV and infants ventilated using modes supporting all breaths~~.

~~3. To determine if ventilation modes that support every breath are associated with shorter duration of mechanical ventilation than SIMV.~~

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5. RATIONALE/JUSTIFICATION

Success of elective extubation is one of the quality measures in neonatal intensive care. This study is designed

~~1.~~ ~~(~~To assess the external validity of the SBT to predict successful extubation in very premature infants. This proposal is the first multicenter study that will assess whether the predictive value of the SBT is better (or not) than other information available to the clinician (Fi02, PIP, PEEP, rate, presence of atelectasis, physiologic stability) to predict successful extubation. ~~;and~~

~~2.~~ ~~To add to the limited body of knowledge regarding relative merits of various forms of synchronized ventilation during weaning.~~ Very little additional coordinator time will be needed to collect information that will be used in multivariate analysis that could build the basis for a future randomized trial.

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6. BACKGROUND AND SIGNIFICANCE

Success of extubation is around 60-73% in extremely low birth weight infants.[2,3]. Higher success rates (80-86%) have been reported in series including all preterm infants[4,5]. Infants who require re-intubation, with its attendant risks, may experience deterioration of their respiratory status due to atelectasis. Intermittent hypoxemia and/or

hypercapnia prior to re-intubation may expose them to additional risks. On the other hand, a relatively large number of infants who self-extubate and remain extubated subsequently.[6a] Those infants may be exposed to mechanical ventilation and potential ventilator-induced lung injury for longer than necessary or for elective reasons such as to facilitate growth or to prepare for surgery.

Thus, a test that improves the clinician's ability to predict readiness for extubation is highly desirable. Kamlin et al[1] compared three tests to predict success of extubation (no reintubation within 72 hours) in 50 infants with birth weight < 1250 grams using a 3-minute ET CPAP trial: (a) expired minute ventilation (VE) during ET CPAP; (b) ratio of minute ventilation during ET CPAP to minute ventilation during mechanical ventilation (VE ratio); (c) the spontaneous breathing test (SBT). The infant passed the SBT if there was no hypoxia or bradycardia during ET CPAP. The median age at the time of the study was 4 and 5 days, , respectively, for successful extubations and for extubations followed by reintubation within 72 hours,.. Kamlin concluded that the SBT had the highest sensitivity (97%), specificity (73%), positive predictive value (93%), negative predictive value (89%), likelihood ratio of a positive test (3.6) and the smallest likelihood ratio of a negative test (0.04) among the three tests.[1] Limitations of this study included small sample size (n=50) and failure to separate infants ventilated by different synchronized modes. In that study infants were weaned by reducing the tidal volume to 3.5 ml/kg using AC or by reducing ventilator rates to 20–30 breaths/minute on SIMV.

A subsequent study (n=180) provided a degree of validation of the SBT, but compared this test to a historical cohort, which differed substantially from the practice at the time of the validation study. Once more, various modes of ventilation were used, and there was no subanalysis by mode.[26] Most babies in the validation cohort were on volume guarantee ventilation (94% vs 26% in the controls), and most of them were ventilated using AC at the time of extubation (81%, compared with 93% using SIMV in controls). The median age at extubation was 0 days (range 0-27) for babies undergoing the SBT and 0 days (range 0-11 days for controls. The sensitivity of the SBT was 83% (compared with 97% in the first study).

It is not known if the SBT is equally predictive in infants with evolving chronic lung disease and prolonged ventilator dependence. It is also not known if the SBT is equally predictive in infants on different modes of synchronized ventilation. It is possible that modes in which every breath is supported mask significant respiratory control center immaturity or afford less respiratory muscle training compared to SIMV. SIMV remains the most widely used mode of assisted ventilation in newborn infants,[7] despite its potential disadvantages related to high work of breathing resulting from the high resistance of small endotracheal tubes (ETT) in extremely low birth weight (ELBW) infants.[8-10] This is especially true as the SIMV rate is decreased during the weaning process. In contrast, AC and PSV (when used as a sole mode of ventilation) support each patient breath, thereby resulting in more even tidal volume, less tachypnea, lower work of breathing and lower tidal volume compared to SIMV.[11-13]

There is no information in the literature describing the success of extubation from various modes of ventilation. A practice survey of NRN investigators conducted in July 2011 yielded data from 10 centers. Ventilators include Draeger 8000 (n=6), Maquet Servol (n=5), Draeger Evita XL (n=2), Draeger VN500 (n=2), Avea (n=2), and Bird VIP (n=1). Pressure-controlled ventilation is predominantly used in 6 NRN centers, and volume-targeted ventilation in 3 centers, while both are used equally in 2 centers. Volume-targeted ventilation is used either often or most of the time in 7 centers, and is used both during the acute phase and during weaning; it is used during weaning by 5 of 10 centers. During weaning and for extubation SIMV is used predominantly by 5 centers and modes supporting all breaths are used predominantly by 5 centers. Extubation from high-frequency ventilation is either rarely or never used. Eight of 10 centers would be ready to perform a 3-min SBT in patients on high-frequency ventilation. In summary the survey showed substantial heterogeneity across centers, with approximate equal distribution of SIMV and modes supporting all breaths.

There are limited data regarding the relative efficacy of ventilation modes that support every breath vs. SIMV in weaning from mechanical ventilation and no large clinical trials to evaluate their effect on survival or the risk of bronchopulmonary dysplasia. Three small studies compared SIMV and AC during weaning. In two of these studies SIMV rate was reduced to10 breaths/min; these studies showed shorter duration of ventilation when using AC. In the third trial, SIMV rate was not reduced below 20 breaths/minute, and the authors showed no difference in duration of ventilation between the two modes.[14,15] These findings support the physiologic explanation that the narrow ETT of ELBW infants increases work of breathing and impairs weaning from mechanical ventilation. Reyes et al showed faster weaning from mechanical ventilation in ELBW infants using SIMV+ PSV, compared to SIMV alone, suggesting that PSV may obviate this problem to some extent.[16] However, this option is not available on all ventilators and may not be widely used. One larger randomized trial enrolled 212 VLBW infants (birth weight 500-1249 g) from initiation of mechanical ventilation through extubation on AC or SIMV.[17] The study showed no differences between the groups in survival, BPD, age at extubation, or length of ventilation in survivors. This study used pressure regulated volume control using the Siemens Servo 300 ventilator, in which the volume targeted mode uses tidal volume measurement at the ventilator end of the circuit, in contrast with ventilator adjusting volume closer to the endotracheal tube. Cross-over for failure occurred in 33% of the infants receiving SIMV and 20% of those who received PRVC.

~~A practice survey of NRN investigators conducted in July 2011 yielded data from 10 centers. Ventilators include Dreager 8000 (n=6), Maquet Servo I (n=5), Dreager Evita XL (n=2), Dreager VN500 (n=2), Avea (n=2), and Bird VIP (n=1). Pressure-controlled ventilation is predominantly used in 6 NRN centers, and volume-targeted ventilation in 3 centers, while both are used equally in 2 centers. Volume-targeted ventilation is used either often or most of the time in 7 centers, and is used both during the acute phase and during weaning; it is used during weaning by 5 of 10 centers. During weaning and for extubation SIMV is used predominantly by 5 centers and modes supporting all breaths are used predominantly by 5 centers. Extubation from high frequency ventilation is either rarely or never used. Eight of 10 centers would be ready to perform a 3 min SBT in patients on high frequency ventilation. In summary the survey showed substantial heterogeneity across centers, with approximate equal distribution of SIMV and modes supporting all breaths.~~

7. METHODS AND PROCEDURES

a) Study design

This is an observational study with prospective data collection.

The study will involve analysis of the operational characteristics of a diagnostic test (SBT) ~~and retrospective analysis of a cohort study (using two cohorts: babies ventilated using SIMV and babies ventilated using modes supporting all breaths)~~.

The spontaneous breathing test (SBT) will be performed by the study team just before extubation decided by the clinicians. Clinicians will remain blinded to the results.

b) Study population

We will use the same population as that for the main study. All patients enrolled in the main study will be approached for informed consent. It is up to each center to decide whether to use a separate consent for the substudy, or an optional consent, indicated by a check on the consent to the main study

c) Inclusion and exclusion criteria

Inclusion criteria:

These will be the same as for the main study, i.e:
Patients eligible for this study will be infants between 14 – 28 postnatal days who:
(a) are <30 weeks estimated gestational age, to be randomized in two strata: $\leq 26^{6/7}$ and $27^{0/7} - 29^{6/7}$ weeks);
(b) were inborn at an NRN site or were admitted to an NRN site before 72 hours postnatal age;
(c) have received ≥ 7days of mechanical ventilation;
(d) are receiving mechanical ventilation through an endotracheal tube .

We anticipate a starting time at the earliest 6/1/2012.

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Exclusion criteria:

Same as for the main study, i.e.:

(a) Major congenital anomalies
(b) Decision to limit support
(c) Indomethacin or ibuprofen treatment within 48 hours of study drug
(d) Previous corticosteroid treatment for BPD
(e) Hydrocortisone treatment for hypotension in the first week of life is common (35) and will not be an exclusion; however, infants will be excluded if they have received hydrocortisone:
  (i) for ≥ 14 cumulative days OR
  (ii) within 7 days of study entry.

In addition, we will exclude for this secondary study patients who have at the time of extubation an ETT size <2.5.

d) Enrollment centers and PIs

Case Western	Michele Walsh
Dallas	Luc P Brion
Wayne State	Seetha Shankaran
Emory	Barbara Stoll
Cincinnati	Kurt Schibler
Indiana	Brenda Poindexter
Brown	Martin Keszler
Stanford	Krisa Van Meurs
Alabama	Waldemar Carlo
Houston	Kathleen Kennedy
Duke	Ronald Goldberg
Iowa	Edward Bell
New Mexico	Kristi Watterberg
Pennsylvania	Barbara Schmidt
Rochester	Carl D'Angio
UCLA	Uday Devaskar
Ohio State	Leif Nelin
Missouri	William Truog

e) Study intervention and procedures

We will perform a maximum of 2 SBTs per patient: one at the time of the first elective extubation and one at the time of the second elective extubation, if any. Spontaneous unplanned extubations will not be analyzed since SBT will not be peformed.

We will request that the clinical team inform the coordinator of a pending extubation after the baby has been enrolled to this study.

The intervention will be similar to that described by Kamlin et al.[1] Specifically, when the clinicians decide a baby is ready to be extubated, the investigator will perform the SBT within 4 hours of the planned extubation. This intervention will be masked in order to prevent bias that would occur if the clinical provider knew the result of the SBT.

The infant's ETT will be suctioned prior to the SBT if suctioning is clinically indicated. The SBT will be done no less than 10 minutes after suctioning.

The researcher will silence any alarms and will place screens around the bedside before initiating the test to minimize the chance of unblinding. After ensuring that the clinical care team, including the patient's nurse, is away from be bedside (to maintain blinding) the investigator (respiratory therapist, fellow, nurse practitioner or attending), who must not be involved with the patient's clinical care, will switch the ventilator to CPAP for 3 minutes at the same pressure as the positive end-expiratory pressure setting. ~~The infant's ETT will be suctioned prior to the SBT if clinically indicated.~~ T~~and~~ the intervention will be done when the infant is in a quiet state, taking care to minimize stimulation and disturbance during the study.

The baby succeeds the SBT if he or she requires no more than a 15% increase in FiO2 for isolated hypoxemia. After 3 minutes on CPAP the study will be stopped, and ventilation will be restarted.

The baby fails the SBT if he or she develops a bradycardia (HR <100) for more than 15 seconds and/or a fall in SpO2 below 85% despite a 15% increase in FIO2. If isolated hypoxemia develops, FiO2 will be increased according to unit protocol. If hypoxemia does not respond to a 15% increase in FiO2, or if bradycardia develops, manual breaths are given through the ventilator and mechanical ventilation is restarted at the previous settings.

~~because of bradycardia or desaturation, this will be considered a failed test. At this point the study will be stopped, and ventilation will be restarted. If manual breaths are given through the ventilator because of bradycardia or desaturation, this will be considered a failed test. Data on the mode of ventilation, success and time of extubation will be collected for subsequent analysis.~~

The baby will be placed back on previous ventilatory settings for~~to~~ 30 minutes, to limit the risk of derecruitment that could have resulted from performing the SBT. The investigator will document in the chart and communicate to the clinical team that the SBT was performed, the exact time of the procedure and the earliest time of extubation (30 min after the SBT). The results of the SBT will not be disclosed to the clinician or documented into the chart unless additional therapy is required as indicated below.

In rare circumstances, the baby may not respond well to the intervention described above. In that case, manual bagging is initiated for 30 seconds, and the clinical team is informed. If the baby responds well, mechanical ventilation is restarted; otherwise appropriate treatment is initiated.

f) Required follow-up

None beyond 72 hours after the second extubation

g) Primary and secondary outcomes

Primary outcomes:

Point estimates and confidence intervals of sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio of a positive test, and likelihood ratio of a negative test to predict successful (defined as no reintubation within 72 hours) extubation using SBT

Secondary outcomes:

1. Point estimates and confidence intervals of sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio of a positive test, and likelihood ratio of a negative test to predict successful extubation using SBT in two subgroups: infants ventilated with SIMV and infants ventilated using modes supporting all breaths at the time of the SBT

2. Point estimates and confidence intervals of sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio of a positive test, and likelihood ratio of a negative test to predict successful extubation using SBT by primary study group.

3. Point estimates and confidence intervals of sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio of a positive test, and likelihood ratio of a negative test to predict successful extubation using SBT according to ETT resistance calculated according to the formula:
$$R \propto L / r^4,$$
where L is the length of the tube and r is its radius

4. Point estimates and confidence intervals of sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio of a positive test, and likelihood ratio of a negative test to predict successful extubation using SBT according to postnatal age

5. Point estimates and confidence intervals of sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio of a positive test, and likelihood ratio of a negative test to predict successful extubation using SBT according to the mode of respiratory support used after extubation: NIPPV, CPAP, high-flow nasal cannula, low flow nasal cannula or room air.

6. Point estimates and confidence intervals of sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio of a positive test, and likelihood ratio of a negative test to predict successful extubation using SBT using different definitions of failed extubation (at 12, 24 and 48 hours instead of 72 hours after extubation)

~~4.~~7. Odds ratio of successful extubation taking into account the SBT and multiple possible confounders

~~5. Duration of mechanical ventilation in two subgroups: infants ventilated with SIMV and infants ventilated using modes supporting all breaths for the majority of the time on the ventilator starting at the time of randomization~~

~~1.~~ Data to collect for this study beyond those in the main trial (see Appendix B):

~~2.~~ Information about the situation before the SBT: ~~At the time of randomization we will obtain the respiratory severity score, which will be calculated as mean airway pressure X FiO2.[18]~~

~~3.~~ Mode of ventilation, ventilatory settings, vital signs, ~~in between the time of randomization and the SBT~~,

1. Most recent blood gas, ~~ventilatory settings and~~ ETT size
2. Response to SBT
3. Repiratory support after the second extubation

~~4. just before SBT~~

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h) Sample size estimate

The Kamlin study,[1] which compared three tests, had a sample size of 50. This study was powered to detect a difference of one standard deviation in mean VE in the group failing extubation but not to detect differences in dichotomous outcomes between the three tests. This was a single-center study with a relatively uniform approach to ventilation. The high degree of variability of clinical practice within the NRN will impact the outcome measures in this proposed multicenter trial, thus clearly requiring a much larger sample size to detect a comparable effect size.

~~The Reyes study,[16] which was also a single center study, focused on a similar population demonstrated no significant difference in duration of mechanical ventilation (median [interquartile range] 22 [10-52] vs 34 d [19-59]). This study was powered to detect a 30% difference in the duration of oxygen dependency between groups at an alpha of 0.05 with a power of 90%; it did not reach statistical significance with n=107.~~

To the extent possible, we will use all available subjects from the total sample size of 800 available in the main trial. At the current date of this proposal, 40 of 800 patients have been enrolled into the main trial. Patients who self extubate before the SBT and remain off mechanical ventilation will not be available for this analysis. Those who are reintubated will have another SBT performed before attempting elective extubation. We estimate that about ~~6~~70% of the total sample size available in the main trial will be available for the analysis of this secondary study; thus sample size is estimated at 373~~550~~.

The primary aim ~~goal~~ of this study is to generate estimates of the operating characteristics (sensitivity [Se], specificity [Sp], positive predictive value [PPV] and negative predictive value [NPV]) of the 3-minute ET CPAP test ("spontaneous breathing test" or SBT) for predicting successful extubation in this population of infants. Each of the operating characteristics of interest is a conditional probability (where the calculation is conditioned on a either success or failure of the extubation or the positive or negative value for the SBT), and the primary sample size consideration for the study is the precision with which these probabilities can be estimated with the available sample sizes. Based on information provided earlier that suggests that 60% to 80% of the extubations are likely to be successful, we assume that between 20% and 80% of the 550 subjects will be used in the denominator of each of the calculations. Furthermore, operating characteristics in the range of 0.7 to 1 are of greatest interest. Given those assumptions the available sample sizes are sufficient to provide confidence intervals with half widths, where a 95% confidence interval is typically computed as the estimate of the sensitivity ± the half width, shown in the table below.

Estimates of Confidence Interval Half Width for Different Levels of True Measure Prevalence and Conditional Denominator

Se, Sp, PPV, NPV Value	Half Interval Width for Available Denominator						
	110	165	220	275	330	385	440
0.70	0.084	0.069	0.059	0.053	0.048	0.045	0.042
0.72	0.082	0.067	0.058	0.052	0.047	0.044	0.041
0.74	0.082	0.067	0.058	0.052	0.047	0.044	0.041
0.76	0.080	0.065	0.056	0.050	0.046	0.043	0.040
0.78	0.077	0.063	0.055	0.049	0.045	0.041	0.039
0.80	0.075	0.061	0.053	0.047	0.043	0.040	0.037
0.82	0.072	0.059	0.051	0.045	0.041	0.038	0.036
0.84	0.069	0.056	0.048	0.043	0.040	0.037	0.034
0.86	0.065	0.053	0.046	0.041	0.037	0.035	0.032
0.88	0.061	0.050	0.043	0.038	0.035	0.032	0.030
0.90	0.056	0.046	0.040	0.035	0.032	0.030	0.028
0.92	0.051	0.041	0.036	0.032	0.029	0.027	0.025
0.94	0.044	0.036	0.031	0.028	0.026	0.024	0.022
0.96	0.037	0.030	0.026	0.023	0.021	0.020	0.018
0.98	0.026	0.021	0.019	0.017	0.015	0.014	0.013

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i) Available population/compatibility with other ongoing protocols

Same as for the main study: Based on GDB data 06-07, and assuming 60% consent rate, 800 infants could be recruited to the main study over 3 years. Since the secondary study will start at the earliest 6/1/2012 we estimate 100 infants will have been recruited already in the main study. We estimate that about 70% of the total sample size available in the main trial will be available for the analysis of this secondary study; thus sample size is estimated at 5050.

~~Since the secondary study will start after the beginning of the main study, the total number of patients in this secondary study will be probably 10% smaller, i.e. 500 patients.~~

j) Projected recruitment time

The projected recruitment time for the main study ~~was~~is 30 months. However, as of November 2011, only 16 had been randomized per month (versus an original main trial estimate of 27 recruited per month). Initiation of the secondary study could be expected within 6 months (i.e., by 6/1/2012). ~~Therefore, projected recruitment time for the main study is estimated to be 24 months.~~Since recruitment into the main study is slower than expected, recruitment may last longer than initially expected.

k) Data Analysis Plan

~~1.~~ We will determine the point estimates and 95% confidence intervals for the operating characteristics (sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio of a positive test, and likelihood ratio of a negative test) of successful extubation using the SBT.

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We will use the same tests in the following subgroups:

1.

2. ~~infants ventilated with SIMV versus infants ventilated using modes supporting all breaths at the time of the SBT.~~
infants with gestational age ≤ $26^{6/7}$ versus those with gestational age $27^{0/7} - 29^{6/7}$ weeks

2. primary study group

3. infants ventilated with SIMV and infants ventilated using modes supporting all breaths at the time of the SBT

4. according to the mode of respiratory support used after extubation: NIPPV, CPAP, high-flow nasal cannula, low flow nasal cannula or room air

~~3.~~ 5. using different definitions of failed extubation (at 12, 24 and 48 hours instead of 72 hours after extubation)

We will use Receiving operator characteristic curve (ROC) to analyze whether the operating characteristics of the SBT vary according to ETT resistance and to postnatal age.

~~Duration of mechanical ventilation will be compared in the two subgroups using non-parametric tests (two-sided Mann-Whitney test, alpha < 0.05) because this variable has a non-normal distribution. We will use multiple regression analysis of the duration of ventilation using as factors the gestational age, the center, the respiratory severity score at the time of randomization, the randomization arm (hydrocortisone versus control), and the mode of ventilation. Additional factors that differ by p < 0.10 on univariate analysis will be tested for significance in the multiple regression analysis.~~

The likelihood of success of extubation may depend on multiple factors other than SBT, including patient characteristics, mode of ventilation, individual clinician and center. For this purpose we will use multivariate logistic analysis using as predictors:[1] gestational age, weight for age at birth, postnatal age, PEEP, mode of ventilation and ventilation settings at the time of SBT (SIMV vs. ventilation supporting every breath), SBT, hydrocortisone (vs. placebo), caffeine,- symptomatic patent ductus arteriosus, center, and mode of respiratory support after extubation (NIPPV, CPAP, high flow nasal cannula, low flow nasal cannula, room air). Additional factors that differ by p ≤ 0.10 on univariate analysis will be tested for significance in the multiple regression analysis.

l) Data safety monitoring plan:

Eight interim blocks are planned in the main study. The DSMC will review data from the main trial and from this secondary study at the same time. For this secondary study, the DSMC will review the frequency of required treatment (bagging, resuscitation) related to the SBT. Serious adverse events to be reported to NICHD within 24 hours include death that would occur after a code related to the SBT.

m) Stopping limits for protocol termination:

The DSMC may decide to stop the main trial or this secondary study.

8. RISK, BENEFITS, LIMITATIONS

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Ethical issues

Benefit: There is no direct benefit to participating in this secondary study.

Risks: Some babies may develop bradycardia or desaturation and may require increase in FiO2 or manual breaths on the ventilator ~~bagging~~ at the time of SBT. It is possible that an occasional infant may require additional interventions. However, n~~N~~o case of resuscitation related to the SBT has been described in the two published studies. Any baby requiring resuscitation will be reported to the IRB as an adverse event.

Blinding: SBT failure may be fairly predictive of failure of extubation. However, it is not part of standard practice in centers in the NRN. If the results of the SBT were provided to the clinical care team, it would result in bias in decision of extubation time. The SBT has been reported in more than Since reported infants undergoing the SBT had an uneventful course even if failing the SBT, ~~, therefore~~ blinding the clinical care team to the results of this test is defensible, except in the rare circumstance of ~~:~~

~~A consent form will be obtained for participation in this study. There is a slight possibility that asking for permission for this secondary study would affect enrollment rate in the primary study. We think it is unlikely with the opt-in checkbox.~~

Consent form: A consent form will be obtained for participation in this study. There is a slight possibility that asking for permission for this secondary study would affect enrollment rate in the primary study. Each center PI will decide whether to use a separate ~~This~~ consent for this secondary study or to ~~could be~~ embedded it in the consent form for the main study.

Limitations

Since this is an observational rather than a randomized study, success of extubation ~~the duration of mechanical ventilation~~ may be affected by multiple factors, biases and confounders, some of which we may not be able to quantify. Based on our survey, it appears that selection of the ventilation mode depends in large part on center and care provider/attending choice than on patient characteristics. For this purpose we will conduct multivariate analysis using patient characteristics (GA, prenatal steroids, disease severity), and information about individual patients. ~~NICU and providers' practices (fluid and salt administration, therapy for PDA, diuretics, caffeine, type of ventilator, choice of ventilator mode, blood gases at the time of extubation).~~

There may be inter-institutional and inter-individual variability in the decision about when to extubate. Variability will be limited by criteria set by Kristi Watterberg in the main trial protocol: "Extubation must be attempted within 72 hours of starting study drug and within 24 hours after meeting the following criteria: the FiO2 is <0.40 to maintain a saturation of 88%, the mean airway pressure is < 8, and the infant is hemodynamically stable (as defined for the SUPPORT trial: "clinically acceptable blood pressure and perfusion in the opinion of the clinical team"). The infant may be extubated from higher settings at the discretion of the attending physician. If the infant does not meet these criteria within 72 hours, he/she will be reassessed every 24 hours during the intervention period and extubation will be attempted within 24 hours of those criteria being met."

Success of extubation depends on absence of apnea. Apnea may not be detected during the 3 minutes during which the SBT will be performed. We expect that majority but not all patients in the current trial may be on caffeine at the time of extubation, since a large multicenter randomized trial has shown it reduces the rate of bronchopulmonary dysplasia (oxygen requirement at 36 weeks postmenstrual age)[20] and improves the rate of survival without neurodevelopmental disability at 18 to 21 months but not in early childhood in infants with very low birth weight infants.[21,22]

Success of extubation will be limited in case of laryngeal edema, which may be more prevalent in the control arm. Hydrocortisone may limit this risk. We will record documentation of stridor and failure of successful extubation related to stridor.

We will not use VE as a predictor for extubation because the tidal volume cannot reliably be measured when the leak around the endotracheal tube is ≥ 30%, In spontaneously breathing infants, the tidal volume is not stable and the number of r breaths over which the VE is averaged varies among different types of ventilators.

SIMV with PS will be classified as a mode modes supporting all breaths; however this mode supports some breaths fully (SIMV) and other breaths to a lower extent (PS), in contrast with AC or PS.

~~Since subgroups for duration of mechanical ventilation will be based on the mode of respiratory support for the majority of the time on the ventilator from the time randomization, there will be possible overlap between the two groups, since some babies may be exposed to more than one mode. However, most changes in mode occur between the acute phase and beginning of weaning. Starting the count at the time of primary study entry (at least 14 d) will minimize this overlap.~~

We did consider alternatives to Kamlin's SBT.

1. During the SBT the baby will need to breathe against the resistance of the endotracheal tube. The resistance of the tube is proportional to L / r^4, where L is the length of the tube and r is its radius. We will record length and radius to assess whether the predictive value of the SBT decreases with increased resistance of the tube. An alternative to the SBT would be to design a modified SBT using PSV with minimal pressure instead of CPAP. Since no complications have been described with the SBT, this may not be necessary. Since this has not been tested in the past, we will not use this option.

2. Wilson et al[23] described a minute ventilation test (MVT) of 10 minutes duration instead of the 3-minute test described by Kamlin. In a single institution, a spontaneous minute ventilation ≥ 50% of the ventilator-generated minute ventilation correctly predicted successful extubation in 86% of preterm infants with birth weight < 2 kg and requiring mechanical ventilation for > 24 hours.[22] In a subsequent randomized trial[23] (mean GA 30 weeks), babies undergoing the MVT were extubated sooner than those in the control group. The positive predictive value of the MVT for extubation was 76% (95% CI, 55 to 89%) and the success of extubation was similar to the control group.[23] Kamlin's SBT is more appropriate for our study for several reasons: his studies only included smaller babies; the SBT only uses 3 minutes and does not require minute ventilation measurement and thus could be used in multicenter setting with various ventilators, and appears at least as good as the 10 minute MVT.

3. Dimitriou et al[5] have described composite indices such as the diaphragmatic pressure–time index and the noninvasive respiratory muscle pressure–time index to predict success of extubation in preterm with mean gestational age of 30 weeks and mean birthweight of 1.36 kg. The test had 86% positive predictive value of successful extubation in the validation group. Kamlin's SBT is more appropriate for our study for the same reasons as described for the 10 minute MVT.

~~There is a slight possibility that asking for permission for this secondary study would affect enrollment rate in the primary study. We think it is unlikely with the opt in checkbox.~~

9. BUDGET

Direct Costs

Cost per patient: $ 190~~113~~

Respiratory therapist: 30~~15~~ minutes x $30 per hour = $ -50~~8~~

Coordinator time: ~~43~~ hours x $35 per hour = $ 140~~105~~

Consent: ~~assuming consent for this secondary study is embedded in the consent for the main trial:~~ 30~~10~~ minutes

Screening for subjects who qualify for extubation: 60~~20~~ minutes

SBT: 60~~60~~ minutes

Data collection/entry/transmission: 90 minutes

Total Capitation ~~Direct~~ Cost for 373~~533~~ patients: $705~~9~~,870~~963~~

Training session at NRN steering committee *$ 2,000*

Total direct costs $72,870

Indirect costs (52.6%): $38,330

Total costs: $111,200

Note: there is no CPT code for the SBT test

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Appendix A: Authorship Plan:

We will follow the Policies and Procedures of the NICHD Neonatal Research Network

For abstracts, Authors of the Secondary Study with be the authors followed by "for the NICHD Neonatal Research Network.

For publications, authors will include Authors of the Protocol Subcommittee, Remaining participating Center PIs (those not serving on the Protocol Subcommittee), listed in order by the Center's combined ranking of the number of infants enrolled and the percent of eligible infants enrolled in the study by the Center, Followed by the phrase "for the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network."

Appendix B1: Data sample sheet

Data obtained for the main study:

Center

Gestational age,

~~B~~birth weight,

Date of birth

~~date and time of birth, prenatal steroids,~~ Ddate and time of randomization,

Rrandomization arm,

~~center~~Symptomatic PDA

Caffeine

HCO5 (first extubation)

Appendix B2: Data sample sheet

~~1.~~ ~~Data obtained for the secondary study: first extubation:~~ Formatted: Normal, No bullets or numbering

~~2.~~ ~~Exclusion criterion: ETT size < 2.5~~ Formatted: Normal, No bullets or numbering

~~3.~~ ~~At the time of randomization:~~ ~~FiO2 ____ Mean airway pressure: _____~~

~~4.~~ ~~Ventilation mode and duration:~~

~~From~~	~~Until~~	~~SIMV~~	~~PS/SIMV +PS/AC/PRVC~~

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~~SBT~~ Planned extubation date and time: _____ ETT diameter: ____ total length: ___

~~5.~~ SBT: ~~(when quiet, change to CPAP at same pressure as prior PEEP for 3 min):~~ date and time Formatted: Normal, No bullets or numbering

~~Planned extubation date and time:~~

Immediately before SBT	During SBT
~~PS/SIMV +PS/AC/PRVC SIMV~~ Ventilation mode: PS SIMV SIMV with PS AC Volume mode Pressure control	Date: _____ From ____ until _____
ETT diameter: ___ length at lips: ___	
Latest pH: ___ pCO2: ___ BE: ____	
PIP: ___ MAP: ___ Ventilator rate: _____ PEEP: ___ cm FiO2: _____ Sat: _____	CPAP: ____ cm
HR > 100: yes ____ no ___	Min HR < 100 for > 15 sec: Yes _____ No

FiO2: ___ Sat: ____	Fall < 85% despite 15% increase in FiO2: Yes _____ No _____
	Max FiO2 Manual breaths through ventilator: number: ___ Resuscitation needed: _bagging ___ minutes: ___ _chest compressions: ____ minutes: _epinephrine: _____

Stridor: ____ Racemic epinephrine: ____

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Appendix B3: Data sample sheet

Data obtained for the secondary study: first extubation:

Planned extubation date and time: ETT diameter: total length:

SBT: date and time

Immediately before SBT	During SBT
Ventilation mode: PS SIMV SIMV with PS AC Volume mode Pressure control	Date: From until
ETT diameter: length at lips:	
Latest pH: pCO2: BE:	
PIP: MAP: Ventilator rate: PEEP: cm FiO2: Sat:	CPAP: cm
HR > 100: yes no	Min HR < 100 for > 15 sec: Yes No
FiO2: Sat:	Fall < 85% despite 15% increase in FiO2: Yes No
	Max FiO2 Manual breaths through ventilator: number: Resuscitation needed: bagging minutes: chest compressions: minutes: epinephrine:

Stridor: Racemic epinephrine:

HCO5: same data as for first extubation in the main trial

~~6. Reintubation within 72 hours after extubation: no yes:~~

~~If yes: date and time:~~

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DATE: January 19, 2012

TO: Brenda Poindexter
Chair, Protocol Review Subcommittee

FROM: Luc Brion

RE: Itemized response to the Protocol Review Subcommittee re: "Predicting Success of Extubation During Hydrocortisone Therapy and the Effect of Different Modes of Synchronized Ventilation"

We thank the protocol review subcommittee for a careful review of our proposal. We added itemized responses to each comment required a response or a change in the protocol. We modified the protocol considerably along the guidelines provided by the committee.

The Protocol Review Subcommittee reviewed this protocol during its conference call on January 3, 2012. Written comments were provided by Kurt Schibler, Brenda Poindexter, and Stephanie Archer and are included below.

The Subcommittee discussed differences between the population of infants studied in the Melbourne trial of spontaneous breathing versus those that will be in the hydrocortisone trial. It was noted that the investigators in Melbourne who described this test were using it every day on rounds, the purpose being to extubate VLBW infants as soon as possible (median age 4-5 days). On the other hand, infants in the hydrocortisone trial are a unique subgroup of babies who are stuck on the ventilator. The investigators need to explain how the results of the spontaneous breathing test (SBT) in the hydrocortisone cohort will be generalizable in the typical NICU setting.

We agree that the postnatal age of patients in the hydrocortisone study is different from those in the Melbourne study. We also agree data in the proposed study will not be generalizable to all patients in the NICU. The proposed study is specifically designed to address the current knowledge gap in the literature, i.e., vailidity of the SBT at later postnatal age. We have clarified the protocol to indicate dand expanded the rationale for the study.

The specific aim related to modes of ventilation was discussed at length by the Subcommittee. Given center differences in the use of assisted modes of ventilation, the consensus of the Subcommittee is that this aim is not feasible. In addition, only a limited amount of data is currently being collected for the Hydrocortisone trial (see HCO4 respiratory data collection form); in order to address the aim related to assisted ventilation, a significant increase in data collection would need to be incorporated into the study design.

We have removed the specific aim related to duration of ventilation based on different modes of ventilation.

Finally, the Subcommittee discussed the potential confounding of post-extubation management. In the current protocol, it is not clear how differences in clinical management following extubation will be handled (many which could significantly impact the success of extubation).

This may actually be a strength of the proposed study, which is aimed at finding out if the SBT is better or not to clinical decision about readiness to extubation across multiple centers and multiple approaches to post-extubation therapy (CPAP, high-flow nasal cannula, NIPPV). We will collect this information and analyze it by secondary subgroup analysis and by multivariate analysis.

As currently written, the Subcommittee had low enthusiasm for the proposed secondary. However, the Subcommittee would be willing to review a revised version of the protocol which addresses the concerns outlined below.

Comments submitted by Kurt Schibler:

This observational study is primarily designed to evaluate whether a short endotracheal continuous positive airway pressure (ET CPAP) test may help predict the success of extubation of very premature infants.

1) The primary aim of this study is evaluate the point estimates and confidence intervals of sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio of a positive test, and likelihood ratio of a negative test for the spontaneous breathing test (SBT).

2) Secondary aims are 1) To evaluate point estimates and confidence intervals of sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio of a positive test, and likelihood ratio of a negative test for the SBT in two subgroups: infants ventilated with SIMV and infants ventilated using modes supporting all breaths and 2) To determine if ventilation modes that support every breath are associated with shorter duration of mechanical ventilation than SIMV.

Methods

Study design - This is an observational study with prospective data collection.

The study will involve analysis of the operational characteristics of a diagnostic test (SBT) and retrospective analysis of a cohort study (using two cohorts: babies ventilated using SIMV and babies ventilated using modes supporting all breaths).

The spontaneous breathing test (SBT) will be performed by the study team just before extubation decided by the clinicians. Clinicians will remain blinded to the results.

Study population - We will use the same population as that for the main study. All patients enrolled in the main study will be approached for an optional consent, indicated by a check on the consent to the main study

Study intervention - when the clinicians decide a baby is ready to be extubated, the investigator will perform the SBT within 4 hours of the planned extubation.

The researcher will silence any alarms and will place screens around the bedside before initiating the test to minimize the chance of unblinding. After ensuring that the clinical care team, including the patient's nurse, is away from be bedside (to maintain blinding) the investigator (respiratory therapist, fellow, nurse practitioner or attending), who must not be involved with the patient's clinical care, will switch the ventilator to CPAP for 3 minutes at the same pressure as the positive end-expiratory pressure setting. The infant's ETT will be suctioned prior to the SBT if clinically indicated, and the intervention will be done when the infant is in a quiet state, taking care to minimize stimulation and disturbance during the study. The baby fails the SBT if he or she develops a bradycardia (HR <100) for more than 15 seconds and/or a fall in SpO2 below 85% despite a 15% increase in FIO2. At this point the study will be stopped, and ventilation will be restarted. If manual breaths are given through the ventilator because of bradycardia or desaturation, this will be considered a failed test. Data on the mode of ventilation, success and time of extubation will be collected for subsequent analysis.

The baby will be placed back on previous ventilatory settings to 30 minutes, to limit the risk of derecruitment that could have resulted from performing the SBT.

Sample size

The investigators estimate that about 70% of the total sample size available in the main trial will be available for the analysis of this secondary study; thus sample size is estimated at 550. Since the secondary study will start after the beginning of the main study, the total number of patients in this secondary study will be probably 10% smaller, i.e. 500 patients.

Analysis plan

The investigators will determine the point estimates and 95% confidence intervals for the operating characteristics (sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio of a positive test, and likelihood ratio of a negative test) of successful extubation using the SBT.

Investigators will use the same tests in subgroups:

1. infants ventilated with SIMV versus infants ventilated using modes supporting all breaths at the time of the SBT.
2. infants with gestational age ≤ $26^{6/7}$ versus those with gestational age $27^{0/7} - 29^{6/7}$ weeks

Receiving operator characteristic curve (ROC) will be used to analyze whether the operating characteristics of the SBT vary according to ETT resistance and to postnatal age.

Comments

1. Allowing time after suctioning and after the SBT for potential re-recruitment of alveoli is important particularly in the lower gestational age strata. – We added a minimum of 10 minutes between suctioning and the SBT.

2. The reasons for failure to remain extubated for 72 hours are multifactorial including individual infant associate factors and factors related to providers or center. – This fact is acknowledged in the protocol and in the limitations. We will use multivariate analysis for this purpose; however we wil not control for individual providers. We may actually consider this as one of the strength of this study: external validation of the SBT test, which so far has been tested in single-center studies.

3. It may not be possible to have SBT performed by someone not involved in clinical care of the study infant. Webelieve it is important to maintain blinding of SBT. It would be up to each center to decide whether the study PI, coordinator, respiratory therapist, fellow, attending, or NNP would be involved in theSBT. Centers who are not able to perform blinding SBT should not participate.

4. The effects of the study medication in the main trial may influence the utility of the SBT to predict extubation success. The study is designed to determine this as one of the secondary outcomes and by using multivariate analysis.

5. The study forms and additional data to be collected should be included with the protocol in order to determine how time intensive the secondary study will be. Appendix B includes all the additional information required for the study, and was edited to include all the comments and suggestions from the reviewer. Further development of the forms will be done in the manual.

6. The respiratory support variable collected around the time of the test may have little bearing on modes of support and their influence on extubation success or failure. We agree with the reviewer that this variable may not affect the validity of the SBT. This will be one among many variables we will test.

7. Whether consent should be imbedded or not should be at the discretion of the centers. We changed the protocol accordingly.

Comments submitted by Brenda Poindexter:

SUMMARY: The proposed study is a secondary study to the hydrocortisone trial to assess the sensitivity, specificity, positive and negative predictive value of the spontaneous breathing test (SBT) in predicting successful extubation in ELBW infants.

1. The authors state that because this is an observational study, there is no primary hypothesis. This needs to be revised to reflect the analyses that will be done (hypothesis could be that the SBT will be more useful than clinical information alone). This was debated during the writing of the protocol. The best way to assess the hypothesis proposed by the reviewer as a primary hypothesis would be

by designing a randomized trial. Since this is an observational study we feel this should not be the primary hypothesis. Therefore, we propose instead to present the following question as a secondary hypothesis: is the rate of successful extubation among infants with a positive SBT similar to the observed success rate based on clinical information alone.

2. In the methods and procedures section of the protocol the authors state that the study will involve analysis of the operational characteristics of the SBT and retrospective analysis of a cohort study. The retrospective analysis is not mentioned anywhere else in the protocol. As currently written, it seems that all infants enrolled as part of the hydrocortisone for extubation main trial will all receive the SBT, so it is is not clear where the retrospective cohort will come from. Thank you for this comment; we agree with you. We have removed this sentence from the study design. If the primary question is whether the SBT has better predictive ability than typical clinical information (such as FiO2, PIP, PEEP, etc.) as stated in the rationale/justification, then wouldn't there need to be a control group of infants who are subjected to the SBT? The primary question is not to determine whether SBT is better predictive than clinical information; this would be best studied by a randomized trial.

3. Secondary aim – the second secondary aim is to determine if ventilation modes that support every breath are associated with shorter duration of mechanical ventilation than SIMV. Although data will be collected related to mode of ventilation at time of extubation, it would seem that detailed data related to respiratory support prior to the time of extubation would be required. The HC04 respiratory form collects only very limited information related to type of ventilator support on study days 1, 3, 5, 7, 10, and 14 and collects no information related to assist control or pressure support. If modes of assisted ventilation shorten the duration of mechanical ventilation, wouldn't the duration of being on an assisted mode also contribute to the outcome? In other words, I would think there would be a difference between infants whose entire course on the ventilator is in SIMV versus those who are only changed to SIMV during the final stages of weaning (for 12-24 hrs) prior to extubation. In the data analysis plan, the subgroups are only divided by mode of ventilation at the time of the SBT. How will duration of time in assisted ventilation mode be dealt with in the analyses? The investigators state that "very little additional coordinator time will be needed to collect information that will be used in multivariate analysis that could build the basis for a future randomized trial" but have not provided a draft of the proposed data collection forms to be utilized in the secondary study. The wide range of practice variation in modes of ventilator management at NRN centers provided by the survery results in the protocol highlight the likelihood that center differences will bias the ability to evaluate this secondary aim (this concern was also raised in the concept comments). We agree with the reviewer's concerns and eliminated this part of the study.

4. Unplanned extubations – the investigators have not taken into account unplanned extubations (some of which are likely to be successful). How will these infants be handled in the analyses? These events will be excluded from the analysis, since SBT is not performed.

5. Post-extubation management – the role of post-extubation management is not addressed in the protocol as a potential confounder to prediction of extubation success. What type of data will be collected during the immediate post-extubation period and what variables (such as extubation to CPAP versus HFNC or SiPAP, use of racemic epinephrine, etc.) will be considered in the analytic plan. This information was added to the protocol and to appendix B.

6. Treatment group – one of the secondary null hypotheses is that the predictive value of the SBT is not affected by whether the baby is randomized to hydrocortisone or placebo. This hypothesis needs to be justified as hydrocortisone, if efficacious as defined by the primary outcome measure of the main trial, could significantly confound the primary outcome of likelihood of extubation success (in addition to the other potential confounders mentioned in the protocol including fluid management, caffeine, etc.). We agree with the reviewer's comments. In this protocol we describe null hypotheses. We hypothesize that hydrocortisone might improve lung compliance and reduce laryngeal edema, thereby improving the success rate of extubation in comparison to the control group. We will analyze potential confounders by using multivariate analysis, which is now listed in the secondary outcome.

7. Masking – the protocol states that the individual performing the SBT should not be involved in the clinical care of the infant. Clarification is needed regarding the duration of time that this individual cannot be involved in the clinical care (before and after performance of the SBT). Regardless of who performs the test, it may be impossible to avoid having this person involved in the clinical care of the infant. It would be helpful to specify the period of time that the person administering the SBT should not be involved in the clinical care of the infant. The issue of clinical documentation and masking also needs to be addressed in the protocol. If an infant has significant hypoxia and/or bradycardia during the SBT, how will the documentation in the medical record be addressed? Given that data from our monitors in the NICU is recorded and reviewed on rounds on a daily basis, significant episodes of desaturation and/or bradycardia will be difficult to not relay to the clinical team; in addition, if the infant does require PPV or other intervention following a failed SBT, the clinical team will need to be informed. I would think that the IRB would question the plan to not inform the clinical team of a significant desaturation or bradycardia event knowing that an extubation attempt is being planned by the clinical team in the immediate future. In this regard, I disagree with the investigators that blinding the clinical team of a failed SBT (at least in the case of significant bradycardia or need for resuscitation) is "defensible". Thank you for your comments. The study cannot be done without masking the clinical team. If the caregivers know whether the baby has passed or failed the SBT, they will be biased by the study, and therefore it will be impossible to determine the outcomes described for the study. The large majority of the babies undergoing an SBT tolerate the procedure well and those who fail the SBT respond rapidly to manual breaths on the ventilator. If an occasional infant requires more than this, e.g., bag and mask ventilation or additional resuscitation. We have modified the protocol accordingly.

8. Budget – Two areas of the proposed budget warrant further consideration – first, there is a budget for a respiratory therapist for 15 minutes – does this mean that the SBT must be performed by a

study respiratory therapist? I would assume that the majority of centers do not have respiratory therapists on their paid research team. For other NRN studies requiring support from respiratory therapists (such as SUPPORT, Benchmarking, and the iNO studies), we have always relied on respiratory therapists at the centers providing their time without reimbursement. The protocol leaves to each center the choice of who will be involved in performing the SBT; in some centers only respiratory therapists are allowed to change ventilator settings. The second point that requires clarification is the 20 minutes of coordinator time for screening for subject who qualify for extubation. This would not be a one-time event, but rather would require daily screening until the infant met criteria for consideration of extubation. In addition, the decision to extubate is often made during morning rounds – therefore, this protocol will require that the clinical team inform the research coordinator of the intent to extubate in a timely manner (within the required 4 hours) or the opportunity to perform the SBT may be missed. In addition, for infants who require reintubation, the protocol states that a second SBT will be performed prior to the next extubation attempt; this effort for continuing to follow the infant after the first reintubation is not accounted for in the budget (nor is it required for the main RCT); the protocol is also inconsistent in this regard as the required follow-up is listed as being none beyond 72 hours after extubation (First extubation? Second if first one fails?). -Finally, the budget needs to be adjusted to reflect the additional data collection for type of respiratory support (as mentioned above, HC04 does not record whether infant is on assist control, SIMV, or pressure support). Thus, the time estimate for coordinator effort for this secondary study is markedly underestimated in the current budget. We now indicate in the protocol that we will use only the first 2 elective extubations after randomization. The coordinator time was increased to 4 hours based on your recommendations. However, please note that we have eliminated the collection of ventilator mode and support except just before and after SBT. We further revised the budget to indicate the above and followed Stephanie Archer's recommendations. We may further revise the budget once we know whether respiratory therapists will be involved in the study. At Parkland, one of the 2 respiratory therapists assigned to the NICU will perform the SBT.

9. Consent – the authors state that they do not feel that the imbedded consent will affect enrollment in the main trial because of the opt-out ability, but I do think that this issue will need to be prospectively monitored to ensure that enrollment in the main trial is not compromised. I am not in favor of imbedding consent for this secondary into the main trial; I would suggest that the decision of whether or not to imbed consent be left to the individual centers. We changed the protocol accordingly and will let each center choose whether to use a separate consent from or to imbed it into the consent for the main trial.

10. Data collection forms – drafts of the proposed data collection forms need to be included in the protocol; without these, it is impossible to ascertain whether the time estimates in the budget are appropriate or not. The data collection form is included in Appendix B and was updated based on all the comments from the review subcommittee.

Comments submitted by Stephanie Archer:

Questions:

- Estimated Start Date. I'm assuming no earlier than 6/1/12. Obviously, the later this is, the smaller the sample size, and the cheaper the cost. We modified the protocol accordingly.
- Consent rate. Not sure how you can say you will capture 70% of the original study population with only a 60% consent rate. I've used 70% in this estimate. We changed to 60%.
- Sample size. This will depend on the start date, consent rate, and the rate of recruitment for the Main trial. As of November 2011, only 16 randomized (versus an original main trial estimate of 27 recruited per month). We changed the protocol accordingly.
- Respiratory therapist. This rate is too low. For IPGE, we used $100/hour, which is probably still too low. We changed the budget accordingly.
- Training costs. Assuming no need for extensive training for this secondary – with any training done at a Steering Committee meeting or via teleconference. We changed the budget accordingly.

Comments submitted during Concept Presentation (17 yes, 3 no votes):

Comments with yes votes

- This study can add critical information to the steroid tria.
- AC vs SIMV length of ventilation comparison is unlikely to yield useful results.
- Simple, inexpensive, important study.
- We'd enthusiastically test this hypothesis.
- Validation of SBT particularly among subgroups would be very valuable. Comparison of ventilator modes will b e hopelessly biased by center difference. It might be worth looking at multiple definitions of failure at 12, 24 and even 48 hours. Comparison of duration of ventilation support by ventilator modes was eliminated from the protocol. We will add various definitions of failure to secondary outcomes.
- Will PDA influence SBT? This will be one of the variables assessed in the multivariate analysis.
- Where is ref 4 cited? All references are cited.
- Good use of the HC extubation main trial to gain additional information.
- Consent should not be embedded as it may decrease consent into main trial. This was changed.
- Coordinator and RTI seemed to be an under-estimate. The budget was revised accordingly.
- SBT validation more worthwhile than trying to get at length of ventilation. Focus on SBT component. The length of ventilation was removed from the protocol.

Comments with no votes

- Not easy to predict by ~ 3 minute of CPAP. Previous studies have shown that the SBT is superior to clinical parameters to predict successful extubation in preterm infants. Issues with upper airway obstruction and apnea despite caffeine. This information is being collected in this study.
- Post extubation variation HFNC/CPAP ;this information will be collected

Neonatal Research Network — Estimated Start Date:

Predicting Success of Extubation during Hydrocortisone Therapy and the Effect of Different Modes of Sync

Detailed Budget — Consent rate: 60%

Cost Category	April 2011-March Projections	
	Unit	Rate
I. Capitation (includes night, weekend, & holiday coverage)		
Months of Recruitment	0 mos	
A. Secondary Study		
Coordinator time (recruitment, data collection)(4 hrs/subject)	0 patients	$140
Respiratory Therapist time (30 minutes)	0 patients	$50
Subtotal Secondary Study		
Total Capitation		
II. Material Costs		
A. Other Direct Costs (indirects applied)		
Subtotal Other Direct Costs (indirects applied)		
B. Training		
Protocol training session at NRN	0	$2,000
Subtotal Additional Training (indirects applied)		
C. Equipment and Supplies (no indirects applied)		
Subtotal Equipment and Supplies (no indirects applied)		
Total Material Costs		
TOTAL DIRECT COSTS (Items I-IV)		
III. Indirect Costs (Unit = Total Direct Costs - Equipment and Supplies)	$0	52.60%
Total Indirect Costs		
ESTIMATED TOTAL COST		

6/1/2012
chronized Ventilation

1 2012		April 2012-March 2013 Projections			April 2013-March 2014 Projections			April 2
Total		Unit	Rate	Total	Unit	Rate	Total	Unit
		10 mos			12 mos			4 mos
	$0	160 patients	$140	$22,400	192 patients	$140	$26,880	21 patients
	$0	160 patients	$50	$8,000	192 patients	$50	$9,600	21 patients
	$0			**$30,400**			**$36,480**	
	$0			**$30,400**			**$36,480**	
	$0			**$0**			**$0**	
	$0	0	$2,000	$0	0	$2,000	$0	0
	$0			**$0**			**$0**	
	$0			**$0**			**$0**	
	$0			**$0**			**$0**	
	$0			**$30,400**			**$36,480**	
	$0	$30,400	52.60%	$15,990	$36,480	52.60%	$19,188	$3,990
	$0			**$15,990**			**$19,188**	
	$0			**$46,390**			**$55,668**	

:014-March 2015 Projections		TOTAL Projections			Add notes in this column to describe each line
Rate	Total	Unit	Rate	Total	
$140	$2,940	373	$140	$52,220	
$50	$1,050	373	$50	$18,650	
	$3,990			**$70,870**	
	$3,990			**$70,870**	
					Listed items are intended as memory joggers; c
	$0			**$0**	
$2,000	$0	0	$2,000	$2,000	
	$0			**$2,000**	
	$0			**$0**	
	$0			**$2,000**	
	$3,990			**$72,870**	
52.60%	$2,099	$72,870	52.60%	$38,330	
	$2,099			**$38,330**	
	$6,089			**$111,200**	

item.

hange or add items as needed.

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Krisa Van Meurs"
Cc: "Valerie Y-L Chock"
Subject: RE: SUPPORT secondary proposal - DRAFT version
Date: Thursday, January 19, 2012 11:53:00 AM

Ok
You may want to get Michele Walsh and Julie DI Fiore at Case involved - Julie has done some work with saturations and saturation swings with severe ROP>?

Thanks
Rose

Rosemary D. Higgins, MD
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-----Original Message-----
From: Krisa Van Meurs [mailto:vanmeurs@stanford.edu]
Sent: Thursday, January 19, 2012 11:37 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Valerie Y-L Chock
Subject: SUPPORT secondary proposal - DRAFT version

Hi Rose,

I wanted to make you aware of this DRAFT proposal we are submitting to the SUPPORT subcommittee, we are also involving Neil F, Wally and Ambal and will add them as co-authors.

Best,

Krisa

From: Maddox, Yvonne (NIH/NICHD) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: Dear1.docx
Date: Thursday, January 19, 2012 8:16:47 AM

Make it your call, and I will support.

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Thursday, January 19, 2012 08:08 AM
To: Maddox, Yvonne (NIH/NICHD) [E]
Cc: Spong, Catherine (NIH/NICHD) [E]
Subject: RE: Dear1.docx

NHLBI funded the capitation. They are aware of the situation. I don't need to include them.
Thanks
Rose

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higginsr@mail.nih.gov

From: Maddox, Yvonne (NIH/NICHD) [E]
Sent: Thursday, January 19, 2012 8:07 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: Dear1.docx

Rose, I do agree with the other cc's you suggest on the letter, with exception of nhlbi, as I don't know significance of them.

From: Maddox, Yvonne (NIH/NICHD) [E]
Sent: Thursday, January 19, 2012 07:56 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: Dear1.docx

Can you give me a quick call 3017851685.

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, January 18, 2012 06:12 PM
To: Maddox, Yvonne (NIH/NICHD) [E]
Cc: Spong, Catherine (NIH/NICHD) [E]; Hirschfeld, Steven (NIH/NICHD) [E]
Subject: Re: Dear1.docx

Yvonne
One more option if you can't attend our NRN steering committee meeting in person - we do have a call in line and could accommodate you at any time. Let me know if that would work better for you

Rose

From: Maddox, Yvonne (NIH/NICHD) [E]
Sent: Wednesday, January 18, 2012 04:49 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Spong, Catherine (NIH/NICHD) [E]; Hirschfeld, Steven (NIH/NICHD) [E]
Subject: RE: Dear1.docx

Rose, thanks for staying on this. I know this has been somewhat unpleasant, given the many successful and outstanding accomplishments of the NRN. We'll get through it.

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, January 18, 2012 4:46 PM
To: Maddox, Yvonne (NIH/NICHD) [E]
Cc: Spong, Catherine (NIH/NICHD) [E]; Hirschfeld, Steven (NIH/NICHD) [E]
Subject: RE: Dear1.docx

I can also put the "IRB stamped or approved" consent form in the letter. I will send you an updated letter.
Thanks
Rose

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From: Maddox, Yvonne (NIH/NICHD) [E]
Sent: Wednesday, January 18, 2012 4:44 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Spong, Catherine (NIH/NICHD) [E]; Hirschfeld, Steven (NIH/NICHD) [E]
Subject: RE: Dear1.docx

Yes, this would be critical for the OHRP to know that the IRB approved the consent form.

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, January 18, 2012 4:42 PM
To: Maddox, Yvonne (NIH/NICHD) [E]
Cc: Spong, Catherine (NIH/NICHD) [E]; Hirschfeld, Steven (NIH/NICHD) [E]
Subject: RE: Dear1.docx

Yes, we can get both the IRB approval letter as well as the consent form – would that be ok??

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higginsr@mail.nih.gov

From: Maddox, Yvonne (NIH/NICHD) [E]
Sent: Wednesday, January 18, 2012 4:41 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Spong, Catherine (NIH/NICHD) [E]; Hirschfeld, Steven (NIH/NICHD) [E]
Subject: RE: Dear1.docx

Yes, but doesn't the IRB approve the consent forms? (b)(5)

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, January 18, 2012 4:39 PM
To: Maddox, Yvonne (NIH/NICHD) [E]
Cc: Spong, Catherine (NIH/NICHD) [E]; Hirschfeld, Steven (NIH/NICHD) [E]
Subject: RE: Dear1.docx

Yvonne
Here is a revised letter with my suggestions. OHRP wants the consent forms, not the IRB approvals. Also, should RTI and NHLBI be included as cc's? RTI is the coordinating center and has provided a response already to OHRP and NHLBI funded the capitation for the SUPPORT Trial. I have spoken with Jim Kiley, Dorothy Gail and Carol Blaisdell about this issue.

I also attached our Steering committee agenda for the next two days – folks will be there until 2ish on Friday. Let me know if any specific time will work for you and we can accommodate your schedule.
Thanks for all your help

Rose

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From: Maddox, Yvonne (NIH/NICHD) [E]
Sent: Wednesday, January 18, 2012 1:12 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Spong, Catherine (NIH/NICHD) [E]; Hirschfeld, Steven (NIH/NICHD) [E]
Subject: Dear1.docx

Rose,

This is a draft of the points to speak about tomorrow and to send in a communications to the PIs. (b)(5) Bottom line Office of Human subjects Protection, DHHS has asked and we need to provide. On the other point we discussed, you will need to make each of the sites know that they are to send all IRB approvals in the future to the DCC, with a copy to you. Call or email if you have questions, etc.

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Maddox, Yvonne (NIH/NICHD) [E]
Cc: Spong, Catherine (NIH/NICHD) [E]; Hirschfeld, Steven (NIH/NICHD) [E]
Subject: RE: Dear1.docx
Date: Wednesday, January 18, 2012 4:56:00 PM
Attachments: sample letter.clean.docx
sample letter.docx

Here is the revised letter – one with track changes and a clean copy. I think we are good to go. Let me know if you have any other suggestions and if you can make it to the meeting. I will send this out via email on Friday to each site PI.
Thanks
Rose

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Sent: Wednesday, January 18, 2012 4:44 PM
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Cc: Spong, Catherine (NIH/NICHD) [E]; Hirschfeld, Steven (NIH/NICHD) [E]
Subject: RE: Dear1.docx

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Subject: RE: Dear1.docx

Yvonne
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Thanks for all your help

Rose

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To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Spong, Catherine (NIH/NICHD) [E]; Hirschfeld, Steven (NIH/NICHD) [E]
Subject: Dear1.docx

Rose,

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Name

Institution

Re: **The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)**

Dear--------:

As you are aware the Neonatal Research Network (NRN) continues to support studies under common protocols, but which require individual institutional IRB review prior to the conduct of these studies at each of the NRN sites. This is to inform you that The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), which provided the Federal support to the NRN, has been requested by the Office of Human Subjects Protection, to provide to the Office the most current consent form approved by your IRB and the corresponding IRB approval for the main SUPPORT Study, including any revisions, as soon as possible. As the NICHD Program Director of the NRN, I am requesting that the most recent consent form with IRB approval for your site for SUPPORT be submitted to me as soon as possible, but no later than January 26, 2012. Thank you for your cooperation.

Cc Spong

Hirschfeld

Maddox

RTI??

??NHLBI

Name

Institution

Re: **The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT)**

Dear---------:

As you are aware the Neonatal Research Network (NRN) continues to support studies under common protocols, but which require individual institutional IRB review prior to the conduct of these studies at each of the NRN sites. This is to inform you that The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), which provided the Federal support to the NRN, has been requested by the Office of Human Subjects Protection, to provide to the Office the most current consent form approved by your ~~all~~ IRB ~~approvals~~ and the corresponding IRB approval for the main SUPPORT Study, including any revisions, as soon as possible. As the NICHD Program Director of the NRN, I am requesting that the most recent consent form with IRB approval for your site for ~~to conduct~~ SUPPORT be submitted to me as soon as possible, but no later than January 26, 2012. Thank you for your cooperation.

Cc ~~spong~~Spong

Hirschfeld

Maddox

RTI??

??NHLBI

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From: Vaucher, Yvonne
To: Gabrio, Jenna; alaptook@WIHRI.org; Bradley Yoder; adas@rti.org; mgantz@rti.org; Higgins, Rosemary (NIH/NICHD) [E]; kurt.schibler@cchmc.org; mcw3@cwru.edu; MPeralta@PEDS.UAB.EDU; nancy newman; Finer, Neil; Roger.Faix@hsc.utah.edu; Wallace, Dennis; Wally Carlo, M.D.; Rich, Wade
Cc: sharon.gough@hsc.utah.edu; Archer, Stephanie (NIH/NICHD) [E]; Brenda Vecchio; Cunningham, Meg; Martinez, Fernando; Huitema, Carolyn Petrie; Zaterka-Baxter, Kristin
Subject: RE: SUPPORT Subcommittee Call to Discuss Secondary Proposal--Availability Request and Slaughter Secondary
Date: Tuesday, December 20, 2011 8:10:35 PM

Any of those days is OK for me.

Yvonne Vaucher

From: Gabrio, Jenna [jgabrio@rti.org]
Sent: Tuesday, December 20, 2011 11:25 AM
To: alaptook@WIHRI.org; Bradley Yoder; adas@rti.org; mgantz@rti.org; Higgins, Rosemary (NIH/NICHD) [E]; kurt.schibler@cchmc.org; mcw3@cwru.edu; MPeralta@PEDS.UAB.EDU; nancy newman; Finer, Neil; Roger.Faix@hsc.utah.edu; Wallace, Dennis; Wally Carlo, M.D.; Rich, Wade; Vaucher, Yvonne
Cc: sharon.gough@hsc.utah.edu; Archer, Stephanie (NIH/NICHD) [E]; Brenda Vecchio; Cunningham, Meg; Martinez, Fernando; Huitema, Carolyn Petrie; Zaterka-Baxter, Kristin
Subject: RE: SUPPORT Subcommittee Call to Discuss Secondary Proposal--Availability Request and Slaughter Secondary

Dear all,

Please find another secondary attached for discussion on the upcoming subcommittee call. We are still working on finding a time for this call.

Please let me know if you would still be available at the following times:

1/6, F, 10:30 AM – 1:00 PM ET

1/13, F, 2:30 PM – 5:00 PM ET

1/16, M, 1:00 PM ET

1/16, M, 4:00 PM ET

1/17, Tu, 1:00 PM ET

Thanks,
Jenna

From: Gabrio, Jenna
Sent: Thursday, December 01, 2011 10:13 AM
To: Abbot Laptook (alaptook@WIHRI.org); Bradley Yoder; Das, Abhik (adas@rti.org); Gantz, Marie (mgantz@rti.org); 'Higgins, Rosemary (NIH/NICHD) [E]'; kurt.schibler@cchmc.org; mcw3@cwru.edu; MPeralta@PEDS.UAB.EDU; nancy newman; 'nfiner@ucsd.edu'; Roger.Faix@hsc.utah.edu; Wallace, Dennis; Wally Carlo, M.D.; 'wrich@ucsd.edu'; 'Yvonne Vaucher'
Cc: (sharon.gough@hsc.utah.edu); 'Archer, Stephanie (NIH/NICHD) [E]'; 'Brenda Vecchio'; Cunningham, Meg; 'fmartinez@ucsd.edu'; Gabrio, Jenna; Huitema, Carolyn Petrie; Zaterka-Baxter, Kristin
Subject: SUPPORT Subcommittee Call to Discuss Secondary Proposal--Availability Request

Dear all,

We would like to schedule a SUPPORT subcommittee call to discuss the attached secondary proposal.

Please provide your availability on this Doodle poll (http://www.doodle.com/rbedq47eq5evy7ye) for the following dates:

Abbot, Kurt, Michele, Nancy, Wally, Rose, Stephanie, Dennis, Abhik: You do NOT need to complete this poll again, as I already have your availability for these dates. Please only complete the poll if your availability has changed since you completed the December General Availability Request.

12/7, W
12/8, Th
12/9, F

12/12, M

12/15, Th
12/16, F

12/19, M
12/20, Tu
12/21, W
12/22, Th

12/27, Tu
12/28, W
12/29, Th
12/30, F
Thanks,
Jenna

Jenna Gabrio
RTI International
Public Health Analyst

701 13th St., NW Suite 750
Washington, DC 20005
Phone: 202-728-1946
Fax: 202-974-7855

From: Walsh, Michele
To: Gabrio, Jenna; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT Subcommittee Call to Discuss Secondary Proposal--Availability Request and Slaughter Secondary
Date: Tuesday, December 20, 2011 2:49:23 PM

Oh.... That was GDB I think. Very similar analyses.

Michele Walsh, MD
Chief, Division of Neonatology
216.844.3759

It's not what you look at that matters, it's what you see. Thoreau

---

From: Gabrio, Jenna [mailto:jgabrio@rti.org]
Sent: Tuesday, December 20, 2011 2:47 PM
To: Walsh, Michele
Subject: RE: SUPPORT Subcommittee Call to Discuss Secondary Proposal--Availability Request and Slaughter Secondary

Hi Michele,

I don't believe this was discussed on the last call. Here are the minutes from the call held on October 11, 2011.

Thanks,
Jenna

From: Walsh, Michele [mailto:Michele.Walsh@UHhospitals.org]
Sent: Tuesday, December 20, 2011 2:32 PM
To: Gabrio, Jenna
Subject: RE: SUPPORT Subcommittee Call to Discuss Secondary Proposal--Availability Request and Slaughter Secondary

I thought this was discussed on the last call?

Michele Walsh, MD
Chief, Division of Neonatology
216.844.3759

It's not what you look at that matters, it's what you see. Thoreau

---

From: Gabrio, Jenna [mailto:jgabrio@rti.org]
Sent: Tuesday, December 20, 2011 2:26 PM
To: alaptook@WIHRI.org; Bradley Yoder; adas@rti.org; mgantz@rti.org; Higgins, Rosemary (NIH/NICHD) [E]; kurt.schibler@cchmc.org; mcw3@cwru.edu; MPeralta@PEDS.UAB.EDU; nancy newman; nfiner@ucsd.edu; Roger.Faix@hsc.utah.edu; Wallace, Dennis; Wally Carlo, M.D.; wrich@ucsd.edu; Yvonne Vaucher
Cc: sharon.gough@hsc.utah.edu; Archer, Stephanie (NIH/NICHD) [E]; Brenda Vecchio; Cunningham,

Meg; fmartinez@ucsd.edu; Huitema, Carolyn Petrie; Zaterka-Baxter, Kristin
Subject: RE: SUPPORT Subcommittee Call to Discuss Secondary Proposal--Availability Request and Slaughter Secondary

Dear all,

Please find another secondary attached for discussion on the upcoming subcommittee call. We are still working on finding a time for this call.

Please let me know if you would still be available at the following times:

1/6, F, 10:30 AM – 1:00 PM ET

1/13, F, 2:30 PM – 5:00 PM ET

1/16, M, 1:00 PM ET

1/16, M, 4:00 PM ET

1/17, Tu, 1:00 PM ET

Thanks,
Jenna

From: Gabrio, Jenna
Sent: Thursday, December 01, 2011 10:13 AM
To: Abbot Laptook (alaptook@WIHRI.org); Bradley Yoder; Das, Abhik (adas@rti.org); Gantz, Marie (mgantz@rti.org); 'Higgins, Rosemary (NIH/NICHD) [E]'; kurt.schibler@cchmc.org; mcw3@cwru.edu; MPeralta@PEDS.UAB.EDU; nancy newman; 'nfiner@ucsd.edu'; Roger.Faix@hsc.utah.edu; Wallace, Dennis; Wally Carlo, M.D.; 'wrich@ucsd.edu'; 'Yvonne Vaucher'
Cc: (sharon.gough@hsc.utah.edu); 'Archer, Stephanie (NIH/NICHD) [E]'; 'Brenda Vecchio'; Cunningham, Meg; 'fmartinez@ucsd.edu'; Gabrio, Jenna; Huitema, Carolyn Petrie; Zaterka-Baxter, Kristin
Subject: SUPPORT Subcommittee Call to Discuss Secondary Proposal--Availability Request

Dear all,

We would like to schedule a SUPPORT subcommittee call to discuss the attached secondary proposal.

Please provide your availability on this Doodle poll (http://www.doodle.com/rbedq47eq5evy7ye) for the following dates:

Abbot, Kurt, Michele, Nancy, Wally, Rose, Stephanie, Dennis, Abhik: You do **NOT** need to complete this poll again, as I already have your availability for these dates. Please only complete the poll *if your availability has changed* since you completed the December General Availability Request.

12/7, W
12/8, Th

12/9, F

12/12, M

12/15, Th
12/16, F

12/19, M
12/20, Tu
12/21, W
12/22, Th

12/27, Tu
12/28, W
12/29, Th
12/30, F

Thanks,
Jenna

Jenna Gabrio
RTI International
Public Health Analyst

701 13th St., NW Suite 750
Washington, DC 20005
Phone: 202-728-1946
Fax: 202-974-7855

specific
written consent of the person to whom it pertains, or as
otherwise permitted
by law.

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From: Vaucher, Yvonne
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Vaucher, Yvonne
Subject: RE: SUPPORT CPAP PAPER NRN InternalReview
Date: Friday, December 16, 2011 3:50:03 PM
Attachments: Vaucher SUPPORT FU CPAP PAPERYEV12152011ForNRNPublicationCommittee.docx

Here is the latest version of the CPAP SUPPORT paper for NRN internal review. I addressed the reviewer comments, shortened the abstract for the NEJMand deleted the medical FUP section. It gets shorter and shorter! Let me know if I need to make other changes. Have a good holiday!

Yvonne

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, November 30, 2011 9:12 AM
To: Vaucher, Yvonne; Finer, Neil
Cc: 'Wally Carlo, M.D.'; 'Myriam Peralta-Carcelen (MPeralta@peds.uab.edu)'; Gantz, Marie; 'Das, Abhik'
Subject: SUPPORT CPAP PAPER

Yvonne -
This looks very good – I have a few suggestions similar to what I suggested to Myriam for the oximetry paper-Since these papers are going to NEJM, we need to stick to exactly what we wrote in the protocol for secondary outcomes (unless we say this is a post hoc analysis).
The secondary outcomes/hypothesis in the protocol are as follows:
A decreased Mortality/NDI at 18-22 months corrected age.
A decreased incidence of blindness of at least one eye at 18-22 month follow-up
· A decreased incidence of neurodevelopmental impairment at 18-22 month follow-up
· A decreased incidence of cerebral palsy at 18-22 month follow-up

We currently have information in the paper relating to :

Outcomes following NICU discharge included rehospitalizations, interim medical history, surgery and medications were recorded at the 18-22 month visit. These should be deleted for at least two reasons – overlap with pulmonary outcomes study and they are not listed in the main SUPPORT protocol (which will be requested by NEJM).

For this paper, I think it is important to include the two GA strata given the difference in death between the CPAP and surf groups in the lower strata – this is of keen interest to clinicians

Let me know what you think

Thanks

Rose

Rosemary D. Higgins, MD
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Early CPAP versus Surfactant in Extremely Preterm Infants: Neurodevelopmental Outcomes in Early Childhood

Yvonne E. Vaucher, MD MPH[1]; Myriam Peralta-Carcelen, MD MPH[2]; Neil N. Finer, MD[1]; Waldemar A. Carlo, MD[2]; Michele C. Walsh, MD MS[3]; Marie G. Gantz, PhD[4]; Abbot R. Laptook, MD[5]; Bradley A. Yoder, MD[6]; Roger G. Faix, MD[6]; Abhik Das, PhD[7]; Kurt Schibler, MD[8]; Wade Rich, RRT[2]; Nancy S. Newman, RN[4]; Betty R. Vohr, MD[5]; Kimberly Yolton, PhD[8]; Roy J. Heyne, MD[9]; Deanne E. Wilson-Costello, MD[4]; Patricia W. Evans, MD[10]; Ricki F. Goldstein, MD[11]; Michael J. Acarregui, MD[12]; Ira Adams-Chapman, MD[13]; Athina Pappas, MD[14]; Susan R. Hintz, MD MS Epi[15]; Anna M. Dusick, MD FAAP[16]; Elisabeth C. McGowan, MD[17]; Richard A. Ehrenkranz, MD[18]; Anna Bodnar, MD[6]; Charles R. Bauer, MD[19]; Janell Fuller, MD[20]; T. Michael O'Shea, MD MPH[21]; Gary J. Myers, MD[22]; Rosemary D. Higgins, MD[23] for the SUPPORT Study Group of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network

Corresponding author and reprints:

Yvonne E. Vaucher, M.D., M.P.H. Telephone: 619-543-3759

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[19] University of Miami Miller School of Medicine, Miami, FL
[20] University of New Mexico Health Sciences Center, Albuquerque, NM
[21] Wake Forest University School of Medicine, Winston-Salem, NC
[22] Department of Pediatrics, University of Rochester Medical Center, Rochester, NY
[23] *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD

University of California, San Diego

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200 West Arbor Drive

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ABSTRACT

BACKGROUND: The randomized controlled SUPPORT trial demonstrated that treatment with early CPAP is an alternative to early intubation with surfactant administration, resulting in similar rates of death or BPD in infants born at 24 to 27 weeks gestation. We hypothesized that, compared to early intubation , early CPAP would decrease the composite outcome of death or neurodevelopmental impairment.

METHODS: We followed surviving infants, 24 0/7 to 27 6/7 weeks gestation, randomized in the SUPPORT trial to receive either early CPAP with limited ventilation or intubation with surfactant administration within one hour after birth and conventional ventilation. The primary composite outcome was death or neurodevelopmental impairment (NDI) at 18-22 months corrected age.

RESULTS: Death or NDI was determined for 1234/1316 (93.8%) of infants enrolled in SUPPORT; 93.6% (990/1058) of survivors to hospital discharge were evaluated at 18-22 months corrected age. Death or NDI occurred in 27.9% (173/621) of the CPAP group and in 29.9% (183/613) of the Surfactant group (RR 95% CI 0.93, 0.78.1.1, p=0.39). There were no significant differences between treatment arms in death (CPAP-18.4 vs. Surf-21.9%), NDI (CPAP-10.9 vs. Surfactant-9.1%,) or components of NDI including cognitive score < 70 (CPAP-7.2 vs. Surfactant-7.6%,), moderate/severe cerebral palsy (CPAP-4.1 vs. Surfactant-4.0%), blindness (CPAP-0.8 vs. Surfactant-1.5%) and hearing impairment (CPAP-3.3 vs. Surfactant-1.5%).

CONCLUSION: We found no significant differences in the composite outcome of death or NDI at 18-22 months corrected age between extremely premature infants who were randomized to receive either early CPAP with a limited ventilation strategy or early intubation with surfactant administration and conventional ventilation.

BACKGROUND

Extremely premature infants are at high risk for death and neurosensory or developmental impairment in early childhood. [1-3] The risk of impairment increases with decreasing gestational age, severity of illness and as consequence of neonatal complications including intraventricular hemorrhage or periventricular leukomalacia, symptomatic patent ductus arteriosus, necrotizing enterocolitis, sepsis, prolonged ventilation, bronchopulmonary dysplasia and severe retinopathy of prematurity. [4-12] Although surfactant administration decreases both death and BPD, randomized controlled trials of respiratory interventions including high frequency oscillatory ventilation, high frequency jet ventilation, and inhaled nitric oxide have failed to consistently decrease mortality and morbidity or improve developmental outcome. [13-17]

The recent, multicenter, randomized controlled Surfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT) demonstrated that treatment with non-invasive continuous positive airway pressure (CPAP) shortly after birth is an alternative to surfactant administration after intubation and results in similar rates of death or BPD in extremely premature infants born at 24 0/7 to 27 6/7 weeks gestation. [18] Compared with randomization to surfactant, randomization to early CPAP resulted in less frequent need for postnatal steroids and shorter duration of mechanical ventilation. Both treatment groups had similar rates of air leak, severe intraventricular hemorrhage and other major outcomes. Mortality was lower in the most immature, 24-25 week gestation, stratum of the CPAP arm.

The SUPPORT trial in extremely low birth weight (ELBW) infants was powered to have adequate sample size to evaluate early childhood neurodevelopmental outcome of enrolled infants. We hypothesized that compared to randomization to treatment with surfactant administration after intubation, randomization to early, non-invasive CPAP and a limited ventilation strategy would decrease the rate of a composite outcome of death or neurodevelopmental impairment at 18-22 months corrected age.

METHODS

Study Design

1316 extremely preterm infants (24 weeks 0 days to 27 weeks 6 days) born between February 2005 and February 2009 at 20 centers in the United States participating in the Neonatal Research Network (NRN) of the Eunice Kennedy Shriver National Institute of Child Health and Human Development were enrolled prior to delivery in the randomized controlled SUPPORT trial. Permuted block randomization was used, with stratification according to center and gestational age (24 weeks 0 days to 25 weeks 6 days or 26 weeks 0 days to 27 weeks 6 days), and multiple births were randomized to the same treatment group. The infants were randomly assigned in the delivery room to receive either CPAP immediately following delivery and a limited ventilation strategy if subsequent intubation was required or intubation with surfactant administration within an hour after birth and subsequent conventional ventilation. Using a 2-by-2 factorial design, participants were also randomly assigned to a target oxygen saturation of 85% to 89% (lower oxygen saturation group) or 91 to 95% (higher oxygenation group). Procedures for enrollment, intervention, and data collection have been previously reported.[18] The study was approved by the institutional review board at each participating site and at RTI International, the independent data coordinating center for the Neonatal Research Network. Written informed consent was obtained from the parent or guardian of each child before delivery.

Assessments

A comprehensive neurodevelopmental assessment was performed on survivors at 18-22 months of age, corrected for prematurity (CA), by neurologic examiners and neurodevelopmental testers who were unaware of the treatment assignments and were annually evaluated for testing reliability during a 2-day workshop. Developmental function was assessed using the Bayley Scales of Infant and Toddler Development, 3rd ed. (BSID-III).[19] Cognitive Composite Scores are reported as a standardized score with a mean of 100 and a standard deviation of 15. Examiners recorded the presence of cerebral palsy defined as a nonprogressive disorder of the central nervous system and characterized by abnormal muscle tone in at least one arm or leg associated with abnormal control of movement or posture with delayed attainment of motor milestones. [20] The modified Gross Motor Function Classification System (GMFCS) was used to classify the gross motor performance using a range from 0 (normal) to 5 (most impaired).[21] Moderate to severe cerebral palsy was defined by a GMFCS ≤ 2. Hearing loss defined as the inability to understand directions of the examiner and communicate with or without amplification and visual impairment defined as vison < 20-200) were determined based on examination and parental report.

Certified research nurses collected demographic and neonatal outcome data using standard NRN definitions. Demographic and outcome data collected included gestational age, birthweight, gender, multiple gestation, race/ethnicity, history of medical or surgical necrotizing enterocolitis (modified Bell's Stage ≥ 2), Grades 3-4 intraventricular hemorrhage (IVH) or periventricular leukomalacia (PVL), late onset sepsis, retinopathy of prematurity (ROP), bronchopulmonary dysplasia (BPD), use of postnatal steroids. Socioeconomic variables included insurance status, maternal marital status, maternal education, household income, language spoken at home, and whether the child was living with biological parents. Outcomes following NICU discharge, including rehospitalizations, interim medical history, surgery, and medications, were recorded at 18-22 month visit. Socioeconomic data were updated during the 18-22 month visit and were used if data from the neonatal period were not available.

Outcome

The primary outcome at follow up for this trial was the composite of death or neurodevelopmental impairment at 18 to 22 months corrected age. This composite outcome was selected because infants who died before 18 months could not be classified as having neurodevelopmental impairment, and death is a competing outcome to the latter. Neurodevelopmental impairment was defined as having any of the following: BSID III cognitive composite score less than 70, GMFCS ≥ 2, presence of moderate or severe cerebral palsy, permanent hearing loss that does not permit the child to understand directions of the examiner and communicate despite amplification with hearing aids or bilateral visual impairment (vision < 20/200).

Statistical Analysis

Pre-specified outcomes at 18 to 22 months corrected age were mortality or NDI,NDI, cerebral palsy, blindness in at least one eye. The sample size calculations were based on NRN data on infants born in the year 2000 which included the rate of death or neurodevelopmental impairment at 18-22 months corrected age. Details regarding sample size calculations for the SUPPORT trial have been previously reported. [18] Exploratory secondary outcomes at 18 to 22 months corrected age were death and components of NDI (i.e., cognitive composite score < 70, GMFCS ≥ 2, moderate/severe cerebral palsy, bilateral blindness and bilateral hearing impairment).

Data were entered in standard forms and were transmitted to RTI International which stored, managed and analyzed the data for this study. All analyses were performed according to the intention-to-treat principle. Unadjusted comparisons of demographic and birth characteristics between treatment groups were conducted

using chi-square tests for categorical variables and t tests for continuous variables. The primary analyses focused on the percentage of infants in each group for whom the primary outcome of death or NDI at 18-22 months corrected age could be assigned. Analysis of this and all other categorical outcomes was performed using robust Poisson regression in a generalized-estimating-equation model to obtain adjusted relative risks with 95% confidence intervals. The denominator that was used to calculate the rate of each outcome was the number of infants for whom that outcome was known. Continuous outcomes were analyzed using mixed-effects linear models to obtain adjusted means and standard errors.

Analyses of all neonatal and 18-22 month outcomes were adjusted, as prespecified, for gestational-age strata, center, and familial clustering because multiple births were assigned to the same treatment group. Two-sided p values of less than 0.05 were considered to indicate statistical significance, and no adjustments have been made for multiple comparisons.

RESULTS

Two hundred fifty-eight children were known to have died before 18-22 months (Figure). Sixty-eight children of the remaining 1058 (6.4%) were lost to follow-up; the survival status of 35/68 of these children was unknown. A neurodevelopmental assessment at 18-22 months corrected age was performed for 990/1058 (93.6%) children. Of the 990 children seen for evaluation, NDI was determined for 976 children; 14 children were seen but had an incomplete evaluation that precluded assigning a NDI status. Ultimately, the pre-specified outcome, death or NDI, was determined for 93.8% (1234/1316) of SUPPORT children. The mean corrected age at neurodevelopmental assessment was similar for both treatment arms (CPAP 19.9 ± 2.4 months vs. Surf 20.1 ± 2.7 months, unadjusted p=0.31). There was no difference in the follow-up rate between the CPAP and Surfactant arms (93.7 vs. 93.4%) of the trial.

Compared with mothers of the 990 children who had a neurodevelopmental assessment at 18-22 months, mothers of the 68 children lost to follow-up were less likely to be married (31 vs. 47%, p=0.01), and more likely to have only public insurance (69 vs. 52%, p=0.008). No other demographic variables or neonatal characteristics were significantly different between the groups.

Trial and Follow-up Cohorts: (Table 1) Almost all mothers (96%) in both treatment arms received antenatal steroids. Thirty-four percent of infants in the CPAP arm were intubated in the delivery room and 67% ultimately received surfactant and ventilation. Compared to the Surfactant arm, infants in the CPAP arm with follow-up at 18-22 months were significantly more likely to have had medical or surgical NEC and less likely to have been exposed to postnatal steroids . Other demographic characteristics and neonatal outcomes were similar in infants in the Surfactant and CPAP arms.

Primary neurodevelopmental outcome: (Table 2) The composite outcome of death or NDI at 18-22 months corrected age was not a significantly different between the CPAP and surfactant arms (27.9 vs. 29.9%, RR 0.93 (95% CI 0.78, 1.1), adjusted p=0.38). There were fewer deaths before 18-22 months corrected age in the CPAP arm but the difference did not reach statistical significance (18.4 vs. 21.9 %, RR 0.83 (95% CI 0.67,1.04), adjusted p=0.10).

Components of NDI: (Table 2) The incidences of cognitive impairment (BSID-III cognitive composite score < 70 (7.2% vs. 7.6%), gross motor function level ≥ 2 (5.1 vs. 4.8%), moderate/severe cerebral palsy (4.1 vs. 4.0%), and blindness (0.8 vs. 1.5%) among survivors were similar in the CPAP and Surfactant treatment groups. There was a higher incidence of hearing impairment in the early CPAP treatment arm compared to the surfactant

treatment arm but the difference was not statistically significant (3.3 vs. 1.5%, adjusted p=.06). Overall 24 infants had hearing loss, 13 of whom had bilateral hearing aids. There were no significant differences in composite outcomes of death or individual NDI components between the CPAP and Surfactant arms (Table 3).

Other neurodevelopmental outcomes: Mean BSID-III composite cognitive scores were similar in both CPAP and Surfactant arms (adjusted means ± standard error 91.3 ± 0.7 vs. 90.4 ± 0.8). Sixty percent of all children seen at 18-22 months corrected age (CPAP 59.7% and Surfactant 59.6%) had normal neuromotor, normal neurosensory and normal developmental (i.e. BSID-III cognitive composite score ≥ 85) evaluations.

Comparisons of outcome between gestational age strata: (Tables 2 and 3)
The difference in death before 18-22 months in the CPAP and surfactant arms was statistically significant in the lower 24 0/7 to 25 6/7 weeks gestation stratum [26.4 vs. 35.5%, adjusted p=0.02, RR 0.74 (95%CI 0.57,0.96)], but not in the higher gestational age stratum (12.3 vs. 11.8%). There were no significant differences in the composite outcome of *death or NDI* at 18-22 months corrected age between the CPAP and surfactant within either of the two gestational age strata (40.1 vs. 44.5% for 24 0/7-25 6/7 weeks gestation; 18.3 vs. 18.7% for 26 0/7 to 27 6/7 weeks gestation). Neither were there significant differences between the CPAP and Surfactant arms in the incidence of *NDI* alone within either of the two gestational age strata (18.1 vs. 12.5, adjusted p=0.22 for 24 0/7-25 6/7 weeks gestation; 6.3 vs. 7.2%, adjusted p=0.81 for 26 0/7-27 6/7 weeks gestation. Within each gestational age stratum the mean BSID-III composite *cognitive scores* were similar in both treatment groups (CPAP 89.2 ± 1.1 vs. Surfactant 88.1 ± 1.2 for 24 0/7-25 6/7 weeks gestation; CPAP 93.4 ± 0.9 vs. Surfactant 92.6 ± 0.9 for 26 0/7 to 27 6/7 weeks gestation, adjusted mean ± standard error).

Although neurodevelopmental outcomes were similar between treatment arms within each gestational age stratum, children in the lower gestational age stratum were at higher risk of adverse outcome. Children in the lower gestational age stratum were less likely to be normal (i.e., BSID-III cognitive score ≥85; neurologic and neurosensory exam normal, GMFCS =0) compared to children in the higher gestational age stratum, (CPAP 47.7% and Surfactant 49.4% for 24 0/7-25 6/7 weeks gestation vs. CPAP 67.5% and Surfactant 65.2% for 26 0/7 to 27 6/7 weeks gestation).

DISCUSSION:
We report the neurodevelopmental outcome in early childhood at 18-22 months corrected age for extremely premature children, 24-27 weeks gestation, enrolled in the SUPPORT trial. There was no significant difference in the primary, pre-specified composite outcome of death or NDI at 18-22 months corrected age between those extremely premature infants randomized to treatment with early CPAP vs. those randomized to treatment with early intubation and surfactant administration. Neither were there significant differences between survivors in the CPAP and Surfactant arms in NDI or its components of severe cognitive impairment (cognitive score < 70), moderate/severe cerebral palsy, moderate/severe motor impairment (GMFSC ≥2), and bilateral blindness, or in mean composite cognitive BSID-III scores.

As reported in previous studies, the most immature infants (24 to 25 weeks gestation) in both CPAP and Surfactant arms were less likely to be normal and were at higher risk for severe cognitive impairment, abnormal gross motor function, moderate/severe cerebral palsy and hearing impairment. [22-24]

Bronchopulmonary dysplasia and longer duration of ventilation are associated with an increased risk of adverse neurodevelopmental outcome. [4,8-10] Although infants in the CPAP arm had significantly fewer days of

ventilation and less often received postnatal steroids compared to the surfactant treated arm, the incidence of physiologic bronchopulmonary dysplasia was similar in both groups before discharge.

The strengths of this study include the large number of extremely premature infants enrolled, sufficient power to detect a clinically significant difference in the pre-specified outcome of death or neurodevelopmental impairment, the very high percentage of participants who were followed and evaluated in early childhood, and the comprehensive and standardized neurodevelopmental evaluation performed on survivors. One third of infants in the CPAP arm were intubated in the delivery room and two thirds ultimately received surfactant treatment and limited ventilation for clinical indications which may have blunted any difference in neurodevelopmental outcomes between the two groups. In addition, an adverse effect on neurodevelopmental outcome associated with the increased incidence of NEC in the CPAP arm may have counterbalanced adverse outcomes associated with the longer duration of ventilation and the increased need for supplemental oxygen and post-natal steroids in the surfactant treatment arm. The generalizability of this study may be limited by the need for antenatal consent which resulted in a trial cohort with higher socioeconomic status and receipt of antenatal steroids than the entire eligible cohort.[25]

In summary, we found no significant differences in the composite outcome of death or NDI, or in any of the individual components of NDI among survivors to 18-22 months corrected age between extremely preterm infants who were randomized at delivery to either early CPAP with a limited ventilation strategy or early intubation with surfactant administration followed by conventional ventilation. In this study early CPAP, an alternative respiratory management strategy for the extremely premature infant, did not result in an increased risk of neurodevelopmental impairment in early childhood.

Acknowledgements

The National Institutes of Health, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), and the National Heart, Lung, and Blood Institute (NHLBI) provided grant support for the Neonatal Research Network's SUPPORT Trial.

Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Drs. Abhik Das (DCC Principal Investigator) and Marie Gantz (DCC Statistician) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study. The following investigators, in addition to those listed as authors, participated in this study:

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Figure : Patient Flow diagram

Table 1: Demographic and neonatal characteristics of trial and follow-up cohorts

Table 2: Pre-specified outcomes and components of NDI for entire cohort and by gestational age strata

Table 3: Death and components of NDI for entire cohort and by gestational age strata

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Figure: Patient Flow Diagram

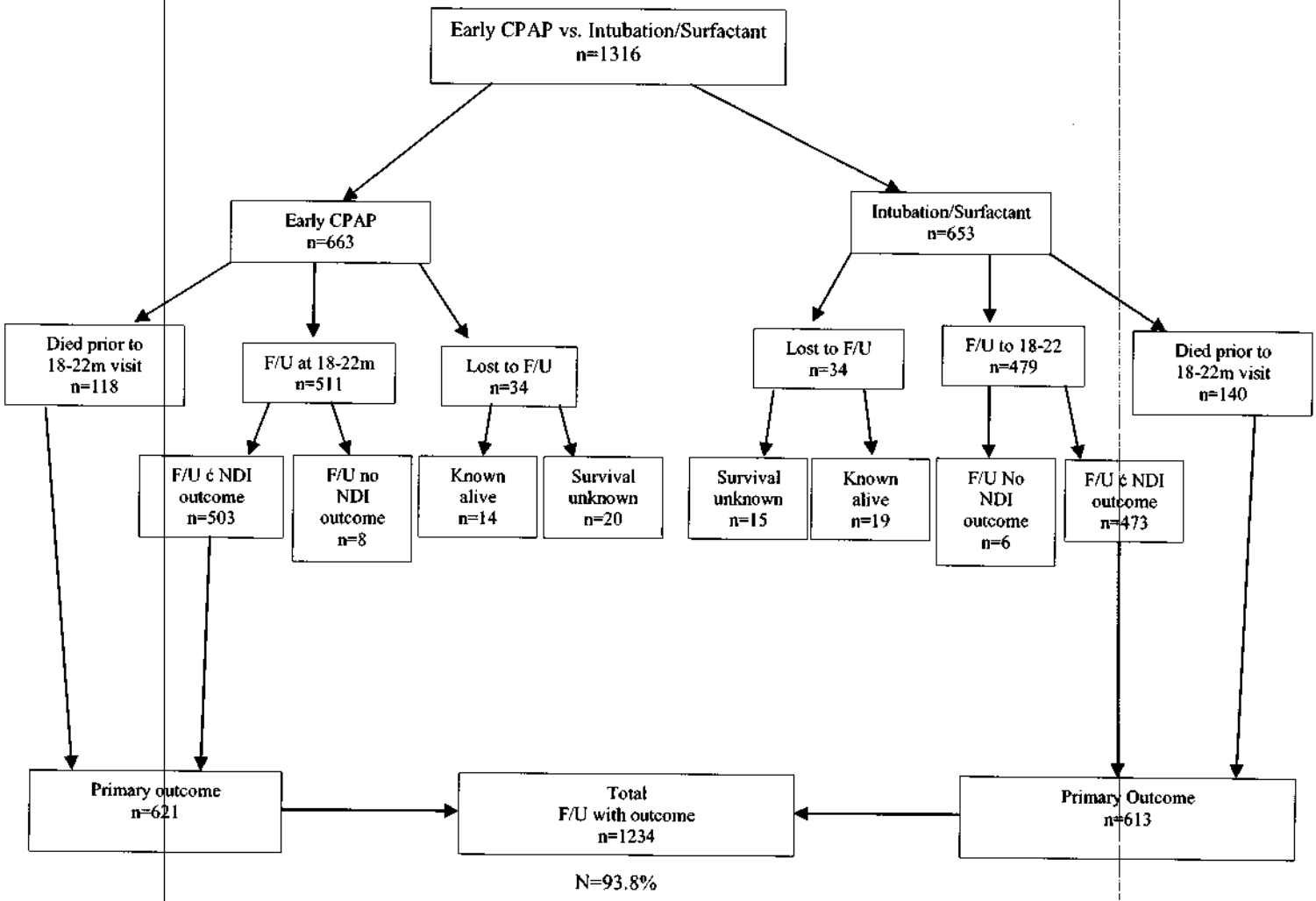

Table 1: Demographics and Characteristics of Trial Cohort and Follow-up Cohorts

	Trial Cohort		Follow-up Cohort	
	CPAP	Surfactant	CPAP	Surfactant
	N=663	N=653	N=511	N=479
Birth weight (grams, Mean ± SD)	835±188	826±198	849±186	852±193
Gestational age (weeks, Mean ± SD)	26.2±1.1	26.2±1.1	26.3±1.1	26.3±1.1
Small for gestational age < 10-no./total no.(%)	37/663(5.6)	59/653(9)**	23/511(4.5)	32/479(6.7)
Male-no./total no.(%)	342/663(51.6)	370/653(56.7)	256/511(50.1)	266/479(55.5)
Race				
Non-Hispanic White-no./total no.(%)	250/663(37.7)	271/653(41.5)	196/511(38.4)	200/479(41.8)
Non-Hispanic Black-no./total no.(%)	254/663(38.3)	235/653(36)	200/511(39.1)	177/479(37)
Hispanic-no./total no.(%)	138/663(20.8)	121/653(18.5)	98/511(19.2)	85/479(17.7)
Other or unknown-no./total no.(%)	21/663(3.2)	26/653(4)	17/511(3.3)	17/479(3.5)
Multiples-no./total no.(%)	178/663(26.8)	159/653(24.3)	138/511(27)	114/479(23.8)
Antenatal steroids(any)-no./total no.(%)	642/663(96.8)	623/652(95.6)	493/511(96.5)	456/479(95.2)
Cesarean section-no./total no.(%)	449/663(67.7)	434/653(66.5)	352/511(68.9)	315/479(65.8)
Public health insurance only-no./total no.(%)	351/661(53.1)	353/649(54.4)	262/511(51.3)	257/479(53.7)
Mother married-no./total no.(%)	305/662(46.1)	287/651(44.1)	244/511(47.7)	221/479(46.1)

With both biological parents†-no./total no.(%)	365/539(67.7)	353/516(68.4)	348/510(68.2)	329/479(68.7)
Maternal education < 12-no./total no.(%)	161/616(26.1)	152/590(25.8)	128/506(25.3)	116/469(24.7)
Income < $30,000/year†-no./total no.(%)	270/514(52.5)	268/488(54.9)	260/493(52.7)	251/461(54.4)
English as primary language at FUP -no./total no.(%)	427/511(83.6)	404/479(84.3)	426/510(83.5)	403/478(84.3)
Severe ROP in survivors to discharge-no./total no.(%)	67/511(13.1)	65/473(13.7)	62/479(12.9)	58/434(13.4)
Bronchopulmonary dysplasia in survivors to 36 weeks gestational age-no./total no.(%)	223/569(39.2)	219/539(40.6)	193/511(37.8)	187/479(39)
IVH grade 3-4/PVL-no./total no.(%)	111/642(17.3)	87/628(13.9)	70/510(13.7)	46/478(9.6)
NEC-stage ≥2 -no./total no.(%)	83/654(12.7)	63/636(9.9)	56/511(11)	30/479(6.3)**
Late onset sepsis/meningitis-no./total no.(%)	224/634(35.3)	230/624(36.9)	167/511(32.7)	154/479(32.2)
Postnatal steroids-no./total no.(%)	47/649(7.2)	83/631(13.2)***	34/508(6.7)	55/476(11.6)**
Died before discharge-no./total no.(%)	109/663(16.4)	128/653(19.6)		

†Not available for infants who did not survive to discharge

p<0.02,*p<0.001

Tests comparing neonatal outcomes (i.e., Severe ROP through Died before discharge) adjusted for stratification factors (study center and gestational age group) and familial clustering

Table 2: Death and NDI for entire cohort and gestational age strata*

CPAP vs. Surfactant (All)	CPAP	Surfactant	RR	p
Death before 18-22 mo CA-no./total no.(%)	118/643(18.4)	140/638(21.9)	0.83(0.67,1.04)	0.10
Death/NDI determined-no./total no.(%)	621/663(93.7)	613/653(93.9)	1(0.97,1.03)	0.83
Death or NDI-no./total no.(%)	173/621(27.9)	183/613(29.9)	0.93(0.78,1.1)	0.38
NDI-no./total no.(%)	55/503(10.9)	43/473(9.1)	1.16(0.79,1.71)	0.44
BSID-III cognitive score < 70-no./total no.(%)	36/502(7.2)	36/472(7.6)	0.95(0.61,1.5)	0.84
Gross motor function level ≥ 2-no./total no.(%)	26/511(5.1)	23/479(4.8)	0.98(0.57,1.69)	0.95
Moderate/severe cerebral palsy-no./total no.(%)	21/511(4.1)	19/479(4)	0.93(0.51,1.72)	0.82
Blindness, bilateral-no./total no.(%)	4/511(0.8)	7/479(1.5)	0.53(0.16,1.78)	0.31
Hearing impairment-no./total no.(%)	17/511(3.3)	7/479(1.5)	2.27(0.96-5.37)	0.06

b. 24 0/7-25 6/7 weeks Gestational Age	CPAP	Surfactant	RR	p
Death before 18-22 mo CA-no./total no.(%)	73/277(26.4)	97/273(35.5)	0.74(0.57,0.96)	0.02
Death/NDI determined-no./total no.(%)	272/285(95.4)	265/280(94.6)	1.01(0.97,1.05)	0.68
NDI or death-no./total no.(%)	109/272(40.1)	118/265(44.5)	0.9 (0.74,1.09)	0.27
NDI-no./total no.(%)	36/199(18.1)	21/168(12.5)	1.37(0.83,2.27)	0.22
BSID-III cognitive score < 70-no./total no.(%)	23/198(11.6)	16/167(9.6)	1.16(0.64,2.12)	0.62
Gross motor function level ≥ 2-no./total no.(%)	17/201(8.5)	9/172(5.2)	1.52(0.7,3.29)	0.29
Moderate/severe cerebral palsy-no./total no.(%)	14/201(7.0)	8/172(4.7)	1.32(0.57,3.04)	0.51
Blindness, bilateral -no./total no.(%)	2/201(1.0)	2/172(1.2)	0.86(0.12,6.02)	0.88
Hearing impairment-no./total no.(%)	11/201(5.5)	3/172(1.7)	3.24(0.9,11.71)	0.07

c. **26 0/7-27 6/7 weeks Gestational Age**	CPAP	Surfactant	RR	p
Death before 18-22 mo CA-no./total no.(%)	45/366(12.3)	43/365(11.8)	1.05(0.71,1.55)	0.82
Death/NDI determined-no./total no.(%)	349/378(92.3)	348/373(93.3)	0.99(0.95,1.03)	0.57
NDI or death-no./total no.(%)	64/349(18.3)	65/348(18.7)	0.99(0.72,1.35)	0.93
NDI-no./total no.(%)	19/304(6.3)	22/305(7.2)	0.93(0.5,1.72)	0.81
BSID-III cognitive score < 70-no./total no.(%)	13/304(4.3)	20/305(6.6)	0.74(0.36,1.51)	0.41
Gross motor function level ≥ 2-no./total no.(%)	9/310(2.9)	14/307(4.6)	0.61(0.27,1.4)	0.24
Moderate/severe cerebral palsy-no./total no.(%)	7/310(2.3)	11/307(3.6)	0.62(0.24,1.58)	0.31
Blindness, bilateral-no./total no.(%)	2/310(0.6)	5/307(1.6)	0.39(0.08,1.99)	0.26
Hearing impairment-no./total no.(%)	6/310(1.9)	4/307(1.3)	1.53(0.44,5.26)	0.50

*Relative risk and p values adjusted for stratification factors (study center and gestational age group) and familial clustering (except blindness was not adjusted for study center due to small N)

Table 3: Death and Components of NDI for entire cohort and gestational age strata*

a. CPAP vs. Surfactant (All)	CPAP	Surfactant	RR	p
Death or cognitive composite<70-no./total no.(%)	154/620(24.8)	176/612(28.8)	0.86(0.72,1.03)	0.11
Death or GMF level ≥2-no./total no.(%)	144/629(22.9)	163/619(26.3)	0.87(0.72,1.05)	0.16
Death or moderate/severe CP-no./total no.(%)	139/629(22.1)	159/619(25.7)	0.86(0.71,1.05)	0.14
Death or blind in both eyes-no./total no.(%)	122/629(19.4)	147/619(23.7)	0.82(0.67,1.02)	0.07
Death or hearing impairment-no./total no.(%)	135/629(21.5)	147/619(23.7)	0.9(0.74,1.11)	0.33
b. 24 0/7-25 6/7 weeks Gestational Age				
Death or cognitive composite<70-no./total no.(%)	96/271(35.4)	113/264(42.8)	0.83(0.67,1.02)	0.08
Death or GMF level ≥2-no./total no.(%)	90/274(32.8)	106/269(39.4)	0.84(0.67,1.04)	0.12
Death or moderate/severe CP-no./total no.(%)	87/274(31.8)	105/269(39)	0.82(0.65,1.02)	0.08
Death or blind in both eyes-no./total no.(%)	75/274(27.4)	99/269(36.8)	0.75(0.58,0.96)	0.03
Death or hearing impairment-no./total no.(%)	84/274(30.7)	100/269(37.2)	0.83(0.65,1.05)	0.12

c. **26 0/7-27 6/7 weeks Gestational Age**	CPAP	Surfactant	RR	p
Death or cognitive composite<70-no./total no.(%)	58/349(16.6)	63/348(18.1)	0.93(0.67,1.29)	0.67
Death or GMF level ≥2-no./total no.(%)	54/355(15.2)	57/350(16.3)	0.94(0.67,1.33)	0.74
Death or moderate/severe CP-no./total no.(%)	52/355(14.6)	54/350(15.4)	0.96(0.68,1.36)	0.82
Death or blind in both eyes-no./total no.(%)	47/355(13.2)	48/350(13.7)	0.97(0.67,1.42)	0.89
Death or hearing impairment-no./total no.(%)	51/355(14.4)	47/350(13.4)	1.07(0.74,1.55)	0.71

*Relative risk and p values adjusted for stratification factors (study center and gestational age group) and familial clustering

Neurodevelopmental Outcome of Extremely Preterm Infants in a Trial of Different Oxygen Saturation Targets

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Word Count

Abstract: 248

Text: 1,148

ABSTRACT

BACKGROUND

Targeting lower (vs. higher) oxygen saturations in the SUPPORT Trial decreased severe retinopathy of prematurity but increased mortality before discharge. Our pre-specified hypothesis was that compared to the treatment of higher oxygen saturation, treatment with lower oxygen saturation will have a decrease in the composite outcome of death and long term neurodevelopmental impairment.

METHODS

Infants born at 24 to 27 week gestation were randomized to higher (91-95%) or lower oxygen saturation targets (85-89%) from birth to 36 weeks corrected age. The outcome of this follow up study was a composite of death or neurodevelopment impairment at 18 to 22 months corrected age. Neurodevelopmental impairment (NDI) was defined as a Bayley III cognitive composite score of less than 70, modified Gross Motor Function Classification System $\geq$2, presence of moderate to severe cerebral palsy, permanent hearing loss, and/or bilateral blindness. Results were adjusted for gestational age stratum, center and familial clustering.

RESULTS

The primary outcome was determined for 1234/1316 (93.8%) of infants enrolled in SUPPORT; 93/6% (990/1058) of survivors were evaluated at 18 to 22 months corrected age. Death or NDI occurred in 30.2% (185/612) infants in the lower oxygen saturation group and 27.5% (171/622) infants in the higher oxygen saturation group (relative risk 1.12; 95% confidence interval 0.94, 1.32; p=0.21). Death occurred in 140 (22.1%) of the children in the lower oxygen saturation

group and in 118 (18.2%) in the higher oxygen saturation group (relative risk 1.25; 95% confidence interval 1, 1.55, p=0.046). NDI was present in 9.5% (45/472) of the lower oxygen saturation group and 10.5 % (53/504) of the higher oxygen saturation group survivors (relative risk 0.87, 95% confidence interval 0.6, 1.28; p=0.49); and blindness was present in 1% (5/479) of the lower oxygen saturation group and 1.2% (6/511) of the higher oxygen saturation group (relative risk 0.9; 95% confidence interval 0.28, 2.9, p= 0.86).

CONCLUSIONS

Among extremely preterm infants targeted at different levels of oxygen saturation, no significant difference in death or neurodevelopmental impairment was observed at 18 to 22 months. Mortality remained significantly higher in the lower oxygen target group at 18 to 22 months.

BACKGROUND

Oxygen supplementation is a vital therapy for survival of many preterm infants with respiratory disorders. However, oxygen supplementation may increase the risk of retinopathy of prematurity, bronchopulmonary dysplasia, [1] periventricular leukomalacia,[2] and cerebral palsy [3] Restrictive oxygen therapy decreases retinopathy but has resulted in increased deaths in recent randomized controlled trials. [4,5,6,7]

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development SUPPORT Trial demonstrated no significant difference in a composite outcome including retinopathy of prematurity and death between a lower oxygen saturation target group (85-89%) and a higher saturation target group (91-95%). However, mortality prior to discharge was increased (19.9% of infants vs. 16.2%; relative risk 1.27; 95% CI 1.01 to 1.6; p=0.04) and severe retinopathy of prematurity among survivors was reduced (8.6% vs. 17.9%; relative risk 0.52; 95% CI 0.37 to 0.73; p<0.001) in the lower oxygen saturation target group compared to the higher saturation target group. [6] A recent meta-analysis that included the SUPPORT Trial and two other concurrent multi-center randomized controlled trials with a total of 3631 infants showed that infants randomized to an oxygen saturation target of 91-95% % had a lower mortality rate than infants randomized to oxygen saturation targets of 85-89% (14.4% versus 17.3% respectively, P=0.015). [7] I would consider rewriting this sentence - The correct reference for #7 should be to the letter published by Stenson et al NEJM 364;17:2011. These analyses compared the studies by algorithm and the overall results for the studies using the old Algorithm – was not significant – SUPPORT is in this group. These analyses did not use our prespecified adjustments. When all studies where compared there was a difference as noted. However these are not all the studies and COT which was completed was not included. I would

indicate that there are further as yet unanalyzed trials evaluating this question and that all of these studies were based on an outcome at 2 year follow-up which will not be available till 2014.

The effects of oxygen on the immature brain are not clearly understood. [8] Oxidative stress injury in the premature infant may have many underlying pathophysiological processes. There has been a keen interest in determining whether higher or lower oxygen supplementation can reduce neurodevelopmental impairment. [7] However, in two non randomized studies of oxygen saturation targeting,[1,9] neurodevelopmental outcome did not differ by oxygen targets.

This study evaluated the composite outcome of death or neurodevelopmental impairment at 18 to 22 months corrected age in the subjects enrolled in the SUPPORT trial and randomized to lower (85-89%) or higher oxygen saturation targets (91-95%) from birth to 36 weeks corrected age. The pre-specified hypothesis in the SUPPORT trial was that compared to higher oxygen saturation target, the lower saturation target group will have less incidence of the composite outcome of death and neurodevelopmental impairment.

METHODS

Study Design

Extremely preterm infants (24 weeks 0 days to 27 weeks 6 days) born between February 2005 and February 2009 at 20 centers in the United States participating in the Neonatal Research Network of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development were enrolled at delivery in the prospective, randomized, controlled SUPPORT trial. Permuted block randomization was used, with stratification according to center and gestational age (24 weeks 0 days to 25 weeks 6 days or 26 weeks 0 days to 27 weeks 6 days).

The infants were randomly assigned ~~in the delivery room~~in the first 2 hours of life to a target range of oxygen saturation of 85% to 89% (the lower oxygen saturation group) or 91 to 95% (the higher oxygenation group). Using a 2-by-2 factorial design, participants were also randomly assigned to receive either CPAP immediately following delivery and a limited ventilation strategy if subsequent intubation was required or intubation with surfactant administration within an hour after birth. Procedures for enrollment, intervention and data collection have been previously reported. [6]. The study was approved by the institutional review board at each participating center and at RTI International which is the independent data coordinating center for the Neonatal Research Network. Written informed consent was obtained from the parents or guardians of each child before delivery. Also consent was obtained for the follow up at 18-22 months corrected age.

Assessments

A comprehensive neurodevelopmental assessment was performed on survivors at 18-22 months corrected age by neurologic examiners and neurodevelopmental testers who were unaware of the treatment assignments and had been trained annually for reliability of assessments during a 2-day workshop. Developmental status was assessed using the Bayley Scales for Infant Development 3rd edition (BSID III) [10]. Cognitive Composite Scores are reported as a standardized score with a mean of 100 and a standard deviation of 15. Examiners also recorded the presence of cerebral palsy defined as a non-progressive disorder of the central nervous system and characterized by abnormal muscle tone in at least one arm or leg associated with abnormal control of movement or posture with delayed attainment of motor milestones.[11] The modified Gross Motor Function Classification System (GMFCS) [12] describes gross motor performance and has a range from 0 (normal) to 5 (most impaired). Cerebral palsy was classified depending on severity into mild

(GMFCS $\leq$1), moderate (GMFCS 2 or 3) or severe (GMFCS $\geq$ 4). Hearing and visual impairment were determined based on parent report and examination.

Certified research nurses collected demographic and neonatal data using NRN definitions. Data collected included gestational age, birth weight, gender, multiple gestation, race/ethnicity, Retinopathy or prematurity (ROP) status, bronchopulmonary dysplasia (BPD), history of medical or surgical necrotizing enterocolitis (modified Bell's stage $\geq$ 2),grades 3-4 intraventricular hemorrhage (IVH) or periventricular leukomalacia (PVL), history of late onset sepsis, use of postnatal steroids. Socioeconomic variables included insurance status, maternal marital status, maternal education, household income, language spoken at home and whether living with biological parents. Socioeconomic data from the neonatal period were used and when not available data updated at the 18-22 month visit were used. Outcomes following NICU discharge included rehospitalizations, interim medical history, surgery and medications were recorded at the 18-22 month visit.

Outcome

The composite of death or neurodevelopmental impairment at 18 to 22 months corrected age for prematurity was the pre-specified primary follow up outcome for the SUPPORT trial. This composite outcome was selected because (a) the data are available on the entire randomized trial cohort, (b) infants who died before 18 months could not be classified as having neurodevelopmental impairment and (c) death can be considered as a competing outcome to neurodevelopmental impairment among survivors. Neurodevelopmental impairment was defined as having any of the following: BSID III cognitive composite score less than 70,

GMFCS $\geq$ 2, presence of moderate or severe cerebral palsy, permanent hearing loss that does not permit the child to understand directions of the examiner and communicate despite amplification with hearing aids, or bilateral visual impairment (vision < 20/200).

Analysis

Data were entered in standard forms and were transmitted to the Neonatal Research Network Data Coordinating Center at RTI International which stored, managed and analyzed the data for this study. Details regarding sample size calculations for the SUPPORT trial have been previously reported [6]. The sample size calculations were based on infants born in the year 2000 which included the rate of death or neurodevelopmental impairment at 18-22 months corrected age. All analyses were performed according to the intention to treat principle. Unadjusted comparisons of birth and demographic characteristics between treatment groups were conducted using chi-square tests for categorical variables and t tests for continuous variables. The primary analysis focused on the percentage of infants in each group for whom the primary outcome of death or NDI at 18 to 22 months corrected age could be assigned. Analysis of this and all other categorical outcomes was performed with the used of robust Poisson regression in a generalized-estimating-equation model to obtain adjusted relative risks with 95% confidence intervals. The denominator that was used to calculate the rate of each outcome was the number of infants for whom the outcome was known. Continuous outcomes were analyzed with the use of mixed-effects linear models to obtain adjusted means and standard errors. Pre-specified subgroup analyses were also conducted within each gestational age strata.

In the analysis of all neonatal and follow-up outcomes, the results were adjusted, as pre-specified, for gestational-age strata I did not think this was meant to be by strata but rather GA- we need to check, center and familial clustering (because multiple births from the same mother were randomized to the same treatment group). Two-sided p values of less than 0.05 was considered to indicate statistical significance. For the 79 secondary outcomes analyzed according to treatment, we would expect no more than 4 tests to have p values of less than 0.05 on the basis of chance alone. Subgroup analyses were conducted within pre-specified gestational age strata for the same outcomes. Although these tests have not been adjusted for multiple comparisons, we would expect no more than 4 tests per stratum to have p values of less than 0.05 on the basis of chance alone.

RESULTS

Characteristics of the Study Sample

The SUPPORT trial enrolled 1316 infants (see flowchart in Figure 1). Five hundred twenty four infants in the lower oxygen saturation group and 555 in the higher oxygen saturation group survived to discharge or transfer from the hospital. The baseline characteristics of the entire group have been reported previously[6] Ten children in the lower oxygen saturation group and 11 children in the higher oxygen saturation group died after discharge from the nursery and prior to the 18 to 22 month corrected age follow up visit. Thirty five children in the lower saturation group and 33 children in the higher saturation group were lost to follow up. However 14/35 in the lower saturation group and 19/33 in the higher saturation group were known to be alive at 18 to 22 months corrected age. Neurodevelopmental assessment was performed in 990/1058 infants who were not known to have died (93.6%). Of those who were evaluated at the 18 to 22 months

corrected age, neurodevelopmental status was determined in 976 children. From the entire cohort the pre- specified outcome of death or neurodevelopmental impairment could be determined in 93.8% (1234/1316) of enrolled children. Compared to mothers of infants who were followed, mothers of infants who were lost to follow up were less likely to be married (31 vs. 47% p=0.01) and more likely to have only public health insurance (69 vs. 52% p=0.008). There were no other significant differences in all the other baseline characteristics of the cohort that was followed up and those lost to follow up.

Baseline characteristics of the follow up cohort and the entire trial cohort are presented in Table 1. Among children who were followed up, the percentage of infants who were small for gestational age was greater in the higher oxygen saturation target group compared to the lower saturation target group. In addition, as reported previously[6] the incidence of severe retinopathy of prematurity was higher in the higher oxygen saturation group compared to the lower saturation group but no other significant differences were found in the baseline and major hospital outcome characteristics of the infants with follow up data.

Primary Outcome

The mean corrected age for neurodevelopmental evaluation was similar between both groups (Lower oxygen saturation, 19.9 $\pm$ 2.4 months vs. higher oxygen saturation 20.2 $\pm$ 2.7 months, p=0.08). The prevalence of the composite primary outcome of death or neurodevelopmental impairment was not significantly different between the lower (185/612, 30%) and higher (171/662, 27.5%) oxygen saturation target groups (relative risk 1.12, 95% confidence interval 0.94, 1.32; p=0.21). (Table 2) In the 24 weeks to 25 weeks gestational age stratum, primary outcome data were available for 261 of 276 children in the lower saturation group and 276 of

289 in the higher saturation group. For the age stratum 26 to 27 weeks gestation outcome data were available for 351 of 378 of the lower oxygen saturation group and 346 of 373 of the higher oxygen saturation group. Similar to the entire cohort there were no significant differences in the prevalence of death or neurodevelopmental impairment within both gestational age strata as shown in table 2.

Components of the Primary Outcome

Death prior to the 18 to 22 month adjusted age visit occurred significantly more often among infants in the lower oxygen saturation target group compared to those in the higher saturation target group. (Lower oxygen saturation, 140/633, 22.1% vs. higher oxygen saturation, 118/648, 18.2%; relative risk 1.25; 95% CI 1, 1.55, p=0.046). However death at 18 to 22 months corrected age was not significantly different within either gestational age stratum (table 2)

The rate of neurodevelopmental impairment among survivors followed at the 18 to 22 month corrected age visit was similar between the lower and the higher oxygen saturation target groups (45/472, 9.5% vs 53/504, 10.5%; relative risk 0.87 95%CI 0.6, 1.28, p=0.49) Rates of neurodevelopmental impairment were not significantly different in either gestational age stratum.

Other outcomes among survivors at follow up

The percentage of children with BSID III cognitive scores below 70 was not significantly different between the lower and higher oxygen saturation group, nor was the percentage of children with cognitive scores below 85. Adjusted means of cognitive composite scores were not significantly different between the two groups and are presented in table 3.

Rates of severe retinopathy of prematurity and eye surgery among survivors to follow up were higher in the higher oxygen target group compared to the lower oxygen target group; however the rate of bilateral (1% vs 1.6%, relative risk 0.67, 95% CI 0.22, 2.02; p=0.48) or unilateral blindness were not significantly different at the 18 to 22 month corrected age visit. Other visual outcomes are presented in Table 3.

Overall readmission rates and readmission rates for respiratory problems were not significantly different between both groups. There were no significantly differences in use after discharge of bronchodilators, steroids, diuretics or any other medication. (Table 3)

DISCUSSION

In this multicenter, follow up study of infants randomized to a lower target range of oxygen saturation (85 to 89%) or to higher target oxygen saturation (91 to 95%) a significant difference was not found in the pre-specified outcome of death or neurodevelopmental impairment at 18-22 months corrected age. To our knowledge this is the only large comprehensive study in the US that has included neurodevelopmental impairment as an outcome for evaluating effects of different oxygen target saturation levels started at birth in extremely premature babies within a randomized multicenter trial. There has been concern about using lower oxygen saturation targets because of potentially increased mortality in extremely premature infants [13]. We found that death prior to discharge in the SUPPORT trial was increased among children who were assigned to lower target saturation levels, and this difference persisted at 18 to 22 months corrected age follow up.

We had reported previously that our lower saturation oxygen target was associated with a large reduction in the incidence of severe retinopathy of prematurity among survivors. [6] It has been

previously reported that severe ROP may be associated with poor visual outcomes even with treatment [14,15] Although our study was not designed to collect detailed data on eye disorders or visual function at 18 to 22 months of age we found that there were no significant differences in the report of unilateral and bilateral blindness between the two groups. Eye surgery was higher in the group with a higher oxygen saturation target and was likely related to higher incidence of severe retinopathy of prematurity in this group and our criteria used to define severe retinopathy of prematurity [6]. Specific visual outcomes of eye function after the presence of retinopathy of prematurity were also not included in the outcome data collected in this trial however we did not find a significant difference in other reported visual outcomes like nystagmus, strabismus or use of corrective lenses.

There had been concerns that lower oxygen saturation targets might increased the risk of long term neurodevelopmental impairment[5]. However NDI as defined in this study was not found to be significantly different between survivors in the lower and higher oxygen saturation groups. In addition the incidence of Cerebral Palsy did not differ between the treatment groups, though it is noteworthy that the incidence of CP was lower than previously reported in other outcome studies.[16]

It has been recognized that higher oxygen levels can be associated with chronic lung disease, however we found no difference in the use of postnatal corticosteroids or diuretics at 18 to 22 months corrected age, or persistent oxygen use at 18 to 22 months of age as well as rehospitalization between the two groups.

A limitation of this study is that it reports only follow up to 18 to 22 months corrected age, which may not been enough time to detect the presence of minor but important disabilities. It has also

been reported that the BSID III may result in higher cognitive scores than an earlier vision of the Bayley Scales of Infant development (BSID-II), therefore missing developmental impairments when the 2 SD cutoff for cognitive composite scores is used[17 18]. Use of a cutoff of less than 85 for the Bayley III cognitive composite scores did ~~not find~~reveal significant differences between the groups. There is an ongoing follow up SUPPORT study that will be reporting the outcome on over half of these children at school age. These children were cared for at tertiary care centers therefore generalizibility is a concern, however we included 20 centers around the country.

In summary we found no significant differences in death or neurodevelopmental impairment at 18 to 22 months corrected age in extremely premature infants who were randomized to a lower target oxygen saturation or higher target oxygen saturation. The increased death rate at discharge that was previously reported in the lower target oxygen saturation group was still present at 18 to 22 months corrected age. Although higher rates of retinopathy of prematurity were associated with higher oxygen saturation target levels, blindness was not significantly different among survivors at 18 to 22 months.

Since you have introduced the other trials in the introduction, I would have a sentence here about them – ie the 2 large trials in that analysis were stopped before full enrollment, and a third trial of similar design has completed enrollment and the primary outcome for these trials was neurodevelopmental outcome at 2 years. Thus there will be no information about this outcome till 2014 and until then we need to consider what we recommend. I would be in favor of saying that until more detailed information is available that the use of an SpO2 range of 85% to 89% cannot be recommended as safe. This may sound controversial but is consistent with the facts and our results, and the results presented in brief by Stenson

I believe we should discuss this before submitting this paper and I believe that this should be a part of the presentation at Hot Topics

I will review those slides and send them back

Thanks for a great effort and very nice paper

Neil

Acknowledgements

The National Institutes of Health, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), and the National Heart, Lung, and Blood Institute (NHLBI) provided grant support for the Neonatal Research Network's SUPPORT Trial.

Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Drs. Abhik Das (DCC Principal Investigator) and Marie Gantz (DCC Statistician) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study. The following investigators, in addition to those listed as authors, participated in this study:

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Emory University, Children's Healthcare of Atlanta, Grady Memorial Hospital, and Emory Crawford Long Hospital (U10 HD27851, RR25008, M01 RR39) – Barbara J. Stoll, MD; Susie Buchter, MD; Anthony J. Piazza, MD; David P. Carlton, MD; Linda Black, MD; Ann M. Blackwelder, RNC BS MS; Sheena Carter, PhD; Elisabeth Dinkins, PNP; Sobha Fritz, PhD; Ellen C. Hale, RN BS CCRC; Amy K. Hutchinson, MD; Maureen Mulligan LaRossa, RN; Gloria V. Smikle, PNP MSN.

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National Heart, Lung, and Blood Institute – Mary Anne Berberich, PhD; Carol J. Blaisdell, MD; Dorothy B. Gail, PhD; James P. Kiley, PhD.

RTI International (U10 HD36790) – W. Kenneth Poole, PhD; Jamie E. Newman, PhD MPH; Betty K. Hastings; Jeanette O'Donnell Auman, BS; Carolyn Petrie Huitema, MS; James W. Pickett II, BS; Dennis Wallace, PhD; Kristin M. Zaterka-Baxter, RN BSN.

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University of New Mexico Health Sciences Center (U10 HD53089, M01 RR997) – Kristi L. Watterberg, MD; Robin K. Ohls, MD; Julie Rohr, MSN RNC CNS; Conra Backstrom Lacy, RN; Jean Lowe, PhD; Rebecca Montman, BSN.

University of Rochester Medical Center, Golisano Children's Hospital (U10 HD40521, M01 RR44) – Nirupama Laroia, MD; Dale L. Phelps, MD; Gary David Markowitz, MD; Linda J. Reubens, RN CCRC; Diane Hust, MS RN CS; Lisa Augostino; Julie Babish Johnson, MSW; Erica Burnell, RN; Rosemary L. Jensen; Emily Kushner, MA; Joan Merzbach, LMSW; Kelley Yost, PhD.

University of Texas Southwestern Medical Center at Dallas, Parkland Health & Hospital System, and Children's Medical Center Dallas (U10 HD40689, M01 RR633) – Pablo J. Sánchez, MD; Charles R. Rosenfeld, MD; Walid A. Salhab, MD; Sally S. Adams, MS RN CPNP; James Allen, RRT; Laura Grau, RN; Alicia Guzman; Gaynelle Hensley, RN; Elizabeth T. Heyne, PsyD PA-C; Melissa H. Lepps, RN; Linda A. Madden, RN CPNP; Melissa Martin, RN; Nancy A. Miller, RN; Janet S. Morgan, RN; Araceli Solis, RRT; Lizette E. Torres, RN; Catherine Twell Boatman, MS CIMI; Diana M Vasil, RNC-NIC; Kerry Wilder, RN.

University of Texas Health Science Center at Houston Medical School and Children's Memorial Hermann Hospital (U10 HD21373) – Kathleen A. Kennedy, MD MPH; Jon E. Tyson, MD MPH; Nora I. Alaniz, BS; Patricia Evans, MD; Beverly Foley Harris, RN BSN; Charles Green, PhD; Margarita Jiminez, MD MPH; Anna E. Lis, RN BSN; Sarah Martin, RN BSN; Georgia E. McDavid, RN; Brenda H. Morris, MD; Margaret L. Poundstone, RN BSN; Stacy Reddoch, BA; Saba Siddiki, MD; Patti L. Pierce Tate, RCP; Laura L. Whitely, MD; Sharon L. Wright, MT (ASCP).

University of Utah Medical Center, Intermountain Medical Center, LDS Hospital, and Primary Children's Medical Center (U10 HD53124, M01 RR64) – Shawna Baker, RN; Karie Bird, RN; Jill Burnett, RN; Laura Cole, RN; Karen A. Osborne, RN BSN CCRC; Cynthia Spencer, RNC; Mike Steffens, PhD; Kimberlee Weaver-Lewis, RN BSN; Karen Zanetti, RN.

Wake Forest University, Baptist Medical Center, Brenner Children's Hospital, and Forsyth Medical Center (U10 HD40498, M01 RR7122) – Robert G. Dillard, MD; Lisa K. Washburn, MD; Nancy J. Peters, RN CCRP; Barbara G. Jackson, RN BSN; Korinne Chiu, MA; Deborah Evans Allred, MA LPA; Donald J. Goldstein, PhD; Raquel Halfond, MA; Carroll Peterson, MA; Ellen L. Waldrep, MS; Cherrie D. Welch, MD MPH; Melissa Whalen Morris, MA; Gail Wiley Hounshell, PhD.

Wayne State University, Hutzel Women's Hospital, and Children's Hospital of Michigan (U10 HD21385) – Seetha Shankaran, MD; Beena G. Sood, MD MS; Rebecca Bara, RN BSN; Elizabeth Billian, RN MBA; Laura A. Goldston, MA; Mary Johnson, RN BSN.

Yale University, Yale-New Haven Children's Hospital, and Bridgeport Hospital (U10 HD27871, UL1 RR24139, MO1 RR125) – Vineet Bhandari, MD DM; Harris C. Jacobs, MD; Pat Cervone, RN; Patricia Gettner, RN; Monica Konstantino, RN BSN; JoAnn Poulsen, RN; Janet Taft, RN BSN; Christine G. Butler, MD; Nancy Close, PhD; Walter Gilliam, PhD; Sheila Greisman, RN; Elaine Romano, MSN; Joanne Williams, RN BSN.

Data and Safety Monitoring Committee – Gordon Avery, MD, chair, Children's National Medical Center; Christine A. Gleason, MD, chair, University of Washington; Marilee C. Allen, MD, Johns Hopkins University School of Medicine; Shrikant I. Bangdiwala, PhD, University of North Carolina; Carol J. Blaisdell, MD, National Heart, Lung, and Blood Institute; Robert J. Boyle, MD, University of Virginia Health System; Traci Clemons, PhD, The EMMES Corporation; Mary E. D'Alton, MD, Columbia University; Abhik Das (ex officio), PhD, RTI International; Dorothy B. Gail, PhD, National Heart, Lung, and Blood Institute; Carl Hunt, MD, National Heart, Lung, and Blood Institute; Martin Keszler, MD, Georgetown University Hospital; W. Kenneth Poole (ex officio), PhD, RTI International; Carol K. Redmond, ScD, University of Pittsburg; Michael G. Ross, MD, MPH; UCLA School of Medicine and Public Health; Merran A. Thomson, MD, Hammersmith Hospital, UK; Steven J. Weiner, MS, The George Washington University; Marian Willinger (ex officio), PhD, Eunice Kennedy Shriver National Institute of Child Health and Human Development.

Retinopathy of Prematurity Adjudication Committee - Gary David Markowitz, MD, University of Rochester; Amy K. Hutchinson, MD, Emory University; David K. Wallace, MD, MPH, Duke University; Sharon F. Freedman, MD, Duke University.

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Table 1. Baseline characteristics of the SUPPORT group

Characteristics	Trial Cohort		Cohort with Follow-up Visit	
	Lower Oxygen Saturation	Higher Oxygen Saturation	Lower Oxygen Saturation	Higher O: Saturat
	N=654	N=662	N=479	N=51
Birth weight – g	835.5± 193.4	824.8± 193	857.8 ± 186.3	843.7± 1
Gestational age – wk	26.2 ± 1.1	26.1 ± 1.1	26.3 ± 1.1	26.2 ±
Small for gestational age – no./total no. (%)	41/654 (6.3)	55/662 (8.3)	17/479 (3.5)*	38/511 (
Male sex – no./total no. (%)	341/654 (52.1)	371/662 (56)	240/479 (50.1)	282/511 (
Race or ethnic group – no./total no. (%)				
Non Hispanic Black	257/654 (39.3)	232/662 (35)	201/479 (42)	176/511 (
Non Hispanic White	242/654 (37)	279/662 (42.1)	178/479 (37.2)	218/511 (
Hispanic	132/654 (20.2)	127/662 (19.2)	86/479 (18)	97/511 (
Other or unknown	23/654 (3.5)	24/662 (3.6)	14/479 (2.9)	20/511 (
Multiple births – no./total no. (%)	161/654 (24.6)	176/662 (26.6)	124/479 (25.9)	128/511
Maternal educational level <high school no./total no. (%)	148/594 (24.9)	165/612 (27)	115/471 (24.4)	129/504 (
Public Health Insurance only – no./total no. (%)	356/650 (54.8)	348/660 (52.7)	253/479 (52.8)	266/511 (

Mother married – no./total no. (%)	284/652 (43.6)	308/661 (46.6)	222/479 (46.3)	243/511 (
Lives with both biological parents – no./total no. (%)†	354/508 (69.7)	364/547 (66.5)	332/478 (69.5)	345/511 (
Household income < $30,000/year – no./total no.(%) †	247/474 (52.1)	291/528 (55.1)	239/456 (52.4)	272/498 (
English as primary language – no./total no. (%)‡	402/477 (84.3)	429/513 (83.6)	402/477 (84.3)	427/511 (
Cesarean section – no./total no. (%)	441/654 (67.4)	442/662 (66.8)	332/479 (69.3)	335/511 (
Antenatal steroids – no./total no. (%)	633/654 (96.8)	632/661 (95.6)	462/479 (96.5)	487/511 (
Severe retinopathy of prematurity – no./total no. (%)†	41/475 (8.6)**	91/509 (17.9)**	38/442 (8.6)**	82/471 (1'
Bronchopulmonary dysplasia – no./total no. (%)¶	205/540 (38)	237/568 (41.7)	177/479 (37)	203/511 (
Intraventricular hemorrhage grade 3 or 4 or Periventricular leukomalacia – no./total no. (%)	98/630 (15.6)	100/640 (15.6)	56/478 (11.7)	60/510 (
Necrotizing enterocolitis – no./total no. (%)	76/641 (11.9)	70/649 (10.8)	42/479 (8.8)	44/511 (
Late onset sepsis/meningitis – no./total no. (%)	228/624 (36.5)	226/634 (35.6)		
155/479 (32.4)	166/511 (32.5)			
Post natal steroids – no./total no. (%)	61/636 (9.6)	69/644 (10.7)		
41/477 (8.6)	48/507 (9.5)			
CPAP – no./total no. (%)	336/654 (51.4)	327/662 (49.4)		
254/479(53)	257/511 (50.3)			
Surfactant – no./total no. (%)	318/654 (48.6)	335/662 (50.6)		
225/479 (47)	254/511 (49.7)			

*p<0.01, **p<0.001

† Available only for infant who survived to discharge or transfer

‡ Only available at 18-22 months corrected age

¶ Among survivors to 36 weeks postmenstrual age

Table 2. Primary Outcomes at 18-22 Months Corrected Age

	Lower Oxygen Saturation	Higher Oxygen Saturation	Adjusted Relative Risk
Lower oxygenation saturation vs higher oxygen saturation	N=654	N=662	
Outcome determined for death or NDI – no./total no. (%)	612/654 (93.6)	622/662 (94)	1 (0.97, 1.03)
Neurodevelopmental impairment or death – no./total no. (%)	185/612 (30.2)	171/622 (27.5)	1.12 (0.94, 1.32)
Died by 18-22 months – no./total no. (%)	140/633 (22.1)	118/648 (18.2)	1.25 (1, 1.55)
Survivors at follow-up			
Neurodevelopmental impairment – no./total no. (%)	45/472 (9.5)	53/504 (10.5)	0.87 (0.6, 1.28)
Bayley III cognitive composite score < 70 – no./total no. (%)	34/471 (7.2)	38/503 (7.6)	0.91 (0.58, 1.43)
Gross motor function level ≥ 2 – no./total no. (%)	26/479 (5.4)	23/511 (4.5)	1.17 (0.68, 2.01)
Moderate/severe cerebral palsy – no./total no. (%)	20/479 (4.2)	20/511 (3.9)	1 (0.54, 1.83)
Blindness – no./total no. (%)	5/479 (1)	6/511 (1.2)	0.9 (0.28. 2.9)
Hearing Impairment – no./total no. (%)	12/479 (2.5)	12/511 (2.3)	1.16 (0.54, 2.49)
24 0/7 to 25 6/7 weeks gestational age strata	276	289	
Neurodevelopmental impairment or death – no./total no. (%)	115/261 (44.1)	112/276 (40.6)	1.09 (0.89, 1.32)
Died by 18-22 months – no./total no. (%)	91/267(34.1)	79/283 (27.9)	1.23 (0.95, 1.59)
Survivors at follow-up			
Neurodevelopmental impairment – no./total no. (%)	24/170 (14.1)	33/197 (16.8)	0.8 (0.49, 1.3)
Bayley III cognitive composite score < 70 – no./total no. (%)	17/169 (10.1)	22/196 (11.2)	0.86 (0.47, 1.56)
Gross motor function level ≥ 2 – no./total no. (%)	13/173 (7.5)	13/200 (6.5)	1.07 (0.53, 2.17)
Moderate/severe cerebral palsy – no./total no. (%)	10/173 (5.8)	12/200(6.0)	0.86(0.39, 1.88)
Blindness – no./total no. (%)	1/173 (0.6)	3/200 (1.5)	0.39 (0.04, 3.69)

Hearing Impairment – no./total no. (%)	4/173 (2.3)	10/200 (5.0)	0.5 (0.16, 1.53)
26 0/7 to 27 6/7 weeks gestational age strata	378	373	
Neurodevelopmental impairment or death – no./total no. (%)	70/351(19.9)	59/346 (17.1)	1.17 (0.85, 1.6)
Died by 18-22 months – no./total no. (%)	49/366(13.4)	39/365(10.7)	1.28 (0.86, 1.89)
Survivors at follow-up			
Neurodevelopmental impairment – no./total no. (%)	21/302(7.0)	20/307(6.5)	0.99(0.54, 1.84)
Bayley III cognitive composite score < 70 – no./total no. (%)	17/302 (5.6)	16/307(5.2)	0.98 (0.49, 1.97)
Gross motor function level ≥ 2 – no./total no. (%)	13/306(4.2)	10/311 (3.2)	1.32(0.57, 3.01)
Moderate/severe cerebral palsy – no./total no. (%)	10/306(3.3)	8/311(2.6)	1.22(0.47, 3.2)
Blindness – no./total no. (%)	4/306 (1.3)	3/311(1.0)	1.38 (0.31, 6.05)
Hearing Impairment – no./total no. (%)	8/306 (2.6)	2/311 (0.6)	4.18(0.88, 19.87)

Table 3. Other Outcomes at 18 to 22 months corrected age by Group

Outcome	Lower Oxygen Saturation (N=479)	Higher Oxygen Saturation (N=510)	Relative Risk for Lower vs. Higher Oxygen Saturation (95% CI)	Adjusted difference in means (95% CI)	Adj P-v
Bayley Scales of Infant Development III					
Cognitive composite < 70	34/471 (7.2)	38/503 (7.6)	0.91 (0.58, 1.43)		0.
Cognitive composite <85	105/471 (22.3)	132/503 (26.2)	0.85 (0.68, 1.07)		0.
Adjusted mean cognitive composite scores ± standard error	92.2 ± 0.8	90.5 ± 0.7		0.7 (-1.2, 2.5)	0.
Median cognitive composite scores (interquartile range)	90 (85, 100)	90 (80, 100)			
Neurologic findings					
Mild cerebral palsy vs. none	23/459 (5.0)	21/490 (4.3)	1.16 (0.66, 2.02)		0.
Moderate cerebral palsy vs. none	11/447 (2.5)	10/479 (2.1)	1.19 (0.52, 2.71)		0.
Severe cerebral palsy vs. none	9/445 (2.0)	10/479 (2.1)	0.95 (0.39, 2.27)		0.
Any cerebral palsy	43/479 (9.0)	41/510 (8.0)	1.12 (0.76, 1.65)		0.
Any abnormal neurologic exam	108/479 (22.5)	114/511 (22.3)	1.02 (0.82, 1.28)		0.
Vision/Eye findings					

Strabismus	46/478 (9.6)	41/510 (8)	1.2 (0.8, 1.8)	0.
Nystagmus	22/479 (4.6)	13/510 (2.4)	1.81 (0.89, 3.69)	0.
Tracks 180 degrees	462/476 (97.1)	492/506 (97.2)	1 (0.98, 1.02)	0.
Corrective lenses both eyes	21/468 (4.5)	20/493 (4.1)	1.14 (0.62, 2.08)	0.
Blind, some function, both eyes vs. normal	3/450 (0.7)	2/475 (0.4)	1.57 (0.27, 8.96)	0.
Blind, no useful vision, both eyes vs. normal	2/449 (0.4)	4/477 (0.8)	0.54 (0.1, 2.96)	0.
Other abnormal eye findings vs. normal	6/453 (1.3)	12/485 (2.5)	0.55 (0.21, 1.46)	0.
Eye surgery	31/477 (6.5)	67/509 (13.2)	0.52 (0.35, 0.78)	0.(
Medicines				
Bronchodilators	159/475 (33.5)	185/506 (36.6)	0.92 (0.78, 1.1)	0.
Steroids	95/475 (20.0)	108/506 (21.3)	0.92 (0.72, 1.18)	0.
Diuretics	15/475 (3.2)	14/506 (2.8)	1.17 (0.58,2.34)	0.
Anticonvulsants	12/478 (2.5)	12/511 (2.3)	1.08 (0.49, 2.37)	0.
Readmission	210/478 (43.9)	239/511 (46.8)	0.94 (0.82, 1.08)	0.
Readmission for respiratory reason	110/470 (23.4)	127/503 (25.2)	0.93 (0.74, 1.16)	0.
Readmission for growth/nutrition	12/470 (2.6)	13/503 (2.6)	1.05 (0.49, 2.25)	0.

From: Vaucher, Yvonne
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Manuscripts
Date: Friday, December 09, 2011 4:55:08 PM

Will send Monday.

Yvonne

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, December 09, 2011 1:01 PM
To: 'Myriam Peralta, M.D.'; Vaucher, Yvonne
Cc: 'Wally Carlo, M.D.'; Finer, Neil
Subject: Manuscripts

Hi,
Can you send me the updated SUPPORT FU papers for internal review and NICHD clearance??
Thanks for all the effort!!
Rose

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From: Pablo Sanchez
To: Higgins, Rosemary (NIH/NICHD) [E]; "Barbara Stoll"; Luc Brion
Cc: JACLYN LEVAN
Subject: RE: GDB SUPPORT protocol
Date: Wednesday, December 07, 2011 12:50:52 PM

I just got backto dallas--i have the old gdb books --let me speak with luc --pablo

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]
Sent: Wednesday, December 07, 2011 11:47 AM
To: 'Barbara Stoll'; Luc Brion
Cc: JACLYN LEVAN; Pablo Sanchez
Subject: RE: GDB SUPPORT protocol

Perhaps Pablo has a copy of the GDB book??

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From: Barbara Stoll [mailto:Barbara.Stoll@oz.ped.emory.edu]
Sent: Wednesday, December 07, 2011 12:34 PM
To: Luc Brion
Cc: Higgins, Rosemary (NIH/NICHD) [E]; JACLYN LEVAN; Pablo Sanchez
Subject: Re: GDB SUPPORT protocol

I don't have the data electronically
BJSLuc Brion <Luc.Brion@utsouthwestern.edu> writes:
Rose and Barbara:

As discussed Jackie and I need to submit Jackie's revised protocol by tomorrow: "Changes in Therapy and Outcomes Associated with The SUPPORT Trial"

We are working at this right now.

Would you please be willing to share with us the GDB databook for 2003 and 2004 today?

This would allow us to respond to one of the questions of the reviewers, i.e., to adjust sample size to the NRN DR intubation rate just before the SUPPORT Trial. This would also allow us to exclude most of the Feasibility trial July 02- Jan 03, which would not reflect current

practice

If this data is not easily available to you, we will enter, into the revised protocol we will submit tomorrow, a comment on the protocol to mention that the sample size analysis will be updated once we obtain the GDB data Feb 2003 – Jan 05 (i.e., between the feasibility trial and the SUPPORT Trial).

Thanks and best regards,

Luc

Luc P. Brion, MD

Professor of Pediatrics

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From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, December 07, 2011 10:50 AM
To: Luc Brion
Cc: Pablo Sanchez; 'Gabrio, Jenna'; JACLYN LEVAN
Subject: RE: GDB SUPPORT protocol

Yes

Thanks
Rose

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Sent: Wednesday, December 07, 2011 11:31 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Pablo Sanchez; 'Gabrio, Jenna'; JACLYN LEVAN
Subject: RE: GDB SUPPORT protocol

Rose:

Could we please have at least have until tomorrow? Please give me the time you would need it.

Thanks

Luc

Luc P. Brion, MD

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Sent: Wednesday, December 07, 2011 7:49 AM
To: Luc Brion
Cc: Pablo Sanchez; 'Gabrio, Jenna'
Subject: GDB SUPPORT protocol

Luc –

Did you send us a revision to Jackie LeVan's protocol? GDB has a call next week and I need put this on the agenda. Please send me the updated version today, if possible
Thanks
Rose

Rosemary D. Higgins, MD

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Confidential - Please do not forward.

From: Finer, Neil
To: Gantz, Marie; Das, Abhik; Vaucher, Yvonne
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.
Subject: RE: Follow-up paper
Date: Thursday, December 01, 2011 3:40:52 PM

I would prefer that we say in the last paragraph that" early CPAP and limited vent strategy was associated with decreased death without any increase in NDI for the most immature infants"
I think this is now solid evidence to support this practice and I would make this conclusion stronger
Neil

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Thursday, December 01, 2011 11:48 AM
To: Das, Abhik; Vaucher, Yvonne
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; Wally Carlo, M.D.
Subject: RE: Follow-up paper

I have added my comments to Abhik and Wally's.

Marie

Marie Gantz, Ph.D.
Senior Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Das, Abhik
Sent: Tuesday, November 29, 2011 9:54 AM
To: yvaucher@ucsd.edu
Cc: Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; 'Wally Carlo, M.D.'
Subject: RE: Follow-up paper

And here are my comments (mostly editorial).

Thanks

Abhik

From: Bradley Yoder [mailto:Bradley.Yoder@hsc.utah.edu]
Sent: Tuesday, November 22, 2011 10:06 AM
To: yvaucher@ucsd.edu
Cc: Das, Abhik; Gantz, Marie
Subject: Follow-up paper

Nicely written Yvonne.
In general I agree with most of Wally's comments.
I have added just a couple other comments & made some typographical changes.

My biggest concern was the issue about not adjusting for multiple comparisons; I'm sure that was done at the RTI level so included Marie & Abhik on this as well.

Bradley A. Yoder, MD
Professor of Pediatrics
Division of Neonatology
University of Utah School of Medicine
PO Box 581289
Salt Lake City, UT 84158-1289

Phone 801-587-3498
Pager 801 (b)(6)
Email Bradley.yoder@hsc.utah.edu

From: Vaucher, Yvonne
To: Gabrio, Jenna; alaptook@WIHRI.org; Bradley Yoder; adas@rti.org; mgantz@rti.org; Higgins, Rosemary (NIH/NICHD) [E]; kurt.schibler@cchmc.org; mcw3@cwru.edu; MPeralta@PEDS.UAB.EDU; nancy newman; Finer, Neil; Roger.Faix@hsc.utah.edu; Wallace, Dennis; Wally Carlo, M.D.; Rich, Wade
Cc: sharon.gough@hsc.utah.edu; Archer, Stephanie (NIH/NICHD) [E]; Brenda Vecchio; Cunningham, Meg; Martinez, Fernando; Huitema, Carolyn Petrie; Zaterka-Baxter, Kristin
Subject: RE: SUPPORT Subcommittee Call to Discuss Secondary Proposal--Availability Request
Date: Thursday, December 01, 2011 10:31:19 AM

I am OOT (traveling) Wed 12/7 and OOT 12/19-12/30 for the holidays.

I am available Thurs 12/8 and Friday 12/9 except between 9-11:30 AM on 12/8 and 10-12:30 on 12/9 PST. Best for me would be 12/8 or 12/9 after 12:30 PM PST

Thanks.

Yvonne Vaucher

San Diego,CA

From: Gabrio, Jenna [jgabrio@rti.org]
Sent: Thursday, December 01, 2011 7:13 AM
To: alaptook@WIHRI.org; Bradley Yoder; adas@rti.org; mgantz@rti.org; Higgins, Rosemary (NIH/NICHD) [E]; kurt.schibler@cchmc.org; mcw3@cwru.edu; MPeralta@PEDS.UAB.EDU; nancy newman; Finer, Neil; Roger.Faix@hsc.utah.edu; Wallace, Dennis; Wally Carlo, M.D.; Rich, Wade; Vaucher, Yvonne
Cc: sharon.gough@hsc.utah.edu; Archer, Stephanie (NIH/NICHD) [E]; Brenda Vecchio; Cunningham, Meg; Martinez, Fernando; Gabrio, Jenna; Huitema, Carolyn Petrie; Zaterka-Baxter, Kristin
Subject: SUPPORT Subcommittee Call to Discuss Secondary Proposal--Availability Request

Dear all,

We would like to schedule a SUPPORT subcommittee call to discuss the attached secondary proposal.

Please provide your availability on this Doodle poll (http://www.doodle.com/rbedq47eq5evy7ye) for the following dates:

Abbot, Kurt, Michele, Nancy, Wally, Rose, Stephanie, Dennis, Abhik: You do NOT need to complete this poll again, as I already have your availability for these dates. Please only complete the poll if your availability has changed since you completed the December General Availability Request.

12/7, W
12/8, Th
12/9, F

12/12, M

12/15, Th
12/16, F

12/19, M
12/20, Tu
12/21, W
12/22, Th

12/27, Tu

12/28, W
12/29, Th
12/30, F
Thanks,
Jenna

Jenna Gabrio
RTI International
Public Health Analyst

701 13th St., NW Suite 750
Washington, DC 20005
Phone: 202-728-1946
Fax: 202-974-7855

From: Bradley Yoder
To: Bell, Edward (Pediatrics); Ehrenkranz, Richard; Laptook, Abbot; Kennedy, Kathleen A
Cc: Walsh, Michele; Poindexter, Brenda B; Wally Carlo, M.D.; Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]; Myriam Peralta, M.D.; Michele Walsh; mgantz@rti.org; Roger Faix; Adas@rti.org; Rich, Wade; kurt.schibler@cchmc.org; nancy newman; Vohr, Betty; Susan Hintz; Kim Yolton; Roy Heyne; Costello, Frank; goldb008@mc.duke.edu; Michael.Acarregui@providence.org; Evans, Patricia W; Adams-Chapman, Ira; Pappas, Athina; Anna M. Dusick, MD; emcgowan@tuftsmedicalcenter.org; abodnar@utah.gov; Bauer, Charles R; JaFuller@salud.unm.edu; Michael O`Shea; gary_myers@URMC.Rochester.edu; Vaucher, Yvonne; Pablo Sanchez; Shankaran, Seetha; Duara, Shahnaz; Barbara Stoll; Krisa Van Meurs; Phelps, Dale; Frantz, Ivan; KWatterberg@salud.unm.edu; Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: SUPPORT CPAP PAPER
Date: Wednesday, November 30, 2011 4:23:53 PM

We are uncertain from the available data at what point in time the lower O2 saturation conveys the slight, but significant, risk for long-term decreased survival, so have not opted to change our guidelines at this time.

For infants < 29 weeks we start at 85-93%; then adjust up to 88-94 when corrected to 29 weeks PMA or greater.
We continue at 88-94 until eye exam clears them for more oxygen or they are in room air.
We increase again at 33-34 weeks unless there is any concern for ROP.
Our discharge goal is >= 92%.

Brad Yoder
Division of Neonatology
University of Utah SOM

From: Bell, Edward (Pediatrics) [mailto:edward-bell@uiowa.edu]
Sent: Wednesday, November 30, 2011 1:47 PM
To: Ehrenkranz, Richard; Laptook, Abbot; Kennedy, Kathleen A
Cc: Walsh, Michele; Poindexter, Brenda B; Wally Carlo, M.D.; Finer, Neil; higginsr@mail.nih.gov; Myriam Peralta, M.D.; Michele Walsh; mgantz@rti.org; Bradley Yoder; Roger Faix; Adas@rti.org; Rich, Wade; kurt.schibler@cchmc.org; nancy newman; Vohr, Betty; Susan Hintz; Kim Yolton; Roy Heyne; Costello, Frank; goldb008@mc.duke.edu; Michael.Acarregui@providence.org; Evans, Patricia W; Adams-Chapman, Ira; Pappas, Athina; Anna M. Dusick, MD; emcgowan@tuftsmedicalcenter.org; abodnar@utah.gov; Bauer, Charles R; JaFuller@salud.unm.edu; Michael O`Shea; gary_myers@URMC.Rochester.edu; Vaucher, Yvonne; Pablo Sanchez; Shankaran, Seetha; Duara, Shahnaz; Barbara Stoll; Krisa Van Meurs; Phelps, Dale; Frantz, Ivan; KWatterberg@salud.unm.edu; archerst@mail.nih.gov
Subject: RE: SUPPORT CPAP PAPER

One potentially important aspect of our practice I forgot to mention is that, although we start with saturation target range of 84-89%, we gradually shift our target range upward with postnatal (postmenstrual) age. This is based on evidence, albeit mostly weak and indirect. Do others do this?
Ed

-----Original Message-----
From: Ehrenkranz, Richard [mailto:richard.ehrenkranz@yale.edu]
Sent: Wednesday, November 30, 2011 2:40 PM
To: Laptook, Abbot; Kennedy, Kathleen A; Bell, Edward (Pediatrics)
Cc: Walsh, Michele; Poindexter, Brenda B; Wally Carlo, M.D.; Finer, Neil; higginsr@mail.nih.gov; Myriam Peralta, M.D.; Michele Walsh; mgantz@rti.org; Bradley Yoder; Roger Faix; Adas@rti.org; Rich, Wade; kurt.schibler@cchmc.org; nancy newman; Vohr, Betty; Susan Hintz; Kim Yolton; Roy Heyne; Costello, Frank; goldb008@mc.duke.edu; Michael.Acarregui@providence.org; Evans, Patricia W; Adams-Chapman, Ira; Pappas, Athina; Anna M. Dusick, MD; emcgowan@tuftsmedicalcenter.org; abodnar@utah.gov; Bauer, Charles R; JaFuller@salud.unm.edu; Michael O`Shea; gary_myers@URMC.Rochester.edu; Vaucher, Yvonne; Pablo Sanchez; Shankaran, Seetha; Duara, Shahnaz; Barbara Stoll; Krisa Van Meurs; Phelps, Dale; Frantz, Ivan; KWatterberg@salud.unm.edu; archerst@mail.nih.gov
Subject: RE: SUPPORT CPAP PAPER

We have been using 85-93% and decided not to change after reviewing the SUPPORT oximetry paper. However, I am sure that it will be re-considered following publication of the FU papers.
Richard

Richard A. Ehrenkranz, MD
Department of Pediatrics
Yale University School of Medicine
333 Cedar Street
PO Box 208064
New Haven, CT 06520-8064
tele: 203-688-2320
fax: 203-688-5426

-----Original Message-----
From: Laptook, Abbot [mailto:ALaprock@WIHRI.org]
Sent: Wednesday, November 30, 2011 3:26 PM
To: Kennedy, Kathleen A; Bell, Edward (Pediatrics)
Cc: Walsh, Michele; Poindexter, Brenda B; Wally Carlo, M.D.; Finer, Neil; higginsr@mail.nih.gov; Myriam Peralta, M.D.; Michele Walsh; mgantz@rti.org; Bradley Yoder; Roger Faix; Adas@rti.org; Rich, Wade; kurt.schibler@cchmc.org; nancy newman; Vohr, Betty; Susan Hintz; Kim Yolton; Roy Heyne; Costello, Frank; goldb008@mc.duke.edu; Michael.Acarregui@providence.org; Evans, Patricia W; Adams-Chapman, Ira; Pappas, Athina; Anna M. Dusick, MD; emcgowan@tuftsmedicalcenter.org; Ehrenkranz, Richard; abodnar@utah.gov; Bauer, Charles R; JaFuller@salud.unm.edu; Michael O'Shea; gary_myers@URMC.Rochester.edu; Vaucher, Yvonne; Pablo Sanchez; Shankaran, Seetha; Duara, Shahnaz; Barbara Stoll; Krisa Van Meurs; Phelps, Dale; Frantz, Ivan; KWatterberg@salud.unm.edu; archerst@mail.nih.gov
Subject: RE: SUPPORT CPAP PAPER

Brown uses sat limits of 82-92%; we will be discussing this next week and I would suspect we will shift our limits up. AL

-----Original Message-----
From: Kennedy, Kathleen A [mailto:Kathleen.A.Kennedy@uth.tmc.edu]
Sent: Wednesday, November 30, 2011 3:24 PM
To: Bell, Edward (Pediatrics)
Cc: Walsh, Michele; Poindexter, Brenda B; Wally Carlo, M.D.; Finer, Neil; higginsr@mail.nih.gov; Myriam Peralta, M.D.; Michele Walsh; mgantz@rti.org; Laptook, Abbot; Bradley Yoder; Roger Faix; Adas@rti.org; Rich, Wade; kurt.schibler@cchmc.org; nancy newman; Vohr, Betty; Susan Hintz; Kim Yolton; Roy Heyne; Costello, Frank; goldb008@mc.duke.edu; Michael.Acarregui@providence.org; Evans, Patricia W; Adams-Chapman, Ira; Pappas, Athina; Anna M. Dusick, MD; emcgowan@tuftsmedicalcenter.org; Ehrenkranz, Richard; abodnar@utah.gov; Bauer, Charles R; JaFuller@salud.unm.edu; Michael O'Shea; gary_myers@URMC.Rochester.edu; Vaucher, Yvonne; Pablo Sanchez; Shankaran, Seetha; Duara, Shahnaz; Barbara Stoll; Krisa Van Meurs; Phelps, Dale; Frantz, Ivan; KWatterberg@salud.unm.edu; archerst@mail.nih.gov
Subject: Re: SUPPORT CPAP PAPER

We use 85-95 and we haven't changed anything yet for a couple of reasons. I'm concerned about the difficulties and problems with over correction with attempts to maintain a narrower range. I'm worried about launching the considerable effort that would be needed to implement the change well only to have to change again if the other ongoing studies have different findings. I'm not sure what we'll decide when the whole group has a chance to review this.

Sent from my iPhone

On Nov 30, 2011, at 2:00 PM, "Bell, Edward (Pediatrics)" <edward-bell@uiowa.edu<mailto:edward-bell@uiowa.edu>> wrote:

For babies <28 weeks, we target sats of 84-89% but use Nellcor oximeters and set the alarm limits at 80 and 93%.

From: Walsh, Michele [mailto:Michele.Walsh@UHhospitals.org]
Sent: Wednesday, November 30, 2011 1:32 PM
To: Poindexter, Brenda B; Wally Carlo, M.D.; Finer, Neil; higginsr@mail.nih.gov<mailto:higginsr@mail.nih.gov>; Myriam Peralta, M.D.; Michele Walsh; mgantz@rti.org<mailto:mgantz@rti.org>; Laptook, Abbot; Bradley Yoder; Roger Faix; Adas@rti.org<mailto:Adas@rti.org>; Rich, Wade; kurt.schibler@cchmc.org<mailto:kurt.schibler@cchmc.org>; nancy newman; Vohr, Betty; Susan Hintz; Kim Yolton; Roy Heyne; Costello, Frank; goldb008@mc.duke.edu<mailto:goldb008@mc.duke.edu>; Michael.Acarregui@providence.org<mailto:Michael.Acarregui@providence.org>; Evans, Patricia W; Adams-Chapman, Ira; Pappas, Athina; Anna M. Dusick, MD; emcgowan@tuftsmedicalcenter.org<mailto:emcgowan@tuftsmedicalcenter.org>; Ehrenkranz, Richard; abodnar@utah.gov<mailto:abodnar@utah.gov>; Bauer, Charles R; JaFuller@salud.unm.edu<mailto:JaFuller@salud.unm.edu>; Michael O'Shea; gary_myers@URMC.Rochester.edu<mailto:gary_myers@URMC.Rochester.edu>
Cc: Vaucher, Yvonne; Pablo Sanchez; Shankaran, Seetha; Duara, Shahnaz; Barbara Stoll; Krisa Van Meurs; Kennedy, Kathleen A;

goldb008@mc.duke.edu<mailto:goldb008@mc.duke.edu>; Phelps, Dale; Bell, Edward (Pediatrics); Frantz, Ivan; KWatterberg@salud.unm.edu<mailto:KWatterberg@salud.unm.edu>; archerst@mail.nih.gov<mailto:archerst@mail.nih.gov>
Subject: RE: SUPPORT CPAP PAPER

We have adopted 90 -95%.

Michele Walsh, MD

Chief, Division of Neonatology

216.844.3759

It's not what you look at that matters, it's what you see. Thoreau

From: Poindexter, Brenda B [mailto:bpoindex@iupui.edu]
Sent: Wednesday, November 30, 2011 2:21 PM
To: 'Wally Carlo, M.D.'; Walsh, Michele; Finer, Neil; higginsr@mail.nih.gov<mailto:higginsr@mail.nih.gov>; Myriam Peralta, M.D.; Michele Walsh; mgantz@rti.org<mailto:mgantz@rti.org>; Laptook, Abbot; Bradley Yoder; Roger Faix; Adas@rti.org<mailto:Adas@rti.org>; Rich, Wade; kurt.schibler@cchmc.org<mailto:kurt.schibler@cchmc.org>; nancy newman; Vohr, Betty; Susan Hintz; Kim Yolton; Roy Heyne; Costello, Frank; goldb008@mc.duke.edu<mailto:goldb008@mc.duke.edu>; Michael.Acarregui@providence.org<mailto:Michael.Acarregui@providence.org>; Evans, Patricia W; Adams-Chapman, Ira; Pappas, Athina; Anna M. Dusick, MD; emcgowan@tuftsmedicalcenter.org<mailto:emcgowan@tuftsmedicalcenter.org>; Ehrenkranz, Richard; abodnar@utah.gov<mailto:abodnar@utah.gov>; Bauer, Charles R; JaFuller@salud.unm.edu<mailto:JaFuller@salud.unm.edu>; Michael O'Shea; gary_myers@URMC.Rochester.edu<mailto:gary_myers@URMC.Rochester.edu>
Cc: Vaucher, Yvonne; Pablo Sanchez; Shankaran, Seetha; Duara, Shahnaz; Barbara Stoll; Krisa Van Meurs; Kennedy, Kathleen A; goldb008@mc.duke.edu<mailto:goldb008@mc.duke.edu>; Phelps, Dale; Bell, Edward (Pediatrics); Frantz, Ivan; KWatterberg@salud.unm.edu<mailto:KWatterberg@salud.unm.edu>; archerst@mail.nih.gov<mailto:archerst@mail.nih.gov>
Subject: RE: SUPPORT CPAP PAPER

We have also made the change to target 91-95%; what I can't comment on is how compliant we are...
Brenda

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Wednesday, November 30, 2011 2:11 PM
To: Walsh, Michele; Finer, Neil; higginsr@mail.nih.gov<mailto:higginsr@mail.nih.gov>; Myriam Peralta, M.D.; Michele Walsh; mgantz@rti.org<mailto:mgantz@rti.org>; Laptook, Abbot; Bradley Yoder; Roger Faix; Adas@rti.org<mailto:Adas@rti.org>; Rich, Wade; kurt.schibler@cchmc.org<mailto:kurt.schibler@cchmc.org>; nancy newman; Vohr, Betty; Susan Hintz; Kim Yolton; Roy Heyne; Costello, Frank; goldb008@mc.duke.edu<mailto:goldb008@mc.duke.edu>; Michael.Acarregui@providence.org<mailto:Michael.Acarregui@providence.org>; Evans, Patricia W; Adams-Chapman, Ira; Pappas, Athina; Anna M. Dusick, MD; emcgowan@tuftsmedicalcenter.org<mailto:emcgowan@tuftsmedicalcenter.org>; Ehrenkranz, Richard; abodnar@utah.gov<mailto:abodnar@utah.gov>; Bauer, Charles R; JaFuller@salud.unm.edu<mailto:JaFuller@salud.unm.edu>; Michael O'Shea; gary_myers@URMC.Rochester.edu<mailto:gary_myers@URMC.Rochester.edu>
Cc: Vaucher, Yvonne; Pablo Sanchez; Shankaran, Seetha; Duara, Shahnaz; Barbara Stoll; Poindexter, Brenda B; Krisa Van Meurs; Kennedy, Kathleen A; goldb008@mc.duke.edu<mailto:goldb008@mc.duke.edu>; Phelps, Dale; Bell, Edward (Pediatrics); Frantz, Ivan; KWatterberg@salud.unm.edu<mailto:KWatterberg@salud.unm.edu>; archerst@mail.nih.gov<mailto:archerst@mail.nih.gov>
Subject: RE: SUPPORT CPAP PAPER

It would be helpful to know which NRN centers have adopted a target similar to the 91-95%. Neil mentioned his unit has. We also have changed to high as in SUPPORT.

Wally

-----Original message-----
From: "Walsh, Michele" <Michele.Walsh@UHhospitals.org<mailto:Michele.Walsh@UHhospitals.org>>
To: "Finer, Neil" <nfiner@ucsd.edu<mailto:nfiner@ucsd.edu>>, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov<mailto:higginsr@mail.nih.gov>>, "Wally Carlo, M.D." <WCarlo@peds.uab.edu<mailto:WCarlo@peds.uab.edu>>, "Myriam Peralta, M.D."

<MPeralta@peds.uab.edu<mailto:MPeralta@peds.uab.edu>>, Michele Walsh
<mcw3@cwru.edu<mailto:mcw3@cwru.edu>>, mgantz@rti.org<mailto:mgantz@rti.org>,
"Laptook, Abbot" <ALaptook@WIHRI.org<mailto:ALaptook@WIHRI.org>>, Bradley Yoder
<Bradley.Yoder@hsc.utah.edu<mailto:Bradley.Yoder@hsc.utah.edu>>, Roger Faix
<Roger.Faix@hsc.utah.edu<mailto:Roger.Faix@hsc.utah.edu>>,
Adas@rti.org<mailto:Adas@rti.org>, "Rich, Wade"
<wrich@ucsd.edu<mailto:wrich@ucsd.edu>>,
kurt.schibler@cchmc.org<mailto:kurt.schibler@cchmc.org>, nancy newman
<nxs5@case.edu<mailto:nxs5@case.edu>>, "Vohr, Betty"
<BVohr@WIHRI.org<mailto:BVohr@WIHRI.org>>, Susan Hintz
<srhintz@stanford.edu<mailto:srhintz@stanford.edu>>, Kim Yolton
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Patricia W" <Patricia.W.Evans@uth.tmc.edu<mailto:Patricia.W.Evans@uth.tmc.edu>>,
"Adams-Chapman, Ira" <iadamsc@emory.edu<mailto:iadamsc@emory.edu>>, "Pappas, Athina"
<apappas@med.wayne.edu<mailto:apappas@med.wayne.edu>>, "Anna M. Dusick, MD"
<adusick@pediatrics.wisc.edu<mailto:adusick@pediatrics.wisc.edu>>,
emcgowan@tuftsmedicalcenter.org<mailto:emcgowan@tuftsmedicalcenter.org>, "Ehrenkranz,
Richard" <richard.ehrenkranz@yale.edu<mailto:richard.ehrenkranz@yale.edu>>,
abodnar@utah.gov<mailto:abodnar@utah.gov>, "Bauer, Charles R"
<CBauer@med.miami.edu<mailto:CBauer@med.miami.edu>>,
JaFuller@salud.unm.edu<mailto:JaFuller@salud.unm.edu>, Michael O'Shea
<moshea@wfubmc.edu<mailto:moshea@wfubmc.edu>>,
gary_myers@URMC.Rochester.edu<mailto:gary_myers@URMC.Rochester.edu>
Cc: "Vaucher, Yvonne" <yvaucher@ucsd.edu<mailto:yvaucher@ucsd.edu>>, Pablo Sanchez
<Pablo.Sanchez@UTSouthwestern.edu<mailto:Pablo.Sanchez@UTSouthwestern.edu>>,
"Shankaran, Seetha" <sshankar@med.wayne.edu<mailto:sshankar@med.wayne.edu>>, "Duara,
Shahnaz" <SDuara@med.miami.edu<mailto:SDuara@med.miami.edu>>, Barbara Stoll
<Barbara.Stoll@oz.ped.emory.edu<mailto:Barbara.Stoll@oz.ped.emory.edu>>, "Poindexter,
Brenda B" <bpoindex@iupui.edu<mailto:bpoindex@iupui.edu>>, Krisa Van Meurs
<vanmeurs@stanford.edu<mailto:vanmeurs@stanford.edu>>, "Kennedy, Kathleen A"
<Kathleen.A.Kennedy@uth.tmc.edu<mailto:Kathleen.A.Kennedy@uth.tmc.edu>>,
goldb008@mc.duke.edu<mailto:goldb008@mc.duke.edu>, "Phelps, Dale"
<Dale_Phelps@URMC.Rochester.edu<mailto:Dale_Phelps@URMC.Rochester.edu>>, "Bell,
Edward (Pediatrics)" <edward-bell@uiowa.edu<mailto:edward-bell@uiowa.edu>>, "Frantz,
Ivan" <Ivan.Frantz@childrens.harvard.edu<mailto:Ivan.Frantz@childrens.harvard.edu>>,
KWatterberg@salud.unm.edu<mailto:KWatterberg@salud.unm.edu>, "Archer, Stephanie
(NIH/NICHD) [E]" <archerst@mail.nih.gov<mailto:archerst@mail.nih.gov>>
Sent: Wed, Nov 30, 2011 18:40:38 GMT+00:00
Subject: RE: SUPPORT CPAP PAPER
I am of a like mind with Neil on this issue: we should take a stand for

The better therapy: high sat.

Michele Walsh, MD

Chief, Division of Neonatology

216.844.3759

It's not what you look at that matters, it's what you see. Thoreau

---

From: Finer, Neil [mailto:nfiner@ucsd.edu<mailto:%5bmailto:nfiner@ucsd.edu%5d>
Sent: Wednesday, November 30, 2011 1:37 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; 'Wally Carlo, M.D.'; 'Myriam
Peralta, M.D.'; 'Michele Walsh'; mgantz@rti.org<mailto:mgantz@rti.org>; 'Laptook,
Abbot';
'Bradley Yoder'; 'Roger Faix'; Adas@rti.org<mailto:Adas@rti.org>; Rich, Wade;
kurt.schibler@cchmc.org<mailto:kurt.schibler@cchmc.org>; 'nancy newman'; 'Vohr,
Betty'; 'Susan Hintz';
'Kim Yolton'; 'Roy Heyne'; Costello, Frank;
goldb008@mc.duke.edu<mailto:goldb008@mc.duke.edu>;
Michael.Acarregui@providence.org<mailto:Michael.Acarregui@providence.org>; 'Evans,
Patricia W'; 'Adams-Chapman,
Ira'; 'Pappas, Athina'; 'Anna M. Dusick, MD';
emcgowan@tuftsmedicalcenter.org<mailto:emcgowan@tuftsmedicalcenter.org>; 'Ehrenkranz,
Richard';
abodnar@utah.gov<mailto:abodnar@utah.gov>; 'Bauer, Charles R';
JaFuller@salud.unm.edu<mailto:JaFuller@salud.unm.edu>; 'Michael
O'Shea'; gary_myers@URMC.Rochester.edu<mailto:gary_myers@URMC.Rochester.edu>

Cc: Vaucher, Yvonne; 'Pablo Sanchez'; 'Shankaran, Seetha'; 'Duara, Shahnaz'; 'Barbara Stoll'; 'Poindexter, Brenda B'; 'Krisa Van Meurs'; 'Kennedy, Kathleen A'; goldb008@mc.duke.edu<mailto:goldb008@mc.duke.edu>; 'Phelps, Dale'; 'Bell, Edward (Pediatrics)'; 'Frantz, Ivan'; KWatterberg@salud.unm.edu<mailto:KWatterberg@salud.unm.edu>; Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: SUPPORT CPAP PAPER

Hi Rose

I to some degree disagree. I think we are obliged to say that our results indicate that there is increased death without any balancing benefit, and that we recommend avoiding this range of SpO2 based on these results

We are not telling people what range to use, rather what range to avoid.

This is the evidence

Besides if we do not say this, the editorialists will, and the British already have, in the NEJM in a letter with much less well developed and reviewed data.

Respectfully

Neil

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]<mailto:%5bmailto:higginsr@mail.nih.gov%5d>
Sent: Wednesday, November 30, 2011 9:15 AM
To: 'Wally Carlo, M.D.'; Finer, Neil; 'Myriam Peralta, M.D.'; 'Michele Walsh'; mgantz@rti.org<mailto:mgantz@rti.org>; 'Laptook, Abbot'; 'Bradley Yoder'; 'Roger Faix'; Adas@rti.org<mailto:Adas@rti.org>; Rich, Wade; kurt.schibler@cchmc.org<mailto:kurt.schibler@cchmc.org>; 'nancy newman'; 'Vohr, Betty'; 'Susan Hintz'; 'Kim Yolton'; 'Roy Heyne'; (b)(6) @aol.com<mailto:(b)(6) @aol.com>; goldb008@mc.duke.edu<mailto:goldb008@mc.duke.edu>; Michael.Acarregui@providence.org<mailto:Michael.Acarregui@providence.org>; 'Evans, Patricia W'; 'Adams-Chapman, Ira'; 'Pappas, Athina'; 'Anna M. Dusick, MD'; emcgowan@tuftsmedicalcenter.org<mailto:emcgowan@tuftsmedicalcenter.org>; 'Ehrenkranz, Richard'; abodnar@utah.gov<mailto:abodnar@utah.gov>; 'Bauer, Charles R'; JaFuller@salud.unm.edu<mailto:JaFuller@salud.unm.edu>; 'Michael O'Shea'; gary_myers@URMC.Rochester.edu<mailto:gary_myers@URMC.Rochester.edu>
Cc: Vaucher, Yvonne; 'Pablo Sanchez'; 'Shankaran, Seetha'; 'Duara, Shahnaz'; 'Barbara Stoll'; 'Poindexter, Brenda B'; 'Krisa Van Meurs'; 'Kennedy, Kathleen A'; goldb008@mc.duke.edu<mailto:goldb008@mc.duke.edu>; 'Phelps, Dale'; 'Bell, Edward (Pediatrics)'; 'Frantz, Ivan'; KWatterberg@salud.unm.edu<mailto:KWatterberg@salud.unm.edu>; Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: SUPPORT CPAP PAPER

For the paper, we need to present the data and conclusions. We should refrain from making practice recommendations - this is really up to individual physicians, groups of physicians and the practice guidelines folks such as COFN/AAP. We can certainly say that survival was improved in the higher saturation of the arm based on the data.

Thanks
Rose

Rosemary D. Higgins, MD

Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network

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From: Wally Carlo, M.D.
[mailto:WCarlo@peds.uab.edu]<mailto:%5bmailto:WCarlo@peds.uab.edu%5d>
Sent: Wednesday, November 30, 2011 11:37 AM
To: Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]; 'Myriam Peralta, M.D.'; 'Michele Walsh'; mgantz@rti.org<mailto:mgantz@rti.org>; 'Laptook, Abbot'; 'Bradley Yoder'; 'Roger Faix'; Adas@rti.org<mailto:Adas@rti.org>; Rich, Wade; kurt.schibler@cchmc.org<mailto:kurt.schibler@cchmc.org>; 'nancy newman'; 'Vohr, Betty'; 'Susan Hintz'; 'Kim Yolton'; 'Roy Heyne'; (b)(6)@aol.com<mailto:(b)(6)@aol.com>; goldb008@mc.duke.edu<mailto:goldb008@mc.duke.edu>; Michael.Acarregui@providence.org<mailto:Michael.Acarregui@providence.org>; 'Evans, Patricia W'; 'Adams-Chapman, Ira'; 'Pappas, Athina'; 'Anna M. Dusick, MD'; emcgowan@tuftsmedicalcenter.org<mailto:emcgowan@tuftsmedicalcenter.org>; 'Ehrenkranz, Richard'; abodnar@utah.gov<mailto:abodnar@utah.gov>; 'Bauer, Charles R'; JaFuller@salud.unm.edu<mailto:JaFuller@salud.unm.edu>; 'Michael O`Shea'; gary_myers@URMC.Rochester.edu<mailto:gary_myers@URMC.Rochester.edu>
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Subject: RE: SUPPORT CPAP PAPER

I think we should be more positive about favoring the 91-95% range. However, I think it is best to let societies, academies, etc make the final recommendations.

Wally

-----Original message-----

From: "Finer, Neil"
To: "Higgins, Rosemary (NIH/NICHD) [E]" ,
"'Myriam Peralta, M.D.'" , "'Wally Carlo, M.D.'" , 'Michele Walsh'
, "'Gantz, Marie'" ,
"'Laptook, Abbot'" , 'Bradley Yoder' , 'Roger Faix'
, "'Abhik Das (Adas@rti.org)&apos<mailto:Adas@rti.org)&apos>;"
, "Rich, Wade" ,
"'kurt.schibler@cchmc.org<mailto:kurt.schibler@cchmc.org>'" ,
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"'goldb008@mc.duke.edu<mailto:goldb008@mc.duke.edu>'" ,
"'Michael.Acarregui@providence.org<mailto:Michael.Acarregui@providence.org>'"
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"'emcgowan@tuftsmedicalcenter.org<mailto:emcgowan@tuftsmedicalcenter.org>'"
, "'Ehrenkranz, Richard'"
, "'abodnar@utah.gov<mailto:abodnar@utah.gov>'"
, "'Bauer, Charles R'"

, "'JaFuller@salud. unm. edu
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O`Shea' ,
"'gary_myers@URMC.Rochester.edu<mailto:gary_myers@URMC.Rochester.edu>'"

Cc: "Vaucher, Yvonne" , 'Pablo Sanchez'
, "'Shankaran, Seetha'"
, "'Duara, Shahnaz'"
, 'Barbara Stoll'
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, 'Krisa Van Meurs'
, "'Kennedy, Kathleen A'"
, "'goldb008@mc.duke.edu<mailto:goldb008@mc.duke.edu>'"
, "'Phelps, Dale'"
, "'Bell, Edward
(Pediatrics)'" , "'Frantz, Ivan'"
, 'Kristi Watterberg'
, "Archer, Stephanie (NIH/NICHD) [E]"

Sent: Wed, Nov 30, 2011 16:18:23 GMT+00:00
Subject: RE: SUPPORT CPAP PAPER

Hi Myriam and Wally and Rose
A very nice paper
I have made a few corrections
My main concern however is our conclusion
I think we need to state that SpO2 range of 85% to 89% cannot be
recommended as safe
I think that we have now introduced the Stenson letter - I have added
the correct reference and so I think we need to weigh in this issue =
This is what everyone will want to know
Our unit has now officially moved to a range of 90-95%.
I had asked Rose whether the NRN had looked at their practices or made
any recommendation internally.
I think this needs to be included in the paper and presentation
We had been somewhat cautious because we did not have the follow-up =
Now we do and it confirms our observations without any downside risks
I look forward to your thoughts
Be well
Neil

From: Higgins, Rosemary (NIH/NICHD) [E]
[mailto:higginsr@mail.nih.gov]<mailto:%5bmailto:higginsr@mail.nih.gov%5d>
Sent: Wednesday, November 23, 2011 7:38 AM
To: 'Myriam Peralta, M.D.'; Finer, Neil; 'Wally Carlo, M.D.'; 'Michele
Walsh'; 'Gantz, Marie'; 'Laptook, Abbot'; 'Bradley Yoder'; 'Roger Faix';
'Abhik Das (Adas@rti.org<mailto:Adas@rti.org>)'; Rich, Wade;
'kurt.schibler@cchmc.org<mailto:kurt.schibler@cchmc.org>';
'nancy newman'; 'Vohr, Betty'; 'Susan Hintz'; 'Kim Yolton'; 'Roy Heyne';
(b)(6) @aol.com<mailto:(b)(6) @aol.com>';
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'abodnar@utah.gov<mailto:abodnar@utah.gov>'; 'Bauer, Charles R'; 'JaFuller@salud. unm.
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(JaFuller@salud.unm.edu<mailto:JaFuller@salud.unm.edu>)'; 'Michael O`Shea';
'gary_myers@URMC.Rochester.edu<mailto:gary_myers@URMC.Rochester.edu>'
Cc: Vaucher, Yvonne; 'Pablo Sanchez'; 'Shankaran, Seetha'; 'Duara,
Shahnaz'; 'Barbara Stoll'; 'Poindexter, Brenda B'; 'Krisa Van Meurs';
'Kennedy, Kathleen A'; 'goldb008@mc.duke.edu<mailto:goldb008@mc.duke.edu>'; 'Phelps,
Dale'; 'Bell,
Edward (Pediatrics)'; 'Frantz, Ivan'; 'Kristi Watterberg'; Archer,
Stephanie (NIH/NICHD) [E]
Subject: RE: SUPPORT CPAP PAPER

Hi All,
Here is the SUPPORT oximetry paper and the CONSORT diagram. Please send
all suggestions back to Myriam by December 6.
The papers will then go for internal NRN review.
I have also included the site PI's.

Thanks for all the hard work and effort!
Rose

Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research
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CDBPM, NIH
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From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Saturday, November 19, 2011 7:55 AM
To: 'Myriam Peralta, M.D.'; 'Finer, Neil'; Wally Carlo, M.D.; Michele Walsh; Gantz, Marie; 'Laptook, Abbot'; 'Bradley Yoder'; 'Roger Faix'; Abhik Das (Adas@rti.org<mailto:Adas@rti.org>); 'Rich, Wade'; 'kurt.schibler@cchmc.org<mailto:kurt.schibler@cchmc.org>'; nancy newman; Vohr, Betty; Susan Hintz; 'Kim Yolton'; 'Roy Heyne'; (b)(6) @aol.com<mailto:(b)(6) @aol.com>'; goldb008@mc.duke.edu<mailto:goldb008@mc.duke.edu>; 'Michael.Acarregui@providence.org<mailto:Michael.Acarregui@providence.org>'; 'Evans, Patricia W'; 'Adams-Chapman, Ira'; Pappas, Athina; 'Anna M. Dusick, MD'; 'emcgowan@tuftsmedicalcenter.org<mailto:emcgowan@tuftsmedicalcenter.org>'; 'Ehrenkranz, Richard'; 'abodnar@utah.gov<mailto:abodnar@utah.gov>'; 'Bauer, Charles R'; 'JaFuller@salud. unm. edu (JaFuller@salud.unm.edu<mailto:JaFuller@salud.unm.edu>)'; 'Michael O`Shea'; 'gary_myers@URMC.Rochester.edu<mailto:gary_myers@URMC.Rochester.edu>'
Cc: yvaucher@ucsd.edu<mailto:yvaucher@ucsd.edu>; Pablo Sanchez; 'Shankaran, Seetha'; 'Duara, Shahnaz'; Barbara Stoll; 'Poindexter, Brenda B'; 'Krisa Van Meurs'; 'Kennedy, Kathleen A'; goldb008@mc.duke.edu<mailto:goldb008@mc.duke.edu>; 'Phelps, Dale'; 'Bell, Edward (Pediatrics)'; 'Frantz, Ivan'; 'Kristi Watterberg'; Archer, Stephanie (NIH/NICHD) [E]
Subject: SUPPORT CPAP PAPER
Importance: High

Hi,
Attached is the SUPPORT CPAP FU Paper for co-author input. Please send your comments to Yvonne Vaucher (yvaucher@ucsd.edu<mailto:yvaucher@ucsd.edu>) by DECEMBER 3. The paper will then go for internal NRN review and clearance. Following this, it will be submitted along with the oximetry FU paper (you will get this in the next few days) to the New England Journal of Medicine. I have also included the steering committee PI's from the sites involved with the study. If you have any suggestions, feel free to forward them to Yvonne. Thanks to everyone for all the hard work, effort and commitment to this study!!
Rose

Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network
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Visit us at www.UHhospitals.org<http://www.UHhospitals.org>.

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From: Finer, Neil
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT CPAP PAPER
Date: Wednesday, November 30, 2011 2:29:21 PM

Hi Rose

I will keep this private -- Here is what we said in the NINOS paper second last paragraph.

We believe that appropriate support by conventional means, including the use of surfactant and high-frequency ventilation by experienced practitioners, should precede the administration of inhaled nitric oxide. If such management does not lead to improvement, however, treatment with nitric oxide, whether there is echocardiographic evidence of pulmonary hypertension or not, will substantially reduce the number of infants who receive extracorporeal membrane oxygenation.

This to me is as specific as I was suggesting for SUPPORT

I realize that you have your policies – but I think that we as investigators have an obligation to put our results in context which to me includes guidance as to the strength of our evidence.

I leave this to the you and the NRN
Be well
Neil

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, November 30, 2011 10:52 AM
To: 'Bell, Edward (Pediatrics)'; Kennedy, Kathleen A; Roger Faix; 'Wally Carlo, M.D.'; Finer, Neil; 'Myriam Peralta, M.D.'; 'Michele Walsh'; mgantz@rti.org; 'Laptook, Abbot'; Bradley Yoder; Adas@rti.org; Rich, Wade; kurt.schibler@cchmc.org; 'nancy newman'; 'Vohr, Betty'; 'Susan Hintz'; 'Kim Yolton'; 'Roy Heyne'; (b)(5) @aol.com; goldb008@mc.duke.edu; Michael.Acarregui@providence.org; Evans, Patricia W; 'Adams-Chapman, Ira'; 'Pappas, Athina'; 'Anna M. Dusick, MD'; emcgowan@tuftsmedicalcenter.org; 'Ehrenkranz, Richard'; abodnar@utah.gov; 'Bauer, Charles R'; JaFuller@salud.unm.edu; 'Michael O`Shea'; gary_myers@URMC.Rochester.edu
Cc: Vaucher, Yvonne; 'Pablo Sanchez'; 'Shankaran, Seetha'; 'Duara, Shahnaz'; 'Barbara Stoll'; 'Poindexter, Brenda B'; 'Krisa Van Meurs'; 'Phelps, Dale'; 'Frantz, Ivan'; KWatterberg@salud.unm.edu; Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: SUPPORT CPAP PAPER

Hi

Let me rephrase – Speakers can answer what they are doing in their unit or they can comment on knowledge that they have garnered from other units. We can certainly say that survival was improved in the higher saturation of the arm based on the data.

The NICHD NRN does not make practice recommendations, we provide data/evidence for the professional societies such as AAP/COFN to make those recommendations.

Thanks for the discussion – certainly a Hot Topic.

Rosemary D. Higgins, MD
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From: Bell, Edward (Pediatrics) [mailto:edward-bell@uiowa.edu]
Sent: Wednesday, November 30, 2011 1:51 PM
To: Kennedy, Kathleen A; Roger Faix; Higgins, Rosemary (NIH/NICHD) [E]; 'Wally Carlo, M.D.'; Finer, Neil; 'Myriam Peralta, M.D.'; 'Michele Walsh'; mgantz@rti.org; 'Laptook, Abbot'; Bradley Yoder; Adas@rti.org; Rich, Wade; kurt.schibler@cchmc.org; 'nancy newman'; 'Vohr, Betty'; 'Susan Hintz'; 'Kim Yolton'; 'Roy Heyne'; drfjcmd@aol.com; goldb008@mc.duke.edu; Michael.Acarregui@providence.org; Evans, Patricia W; 'Adams-Chapman, Ira'; 'Pappas, Athina'; 'Anna M. Dusick, MD'; emcgowan@tuftsmedicalcenter.org; 'Ehrenkranz, Richard'; abodnar@utah.gov; 'Bauer, Charles R'; JaFuller@salud.unm.edu; 'Michael O`Shea'; gary_myers@URMC.Rochester.edu
Cc: Vaucher, Yvonne; 'Pablo Sanchez'; 'Shankaran, Seetha'; 'Duara, Shahnaz'; 'Barbara Stoll'; 'Poindexter, Brenda B'; 'Krisa Van Meurs'; 'Phelps, Dale'; 'Frantz, Ivan'; KWatterberg@salud.unm.edu; Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: SUPPORT CPAP PAPER

I like this approach.

From: Kennedy, Kathleen A [mailto:Kathleen.A.Kennedy@uth.tmc.edu]
Sent: Wednesday, November 30, 2011 12:48 PM
To: Roger Faix; Higgins, Rosemary (NIH/NICHD) [E]; 'Wally Carlo, M.D.'; Finer, Neil; 'Myriam Peralta, M.D.'; 'Michele Walsh'; mgantz@rti.org; 'Laptook, Abbot'; Bradley Yoder; Adas@rti.org; Rich, Wade; kurt.schibler@cchmc.org; 'nancy newman'; 'Vohr, Betty'; 'Susan Hintz'; 'Kim Yolton'; 'Roy Heyne'; (b)(6) @aol.com; goldb008@mc.duke.edu; Michael.Acarregui@providence.org; Evans, Patricia W; 'Adams-Chapman, Ira'; 'Pappas, Athina'; 'Anna M. Dusick, MD'; emcgowan@tuftsmedicalcenter.org; 'Ehrenkranz, Richard'; abodnar@utah.gov; 'Bauer, Charles R'; JaFuller@salud.unm.edu; 'Michael O`Shea'; gary_myers@URMC.Rochester.edu
Cc: Vaucher, Yvonne; 'Pablo Sanchez'; 'Shankaran, Seetha'; 'Duara, Shahnaz'; 'Barbara Stoll'; 'Poindexter, Brenda B'; 'Krisa Van Meurs'; 'Phelps, Dale'; Bell, Edward (Pediatrics); 'Frantz, Ivan'; KWatterberg@salud.unm.edu; Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: SUPPORT CPAP PAPER

I didn't mean that we wanted to encourage a recommendation. I just don't think we want to presenter to be caught off guard. What about a planned response like "Individual practice groups need to make their own recommendations based on their interpretation of the evidence." One might or might not want to add "Some Network centers have changed their O2 sat goals. Others have not. Others are waiting for the results of the other ongoing trials."

Kathleen A. Kennedy, MD, MPH
Richard W. Mithoff Professor of Pediatrics
Director, MS in Clinical Research Degree Program
UT-Houston Medical School

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From: Roger Faix [mailto:Roger.Faix@hsc.utah.edu]
Sent: Wednesday, November 30, 2011 11:22 AM
To: Kennedy, Kathleen A; Higgins, Rosemary (NIH/NICHD) [E]; 'Wally Carlo, M.D.'; Finer, Neil; 'Myriam Peralta, M.D.'; 'Michele Walsh'; mgantz@rti.org; 'Laptook, Abbot'; Bradley Yoder; Adas@rti.org; Rich, Wade; kurt.schibler@cchmc.org; 'nancy newman'; 'Vohr, Betty'; 'Susan Hintz'; 'Kim Yolton'; 'Roy Heyne'; (b)(6) @aol.com; goldb008@mc.duke.edu; Michael.Acarregui@providence.org; Evans, Patricia W; 'Adams-Chapman, Ira'; 'Pappas, Athina'; 'Anna M. Dusick, MD'; emcgowan@tuftsmedicalcenter.org; 'Ehrenkranz, Richard'; abodnar@utah.gov; 'Bauer, Charles R'; JaFuller@salud.unm.edu; 'Michael O`Shea'; gary_myers@URMC.Rochester.edu
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Subject: RE: SUPPORT CPAP PAPER

I agree with Kathleen and Neil. Being public about our take on how our practice has changed and what our evidence-based personal recommendations are will be important for multiple reasons.

Roger

From: Kennedy, Kathleen A [Kathleen.A.Kennedy@uth.tmc.edu]
Sent: Wednesday, November 30, 2011 10:18 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; 'Wally Carlo, M.D.'; Finer, Neil; 'Myriam Peralta, M.D.'; 'Michele Walsh'; mgantz@rti.org; 'Laptook, Abbot'; Bradley Yoder; Roger Faix; Adas@rti.org; Rich, Wade; kurt.schibler@cchmc.org; 'nancy newman'; 'Vohr, Betty'; 'Susan Hintz'; 'Kim Yolton'; 'Roy Heyne'; (b)(6) @aol.com; goldb008@mc.duke.edu; Michael.Acarregui@providence.org; Evans, Patricia W; 'Adams-Chapman, Ira'; 'Pappas, Athina'; 'Anna M. Dusick, MD'; emcgowan@tuftsmedicalcenter.org; 'Ehrenkranz, Richard'; abodnar@utah.gov; 'Bauer, Charles R'; JaFuller@salud.unm.edu; 'Michael O`Shea'; gary_myers@URMC.Rochester.edu
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Subject: RE: SUPPORT CPAP PAPER

I agree, but I think we should prepare the presenter regarding how to respond to the "What do you recommend/What do you do/ What do others in the Network do?" questions.

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Richard W. Mithoff Professor of Pediatrics
Director, MS in Clinical Research Degree Program
UT-Houston Medical School
6431 Fannin, Suite 2.106
Houston, TX 77030
713 500-6708

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, November 30, 2011 11:15 AM
To: 'Wally Carlo, M.D.'; Finer, Neil; 'Myriam Peralta, M.D.'; 'Michele Walsh'; mgantz@rti.org; 'Laptook, Abbot'; 'Bradley Yoder'; 'Roger Faix'; Adas@rti.org; Rich, Wade; kurt.schibler@cchmc.org; 'nancy newman'; 'Vohr, Betty'; 'Susan Hintz'; 'Kim Yolton'; 'Roy Heyne'; drfjcmd@aol.com; goldb008@mc.duke.edu; Michael.Acarregui@providence.org; Evans, Patricia W; 'Adams-Chapman, Ira'; 'Pappas, Athina'; 'Anna M. Dusick, MD'; emcgowan@tuftsmedicalcenter.org; 'Ehrenkranz, Richard'; abodnar@utah.gov; 'Bauer, Charles R'; JaFuller@salud.unm.edu; 'Michael O`Shea'; gary_myers@URMC.Rochester.edu

Cc: Vaucher, Yvonne; 'Pablo Sanchez'; 'Shankaran, Seetha'; 'Duara, Shahnaz'; 'Barbara Stoll'; 'Poindexter, Brenda B'; 'Krisa Van Meurs'; Kennedy, Kathleen A; goldb008@mc.duke.edu; 'Phelps, Dale'; 'Bell, Edward (Pediatrics)'; 'Frantz, Ivan'; KWatterberg@salud.unm.edu; Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: SUPPORT CPAP PAPER

For the paper, we need to present the data and conclusions. We should refrain from making practice recommendations – this is really up to individual physicians, groups of physicians and the practice guidelines folks such as COFN/AAP. We can certainly say that survival was improved in the higher saturation of the arm based on the data.

Thanks
Rose

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From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Wednesday, November 30, 2011 11:37 AM
To: Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]; 'Myriam Peralta, M.D.'; 'Michele Walsh'; mgantz@rti.org; 'Laptook, Abbot'; 'Bradley Yoder'; 'Roger Faix'; Adas@rti.org; Rich, Wade; kurt.schibler@cchmc.org; 'nancy newman'; 'Vohr, Betty'; 'Susan Hintz'; 'Kim Yolton'; 'Roy Heyne'; (b)(6) @aol.com; goldb008@mc.duke.edu; Michael.Acarregui@providence.org; 'Evans, Patricia W'; 'Adams-Chapman, Ira'; 'Pappas, Athina'; 'Anna M. Dusick, MD'; emcgowan@tuftsmedicalcenter.org; 'Ehrenkranz, Richard'; abodnar@utah.gov; 'Bauer, Charles R'; JaFuller@salud.unm.edu; 'Michael O`Shea'; gary_myers@URMC.Rochester.edu
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Subject: RE: SUPPORT CPAP PAPER

I think we should be more positive about favoring the 91-95% range. However, I think it is best to let societies, academies, etc make the final recommendations.

Wally

-----Original message-----
From: "Finer, Neil" <nfiner@ucsd.edu>
To: "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>, "'Myriam Peralta, M.D.'" <MPeralta@peds.uab.edu>, "'Wally Carlo, M.D.'"

<WCarlo@peds.uab.edu>, 'Michele Walsh' <mcw3@cwru.edu>, "'Gantz, Marie'" <mgantz@rti.org>, "'Laptook, Abbot'" <ALaptook@WIHRI.org>, 'Bradley Yoder' <Bradley.Yoder@hsc.utah.edu>, 'Roger Faix' <Roger.Faix@hsc.utah.edu>, "'Abhik Das (Adas@rti.org)'" <Adas@rti.org>, "Rich, Wade" <wrich@ucsd.edu>, "'kurt.schibler@cchmc.org'" <kurt.schibler@cchmc.org>, 'nancy newman' <nxs5@case.edu>, "'Vohr, Betty'" <BVohr@WIHRI.org>, 'Susan Hintz' <srhintz@stanford.edu>, 'Kim Yolton' <kimberly.yolton@cchmc.org>, 'Roy Heyne' <Roy.Heyne@UTSouthwestern.edu>, "&apos(b)(6)@aol.com'" (b)(6)@aol.com>, "'goldb008@mc.duke.edu'" <goldb008@mc.duke.edu>, "'Michael.Acarregui@providence.org'" <Michael.Acarregui@providence.org>, "'Evans, Patricia W'" <Patricia.W.Evans@uth.tmc.edu>, "'Adams-Chapman, Ira'" <iadamsc@emory.edu>, "'Pappas, Athina'" <apappas@med.wayne.edu>, "'Anna M. Dusick, MD'" <adusick@pediatrics.wisc.edu>, "'emcgowan@tuftsmedicalcenter.org'" <emcgowan@tuftsmedicalcenter.org>, "'Ehrenkranz, Richard'" <richard.ehrenkranz@yale.edu>, "'abodnar@utah.gov'" <abodnar@utah.gov>, "'Bauer, Charles R'" <CBauer@med.miami.edu>, "'JaFuller@salud. unm. edu (JaFuller@salud.unm.edu)'" <JaFuller@salud.unm.edu>, 'Michael O`Shea' <moshea@wfubmc.edu>, "'gary_myers@URMC.Rochester.edu'" <gary_myers@URMC.Rochester.edu>

Cc: "Vaucher, Yvonne" <yvaucher@ucsd.edu>, 'Pablo Sanchez' <Pablo.Sanchez@UTSouthwestern.edu>, "'Shankaran, Seetha'" <sshankar@med.wayne.edu>, "'Duara, Shahnaz'" <SDuara@med.miami.edu>, 'Barbara Stoll' <Barbara.Stoll@oz.ped.emory.edu>, "'Poindexter, Brenda B'" <bpoindex@iupui.edu>, 'Krisa Van Meurs' <vanmeurs@stanford.edu>, "'Kennedy, Kathleen A'" <Kathleen.A.Kennedy@uth.tmc.edu>, "'goldb008@mc.duke.edu'" <goldb008@mc.duke.edu>, "'Phelps, Dale'" <Dale_Phelps@URMC.Rochester.edu>, "'Bell, Edward (Pediatrics)'" <edward-bell@uiowa.edu>, "'Frantz, Ivan'" <Ivan.Frantz@childrens.harvard.edu>, 'Kristi Watterberg' <KWatterberg@salud.unm.edu>, "Archer, Stephanie (NIH/NICHD) [E]" <archerst@mail.nih.gov>

Sent: Wed, Nov 30, 2011 16:18:23 GMT+00:00

Subject: RE: SUPPORT CPAP PAPER

Hi Myriam and Wally and Rose
A very nice paper
I have made a few corrections
My main concern however is our conclusion
I think we need to state that SpO2 range of 85% to 89% cannot be recommended as safe
I think that we have now introduced the Stenson letter - I have added the correct reference and so I think we need to weigh in this issue = This is what everyone will want to know
Our unit has now officially moved to a range of 90-95%.
I had asked Rose whether the NRN had looked at their practices or made any recommendation internally.
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We had been somewhat cautious because we did not have the follow-up = Now we do and it confirms our observations without any downside risks
I look forward to your thoughts
Be well
Neil

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, November 23, 2011 7:38 AM
To: 'Myriam Peralta, M.D.'; Finer, Neil; 'Wally Carlo, M.D.'; 'Michele Walsh'; 'Gantz, Marie'; 'Laptook, Abbot'; 'Bradley Yoder'; 'Roger Faix'; 'Abhik Das (Adas@rti.org)'; Rich, Wade; 'kurt.schibler@cchmc.org'; 'nancy newman'; 'Vohr, Betty'; 'Susan Hintz'; 'Kim Yolton'; 'Roy Heyne'; (b)(6) @aol.com'; 'goldb008@mc.duke.edu'; 'Michael.Acarregui@providence.org'; 'Evans, Patricia W'; 'Adams-Chapman, Ira'; 'Pappas, Athina'; 'Anna M. Dusick, MD'; 'emcgowan@tuftsmedicalcenter.org'; 'Ehrenkranz, Richard'; 'abodnar@utah.gov'; 'Bauer, Charles R'; 'JaFuller@salud. unm. edu (JaFuller@salud.unm.edu)'; 'Michael O`Shea'; 'gary_myers@URMC.Rochester.edu'
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Hi All,
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The papers will then go for internal NRN review.
I have also included the site PI's.

Thanks for all the hard work and effort!
Rose

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From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Saturday, November 19, 2011 7:55 AM
To: 'Myriam Peralta, M.D.'; 'Finer, Neil'; Wally Carlo, M.D.; Michele Walsh; Gantz, Marie; 'Laptook, Abbot'; 'Bradley Yoder'; 'Roger Faix'; Abhik Das (Adas@rti.org); 'Rich, Wade'; 'kurt.schibler@cchmc.org'; nancy newman; Vohr, Betty; Susan Hintz; 'Kim Yolton'; 'Roy Heyne'; (b)(6) @aol.com'; goldb008@mc.duke.edu; 'Michael.Acarregui@providence.org'; 'Evans, Patricia W'; 'Adams-Chapman, Ira'; Pappas, Athina; 'Anna M. Dusick, MD'; 'emcgowan@tuftsmedicalcenter.org'; 'Ehrenkranz, Richard'; 'abodnar@utah.gov'; 'Bauer, Charles R'; 'JaFuller@salud. unm. edu (JaFuller@salud.unm.edu)'; 'Michael O`Shea'; 'gary_myers@URMC.Rochester.edu'
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Subject: SUPPORT CPAP PAPER
Importance: High

Hi,
Attached is the SUPPORT CPAP FU Paper for co-author input. Please send your comments to Yvonne Vaucher (yvaucher@ucsd.edu) by DECEMBER 3. The paper will then go for internal NRN review and clearance. Following this, it will be submitted along with the oximetry FU paper (you will get this in the next few days) to the New England Journal of Medicine.
I have also included the steering committee PI's from the sites involved with the study. If you have any suggestions, feel free to forward them to Yvonne. Thanks to everyone for all the hard work, effort and commitment to this study!!
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From: Susan Hintz
To: Yvonne Vaucher
Cc: Higgins, Rosemary (NIH/NICHD) [E]; das Das
Subject: Re: Confidential:SUPPORT CPAP SLIDES
Date: Wednesday, November 30, 2011 11:32:53 AM

Hi Yvonne

Great job, and enormous amount of work. Congratulations!

My only thought is that some may ask about other cognitive score cut points, particularly with all the Bayley III questions and concerns. I realize that it was <70 that was specified in the revised protocol, but I wonder if you might want to have some "back up slides" about the <80 or <85 cut points. Or perhaps you looked in secondary exploratory analyses at other alternative NDI definitions that included different cognitive score cutpoints?

Again, great job! You will do great at Hot Topics!

Susan

On Nov 29, 2011, at 12:09 PM, Higgins, Rosemary (NIH/NICHD) [E] wrote:

> <SUPPORT CPAP Hot Topics CPAP slides11292011To Subcommittee.pptx>

From: Finer, Neil
To: Higgins, Rosemary (NIH/NICHD) [E]; "Myriam Peralta, M.D."; "Wally Carlo, M.D."; "Michele Walsh"; "Gantz, Marie"; "Laptook, Abbot"; "Bradley Yoder"; "Roger Faix"; "Abhik Das (Adas@rti.org)"; Rich, Wade; "kurt.schibler@cchmc.org"; "nancy newman"; "Vohr, Betty"; "Susan Hintz"; "Kim Yolton"; "Roy Heyne"; (b)(6) @aol.com"; "goldb008@mc.duke.edu"; "Michael.Acarregui@providence.org"; "Evans, Patricia W"; "Adams-Chapman, Ira"; "Pappas, Athina"; "Anna M. Dusick, MD"; "emcgowan@tuftsmedicalcenter.org"; "Ehrenkranz, Richard"; "abodnar@utah.gov"; "Bauer, Charles R"; "JaFuller@salud. unm. edu (JaFuller@salud.unm.edu)"; "Michael O`Shea"; "gary_myers@URMC.Rochester.edu"
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Subject: RE: SUPPORT CPAP PAPER
Date: Wednesday, November 30, 2011 11:18:38 AM
Attachments: Support NDI 11-20-2011 (2 SpO2 NF Rev Nov 30.doc

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Neurodevelopmental Outcome of Extremely Premature Infants Enrolled in the SUPPORT trial: Early CPAP versus Intubation with Surfactant Administration

Yvonne E. Vaucher YE; Myriam Peralta-Carcelen;
Neil N. Finer; and Waldemar A. Carlo;
for the SUPPORT Study Group
of the NICHD Neonatal Research Network

Disclosures

Speaker: Yvonne E. Vaucher, M.D., M,P,H.

1. Dr. Vaucher has no financial relationships to disclose or Conflicts of Interest to resolve. Any real or apparent conflicts of interest related to the content of this presentation have been resolved.

2. This presentation will not involve discussion of unapproved or off-label, experimental or investigational use of a drug.

Neurodevelopmental Outcome of Extremely Preterm Infants in the SUPPORT trial Early CPAP vs. Surfactant

Presented by Yvonne E. Vaucher, M.D., M.P.H.
for the
SUPPORT Study Group
Eunice Kennedy Shriver NICHD
Neonatal Research Network

Background

- Extremely premature infants have high rates of disability including cognitive impairment, neurosensory deficits and cerebral palsy.

- Neonatal complications (e.g., IVH, PVL, NEC, PDA, ROP, BPD) each contribute independently to neurodevelopmental disability in extremely premature infants

Background: Respiratory Interventions

- The goal of respiratory interventions is to reduce mortality without increasing the risk of complications (e.g., IVH, PVL, PDA, NEC, ROP, BPD) adversely affecting neurodevelopment

- Multiple RCTs have failed to demonstrate consistent superiority in neurodevelopmental outcome of any respiratory intervention (e.g., surfactant, conventional ventilation, HFOV, HFJV, iNO)

Slide 5

h1

higginsr, 9/27/2011

SUPPORT Trial

Randomized 1316 24 to 27 weeks GA newborns to:

Early CPAP in the delivery room followed, if needed, by limited ventilation for 2 weeks

vs.

Intubation in the delivery room and receipt of surfactant within 1 hour of birth with continued ventilation

Hypothesis: Early CPAP would increase survival without BPD at 36 weeks PMA

SUPPORT Study Group. **NEJM** 2010; 362:1970-9

SUPPORT Trial: Neonatal outcomes

Infants treated with early CPAP had:

No differences in PDA, NEC, Grades 3-4 IVH, severe ROP

Trend towards decreased death by 36 wks PMA
(14.2% vs. 17.5%, p=0.09)

Fewer days of mechanical ventilation among survivors
(25 vs. 28 days, p=0.03)

Increased survival without need for HFOV or CV at 7 days
[55% vs. 49%, RR 1.14 (1.03 to 1.25) p=0.01]

Less need for postnatal steroids
[7% vs. 13%, RR 0.57 (0.41-0.78) p=0.001]

SUPPORT Study Group. NEJM 2010; 362:1970-9

SUPPORT Trial: Primary Outcome

After adjustment for gestational age, center, familial clustering there was **no difference in the composite primary outcome of death or BPD** at 36 weeks post-menstrual age (PMA).

Conclusion: Early CPAP is an alternative to immediate intubation and surfactant administration

SUPPORT Study Group. **NEJM** 2010; 362:1970-9

SUPPORT Trial: Neurodevelopmental Outcome Pre-specified hypothesis

The composite outcome of **death or neurodevelopmental impairment** (NDI) at 18-22 months corrected age will be decreased by use of early CPAP compared to intubation and surfactant administration.

Study powered to detect a 10% absolute difference for Death or NDI at 18-22 months corrected age

SUPPORT Trial: Neurodevelopmental Outcome Follow-Up Assessment at 18-22 months CA

Comprehensive neurodevelopmental evaluation by examiners certified annually

- Bayley Scales of Infant and Toddler Development, 3rd ed. (BSID-III) Cognitive Composite Score
- Amiel-Tison neurologic examination
- Gross Motor Function Classification System (GMFCS)
- Medical history
- Parent questionnaire

Definition
Neurodevelopmental Impairment (NDI)

- **One or more of the following criteria:**
  - Cognitive composite score < 70 (BSID-III)
  - Gross Motor Function Classification Level ≥ 2
  - Moderate/severe cerebral palsy (CP)
  - Blind in both eyes (vision < 20/200)
  - Hearing impairment with or without amplification

SUPPORT Trial: Neurodevelopmental Outcome

Demographic, neonatal and outcome variables

At discharge: GA, BW, gender, multiple gestation, race/ethnicity, medical/surgical NEC (≥ Bells Stage 2), Grade 3-4 IVH, PVL, late onset sepsis, ROP, BPD, post-natal steroids

Maternal education, maternal marital status, insurance status, household income, primary language spoken at home, child living with biological parents

At 18-22 mo FUP: Interim medical history, medications, rehospitalizations, post-discharge surgery

SUPPORT Trial: Neurodevelopmental Outcome Analyses

- Intention to treat
- Adjustment for gestational age stratum, center, familial clustering
- Relative risks and 95% CI for categorical variables were estimated using robust Poisson regression in a generalized-estimating-equation model; adjusted means and 95% CI for continuous variables were estimated using linear mixed models
- 2 sided $p < 0.05$

SUPPORT Trial
Neurodevelopmental Outcome

Results

Demographics: FUP cohort

	CPAP	Surf
	N=511	N=479
• Birthweight (g)	849 ±186	852 ± 193
• Gestational age (wks)	26.3 ± 1.1	26.3 ± 1.1
– 26 1/7 to 27 6/7 wks	N=304	N=305
– 24 1/7 to 25 6/7 wks	N=199	N=168
• SGA	4.5%	6.7%
• Male	50.1%	55.5%
• Non-Hispanic white	38.4%	41.8%
• Multiples	27%	23.8%
• Mothers married	47.7%	46.1%
• Public Insurance	51.3%	53.7%
• Maternal Education < 12^{th} grade	25.3%	24.7%
• English primary language	83.5%	84.3%

Perinatal/Neonatal Outcomes: FUP cohort

	CPAP	Surf
• Antenatal Steroids	96.4%	95.2%
• C-section	68.9%	65.8%
• Received Surfactant	67.1%	98.9%***
• Severe ROP	12.9%	13.4%
• BPD (physiologic)	37.8%	39%
• Grade 3-4 IVH/PVL	13.7%	9.6%
• NEC ≥ Stage 2	11%	6.3%**
• Late onset sepsis	32.7%	32.2%
• Postnatal steroids	6.7%	11.6%**

**p< 0.02; ***p<0.001

Primary Composite Outcome
Death or NDI at 18-22 months

Died before FUP at 18-22 mo CA **19.6%** (258/1316)

Survivors seen at 18-22 mo CA **93.6%** (990/1058)

NDI status determined **98.6%** (976/990)

- No differences in 68 children lost to FUP except their mothers less likely to be married, more likely to have public insurance
- No difference in FUP rates or age at FUP (20 mo CA) between treatment arms

Death or NDI determined: 93.8% (1234/1316)

Death or NDI at 18-22 months

	CPAP	Surf
Death or NDI determined	93.7%.	93.9% ,
	RR 1(0.97,1.03) p=0.83	
Death before 18-22 mo CA	18.4%.	21.9% ,
	RR 0.83(0.67,1.04) p=0.10	
NDI	10.9%	9.1% ,
	RR 1.16(0.79,1.71) p=0.44	

No difference in pre-specified outcome of Death or NDI at 18-22 months

Early CPAP **Early Surfactant**

27.9% **vs.** **29.9%**

RR 0.93(95% CI 0.78,1.1) p=0.38

Individual Components of NDI

	CPAP	Surf	p
Cognitive score < 70	7.2%	7.6%	0.62
GMFCS ≥ 2	5.1%	4.8%	0.29
Moderate/severe CP	4.1%	4.0%	0.51
Bilateral blindness	0.8%	1.5%	0.88
Hearing impairment	3.3%	1.5%	0.06

Combined Outcome:
Death or Individual Components of NDI

	CPAP	Surf	p
Cognitive score < 70	24.8%	28.8%	0.11
GMFCS ≥ 2	22.9%	26.3%	0.16
Moderate/severe CP	22.1%	25.7%	0.14
Bilateral blindness	19.4%	23.7%	0.07
Hearing impairment	21.5%	23.7%	0.33

Outcome by Gestational Age Strata
Normal

	CPAP	Surf	p
NL neuromotor exam	75.5%	79.2%	0.23
NL neurosensory exam			
NL cognitive score (≥85)	77.9%	73.3%	0.08
Normal on all exams	59.7%	59.6%	0.60

Medical Outcome

	CPAP	Surf
Any readmission	44.7%	46.1%
Respiratory	23.5%	25.3%
Growth/nutrition	2.8%	2.3%
Any respiratory medication	37.9%	38.3%
Bronchodilators	34.7%	35.4%
Steroids	22.7%	18.6%
Diuretics	3%	3%
Any surgery	47%	44.3%
Eye	9.8%	10%

SUPPORT Trial: Neurodevelopmental Outcome Gestational Age Strata

Outcome by Gestational Age Strata
Normal outcome on cognitive, motor, and neurosensory exams

	CPAP	Surf	p
Normal Outcome			
26-27 weeks	**67.5%**	**65.2%**	0.36
24-25weeks	**47.5%**	**49.4%**	0.75

Cognitive Outcome by Gestational Age Strata

	CPAP	Surf	p
Cognitive composite score*			
26-27 weeks	**93.5 ± 0.9**	**92.6 ± 0.9**	0.48
24-25weeks	**89.2 ± 1.09**	**88.3 ± 1.17**	0.53
Cognitive score < 70			
26-27 weeks	**4.3%**	**6.6%**	0.41
24-25weeks	**11.6%**	**9.6%**	0.62

* BSID-III (Mean ± SEM)

Motor Outcome by Gestational Age Strata
Cerebral Palsy

	CPAP	Surf	p
Any CP			
26-27 weeks	**5.8%**	**5.5%**	0.83
24-25weeks	**15.9%**	**9.9%**	0.18
Mod/Severe CP			
26-27 weeks	**2.3%**	**3.6%**	0.31
24-25weeks	**7.0%**	**4.7%**	0.62
GMF level ≥2			
26-27 weeks	**2.9%**	**4.6%**	0.24
24-25weeks	**8.5%**	**5.2%**	0.29

Neurosensory Outcome by Gestational Age Strata

	CPAP	Surf	p
Bilateral blindness			
26-27 weeks	**0.6%**	**1.6%**	0.26
24-25weeks	**1.0%**	**1.2%**	0.88
Hearing impairment			
26-27 weeks	**1.9%**	**1.3%**	0.50
24-25weeks	**5.5%**	**1.7%**	0.07

Composite Outcome by Gestational Age Strata
Death or NDI

	CPAP	Surf	p
Death (<18-22 mo CA)			
26-27 weeks	**12.3%**	**11.8%**	0.82
24-25weeks	**26.4%**	**35.5%**	**0.02**
NDI			
26-27 weeks	**6.3%**	**7.2%**	0.81
24-25weeks	**18.1%**	**12.5%**	0.22
Death or NDI			
26-27 weeks	**18.3%**	**18.7%**	0.93
24-25weeks	**40.1%**	**44.5%**	0.27

Study Strengths and Weaknesses

- National, multicenter trial
- Powered to detect pre-specified neurodevelopmental outcome
- Large FUP cohort of extremely premature newborns from 24 to 27 weeks gestation
- Comprehensive, standardized FUP examination
- Excellent FUP rate

Study Strengths and Weaknesses

- 1/3 of Early CPAP infants were intubated in the DR and 2/3 of Early CPAP infants received surfactant in the DR or NICU
- Requirement for antenatal consent resulted in the eligible/enrolled trial cohort having higher SES status and receipt of ANS compared to eligible/non-enrolled mothers may limit generalizability
- Study not powered for individual lower prevalence outcomes

Summary
SUPPORT Trial Neurodevelopmental Outcome
Early CPAP vs. Surfactant treatment

- No significant difference in pre-specified composite outcome of **Death or NDI**
- No significant differences in individual components of NDI
- No significant differences in composite outcome of death or individual components of NDI
- No significant differences between composite outcome or components of NDI within the two gestational age strata

Conclusion

Compared to intubation with surfactant administration, early CPAP, an alternative strategy for the respiratory management of extremely premature infants, was not associated with a significant difference in the combined risk of death or neurodevelopmental impairment in early childhood

Neonatal Research Network Centers (2004-2009)

- Brown University
- Case Western Reserve University
- Cincinnati Children's Medical Center
- Duke University
- Emory University
- Indiana University
- RTI International
- Stanford University
- Tufts Medical Center
- University of Alabama at Birmingham
- University of California – San Diego
- University of Iowa
- University of Miami
- University of New Mexico
- University of Rochester
- University of Texas Southwestern
- University of Texas Health Science Center
- University of Utah
- Wake Forest University
- Wayne State University
- Yale University

From: Vaucher, Yvonne
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Acknowledgement slide
Date: Tuesday, November 29, 2011 3:06:53 PM
Attachments: SUPPORT CPAP Hot Topics CPAP slides11292011To Subcommittee.pptx

Rose,
Here is the presentation. One piece of data still needed if Marie can provide it time (neurosensory impairment with HI and vision combined)
Since Myriam is talking first I will skip the same information in Methods which is still included in slide presentation.
Looking at the Hot Topics schedule it appears we have 20 minutes each to present back to back followed by a 20 minutes discussion afterwards. We could shorten our presentations to 15 minutes and then have a combined discussion. It is the end of the day and many people will be leaving to catch their planes home.

Yvonne

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, November 29, 2011 8:29 AM
To: Vaucher, Yvonne; Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: Acknowledgement slide

Yvonne
Can you send us your Hot Topics slides so the subcommittee and Steering Committee can see them prior to next week's presentation?
Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network
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301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

-----Original Message-----
From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]
Sent: Tuesday, November 29, 2011 10:14 AM
To: Archer, Stephanie (NIH/NICHD) [E]
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Acknowledgement slide

Thanks!

Yvonne

From: Archer, Stephanie (NIH/NICHD) [E] [archerst@mail.nih.gov]
Sent: Tuesday, November 29, 2011 6:02 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Vaucher, Yvonne
Cc: Myriam Peralta-Carcelen (MPeralta@peds.uab.edu)
Subject: RE: Acknowledgement slide

Sorry.

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tuesday, November 29, 2011 9:02 AM
To: Archer, Stephanie (NIH/NICHD) [E]; 'yvaucher@ucsd.edu'
Cc: Myriam Peralta-Carcelen (MPeralta@peds.uab.edu)
Subject: RE: Acknowledgement slide

No attachment - can you resend?
Thanks
Rose

Rosemary D. Higgins, MD
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301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov<mailto:higginsr@mail.nih.gov>

From: Archer, Stephanie (NIH/NICHD) [E]
Sent: Tuesday, November 29, 2011 9:01 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; 'yvaucher@ucsd.edu'
Cc: Myriam Peralta-Carcelen (MPeralta@peds.uab.edu)
Subject: RE: Acknowledgement slide

We don't normally name the people on the slides (too many to list), just the sites involved. Attached is a version for the SUPPORT FU presentations. I've also copied Myriam here, in case she wants to use it too.

Stephanie

Stephanie Wilson Archer
The Eunice Kennedy Shriver
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6100 Executive Boulevard, Room 4B03
Rockville, MD 20852

Tel. 301-496-0430
Fax 301-496-3790
archerst@mail.nih.gov<mailto:archerst@mail.nih.gov>
From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tuesday, November 29, 2011 6:19 AM
To: 'yvaucher@ucsd.edu'; Archer, Stephanie (NIH/NICHD) [E]
Subject: Re: Acknowledgement slide

Do we have this one? Nrn from 2004-09

From: Vaucher, Yvonne <yvaucher@ucsd.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Vaucher, Yvonne <yvaucher@ucsd.edu>
Sent: Mon Nov 28 22:36:18 2011
Subject: Acknowledgement slide
Rose,
Is there a standard acknowledgement slide I can use for the SUPPORT subcommittee, RTI and FUP PIs?
Thanks.

Yvonne

Yvonne E. Vaucher, M.D., M.P.H.
Division of Neonatal/Perinatal Medicine
Clinical Professor of Pediatrics
UCSD School of Medicine

tele: 619-543-3759
FAX: 619-543-3812

From: Roger Faix
To: mperalta@peds.uab.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: Confidential:SUPPORT Oximetry 1.pptx
Date: Tuesday, November 29, 2011 1:44:17 PM
Attachments: SUPPORT Oximetry 1.pptx

Hi Myriam!

I suggest that you give your full name on the title slide, i.e., 'Miryam Peralta-Carcelen for the... ' rather than 'Myriam Presents...'

Roger

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]
Sent: Tuesday, November 29, 2011 10:20 AM
To: Bradley Yoder; Roger Faix; 'abodnar@utah.gov'; 'Finer, Neil'; 'Rich, Wade'; 'Vaucher, Yvonne'; 'Ehrenkranz, Richard'; 'Michael O`Shea'; 'Duara, Shahnaz'; 'Bauer, Charles R'; 'emcgowan@tuftsmedicalcenter.org'; 'Frantz, Ivan'; 'gary_myers@URMC.Rochester.edu'; (b)(6) @aol.com'; 'Roy Heyne'; 'Pappas, Athina'; Adams-Chapman, Ira; 'Kim Yolton'; 'Anna M. Dusick, MD'; 'Vohr, Betty'; 'Susan Hintz'; golds005@mc.duke.edu; 'Michael.Acarregui@providence.org'; 'JaFuller@salud. unm. edu (JaFuller@salud.unm.edu)'; (suhas.kallapur@cchmc.org); Abbot Laptook (alaptook@wihri.org); Abhik Das (adas@rti.org); Ambal (ambal@uab.edu); Anna Maria Hibbs (AnnaMaria.hibbs@cwru.edu); barbara_stoll@oz.ped.emory.edu; bpoindex@iupui.edu; carl_dangio@urmc.rochester.edu; Carlton, David P; cotte010@mc.duke.edu; dstevenson@stanford.edu; dwallace@rti.org; Ed Bell (edward-bell@uiowa.edu); goldb008@mc.duke.edu; Greg Sokol (gsokol@iupui.edu); Haresh Kirpalani (KIRPALANIH@email.chop.edu); John Barks; Jon.E.Tyson@uth.tmc.edu; Kennedy, Kathleen A; Krisa Van Meurs (vanmeurs@stanford.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); Kurt Schibler [kurt.schibler@cchmc.org]; Luc Brion (luc.brion@utsouthwestern.edu); Martin Keszler (mkeszler@wihri.org); mcw3@po.cwru.edu; Meena Garg (mgarg@mednet.ucla.edu); Nelin, Leif; Pablo.Sanchez@UTSouthwestern.edu; Polin, Richard; Robin Ohls (rohls@salud.unm.edu); ronnie_guillet@urmc.rochester.edu; Satyan Lakshminrusimha; Schmidt, Barbara (Neonatology); Seetha Shankaran ; Sood, Beena [bsood@med.wayne.edu]; Truog, William (MD); Uday Devaskar (UDEVASKAR@MEDNET.UCLA.EDU); Wally Carlo (wacarlo@uab.edu)
Cc: Archer, Stephanie (NIH/NICHD) [E]; Myriam Peralta-Carcelen (MPeralta@peds.uab.edu)
Subject: Confidential:SUPPORT Oximetry 1.pptx

Hi
Attached are the slides for Myriam Peralta's presentation one week from today at Hot Topics.
Please treat these as confidential. If you have any suggestions, please send them to Myriam.

Thanks
Rose

Neurodevelopmental Outcome of Extremely Preterm Infants in the SUPPORT trial Pulse Oximetry Trial

Myriam Presented for the SUPPORT Study Group

NICHD Neonatal Research Network

Background

- Oxygen supplementation is vital therapy for survival in many preterm infants with respiratory disorders
- However, oxygen supplementation may increase risk of retinopathy of prematurity and BPD
- There have been concerns that restrictive oxygen practice can increase mortality and neurodevelopmental impairment

SUPPORT trial: Design

- 1316 – 24 to 27 weeks GA infants
- Randomized to lower oxygen saturation target group 85-89% vs. higher oxygen saturation group 91-95%

SUPPORT study group NEJM 2010; 362: 1959-1969

SUPPORT trial: Results

- Retinopathy of prematurity or death did not differ significantly between the two groups
- However death before discharge was higher in the lower oxygen saturation group (19.9% vs. 16.2 %, RR 1.27 95% CI, 1.01 to 1.60; P=0.04)
- Severe ROP among survivors to discharge was reduced in the lower saturation group (8.6% vs. 17.9% RR 0.53; 95% CI 0.37 to 0.73; P<0.001)

SUPPORT study group NEJM 2010; 362: 1959-1969

Hypothesis

- The composite outcome of death or neurodevelopmental impairment will be decreased in the lower saturation target oxygenation group compared to the higher oxygen saturation target group at 18 to 22 months corrected age.

Assessments at 18-22 months

- Masked neurodevelopmental examiners, certified yearly
- Bayley Scales of Infant Development 3rd edition: Cognitive Composite Score
- Modified Gross Motor Function Classification System (GMFCS)
- Neurologic examination (Amiel Tison)
- Standard questionnaires and medical history provided by parent or primary caregiver

Definitions

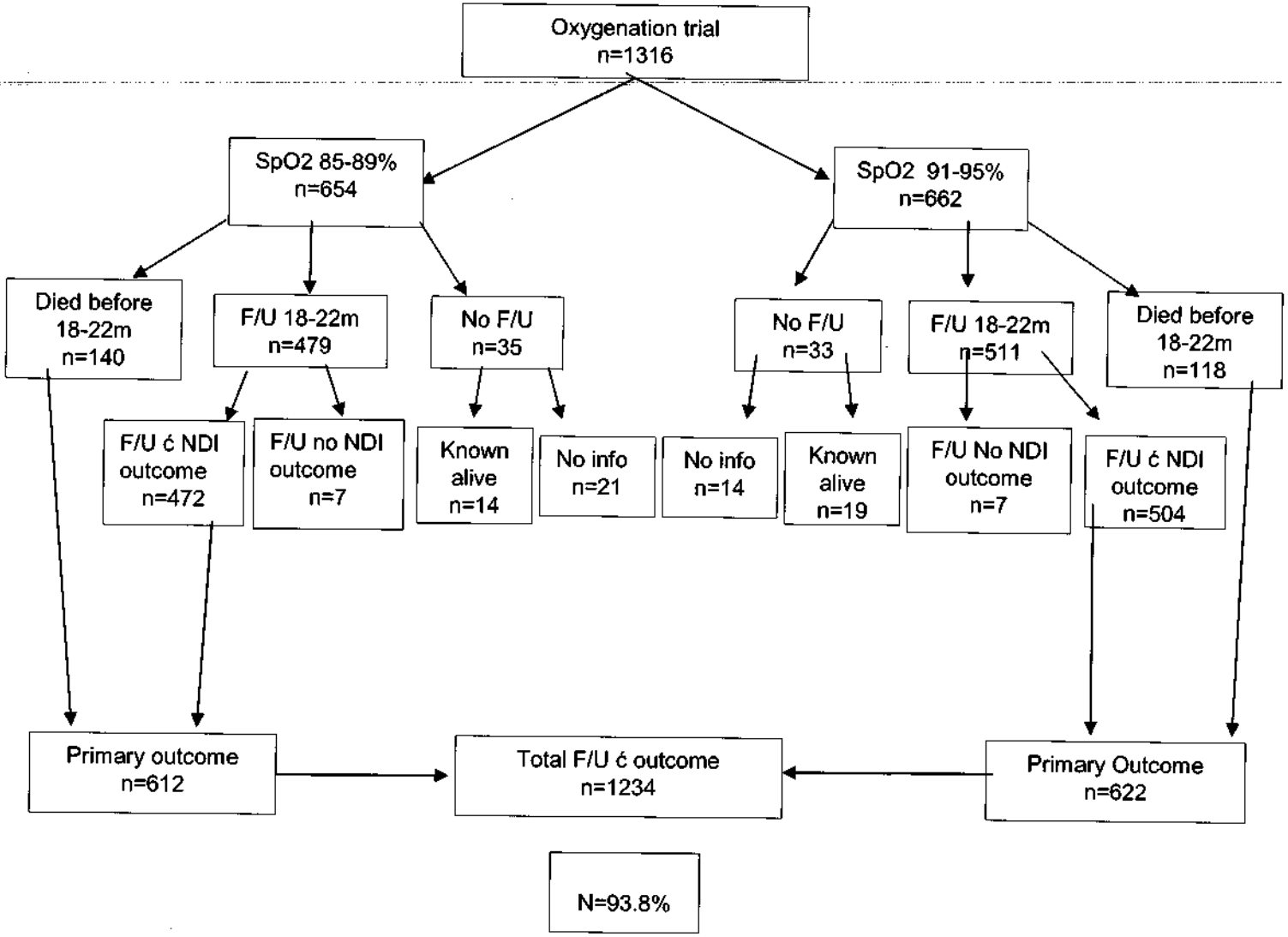
- Neurodevelopmental Impairment (NDI) defined as any of:
  - Bayley III cognitive composite score < 70
  - GMFCS $\geq$ 2
  - Moderate to Severe Cerebral Palsy (CP)
  - Hearing impairment despite amplification
  - Bilateral visual impairment (<20/200)

Outcomes

- Primary: Presence of death or NDI at 18 to 22 months adjusted age
- Other:
  - CP at 18 to 22 m adjusted age
  - Blindness at 18 to 22 m adjusted age

Data collection and analysis

- Data collected in standard forms transmitted to and analyzed by RTI International
- Analysis
  - Intention to treat
  - Adjusted for GA stratum, center, familial clustering
  - 2 sided $P < .05$
  - Adjusted relative risks and 95% CI for categorical variables were estimated using robust Poisson regression in a generalized-estimated-equation model; adjusted means and 95% CI for continues variables were estimated using linear mixed models



Baseline characteristics

	Trial Cohort		Cohort with FU visit	
Characteristic	85-89%	91-95%	85-89%	91-95%
	N=654	N=662	N=479	N=511
Birth weight - g	835.5	824.8	857.8	843.7
Gestational age - wk	26.2	26.1	26.3	26.2
SGA – (%)	6.3	8.3	3.5*	7.4*
Male sex (%)	52.1	56	50.1	55.2
Race (%)				
Non hispanic black	39.3	35	42	34.4
Non hispanic white	37	42.1	37.2	42.1
Hispanic	20.2	19.2	18	19
Maternal education < HS	24.9	27	24.4	25
Public Health Insurance	54.8	52.7	52.8	52
Mother married	43.6	46.6	46.3	47

Perinatal characteristics

	Trial Cohort		Cohort with FU visit	
Characteristic	85-89%	91-95%	85-89%	91-95%
	N=654	N=662	N=479	N=511
CPAP (%)	51.4	49.4	53	50.3
Surfactant (%)	48.6	50.6	47	49.7
Postnatal steroids (%)	9.6	10.7	8.6	9.5
BPD (%)	38	41.7	37	39
Severe ROP (%)	8.6*	17.9*	8.6*	17.4*
IVH grade 3 or 4 or PVL	15.6	15.6	11.7	11.8
NEC	11.9	10.8	8.8	8.6
LO sepsis/meningitis	36.5	35.6	32.4	32.5
Antenatal steroids	96.8	95.6	96.5	95.8
Cesarean section	67.4	66.8	69.3	65.0
Multiple births	24.6	26.6	25.9	25

Primary Oucomes at 18-22 months corrected age

Outcome (%)	85-89%	91-95%	Adjusted RR	P-value
	N=654	N=662		
Outcome determined	93.6	94	1 (0.97, 1.03)	0.79
NDI or Death	30.2	27.5	1.12 (0.94,1.32)	0.2098
Died by 18-22 mo	22.1	18.2	1.25 (1, 1.55)	0.046

Oucomes of Survivors at 18-22 months corrected age

Outcome (%)	85-89%	91-95%	Adjusted RR	P-value
	N=479	N=511		
NDI	9.5	10.5	0.87(0.6, 1.28)	0.49
Bayley III cognitive<70	7.2	7.6	0.91(0.58,1.43)	0.69
GMFCS $\geq$ 2	5.4	4.5	1.17(0.68,2.01)	0.56
Mod/severe CP	4.2	3.9	1 (0.54, 1.83)	0.99
Blindness	1	1.2	0.9 (0.28, 2.9)	0.86
Deafness	2.5	2.3	1.16 (0.54,2.49)	0.70

Bayley III cognitive composite scores among survivors at 18-22 months corrected age

Outcome (%)	85-89%	91-95%	Adjusted RR	P-value
	N=479	N=511		
Bayley III				
Cognitive composite<70	7.2	7.6	0.91(0.58,1.43)	0.69
Cognitive composite<85	22.3	26.2	0.85(0.68,1.07)	0.16
Adjusted means Cognitive composite	92.2±0.8	90.5±0.7	0.7(-1.2, 2.5)	0.48
Median cognitive composite scores	90 (85,100	90 (80, 100)		

Neurological Findings among survivors at 18-22 months corrected age

Outcome (%)	85-89%	91-95%	Adjusted RR	P-value
	N=479	N=511		
Abnormal Neuro exam	22.5	22.3	1.02(0.82,1.28)	0.84
Any CP	9	8	1.12(0.76,1.65)	0.57
Mild CP	5	4.3	1.16(0.66,2.02)	0.61
Mod CP	2.5	2.1	1.19(0.52,2.71)	0.68
Severe CP	2	2.1	0.95(0.39,2.27)	0.90

Eye findings among survivors at 18-22 months corrected age

Outcome (%)	85-89%	91-95%	Adjusted RR	P-value
	N=479	N=511		
Severe ROP	8.6	17.4		0.0001
Eye surgery	6.5	13.2	0.52(0.35,0.78)	0.001
Strabismus	9.6	8	1.2(0.8,1.8)	0.38
Nystagmus	4.6	2.4	1.81(0.89,3.69)	0.10
Tracks 180 degrees	97.1	97.2	1(0.98,1.02)	0.93
Corrective lenses	4.5	4.1	1.14(0.62,2.08)	0.65
Blind some function	0.7	0.4	1.57(0.27,8.96)	0.61
Blind no function	0.4	0.8	0.54(0.1,2.96)	0.48
Other abnormality vision	1.3	2.5	0.55(0.21,1.46)	0.23

Other medical outcomes among survivors at 18-22 months corrected age

Outcome (%)	85-89%	91-95%	Adjusted RR	P-value
	N=479	N=511		
Medications				
Bronchodilators	33.5	36.6	0.92(0.78,1.1)	0.37
Steroids	20.0	21.3	0.92(0.72,1.18)	0.51
Diuretics	3.2	2.8	1.17(0.58,2.34)	0.67
Anticonvulsants	2.5	2.3	1.08(0.49,2.37)	0.85
Readmissions	43.9	46.8	0.94(0.82,1.08)	0.40
Readmission for respiratory illness	23.4	25.2	0.93(0.74,1.16)	0.51
Readmission for growth/nutrition	2.6	2.6	1.05(0.49,2.25)	0.90

Conclusions

- There were no significant differences in the pre-specified outcome of death or neurodevelopmental impairment at 18 to 22 months corrected age
- Death remained higher in the lower target oxygenation group at 18 to 22 months corrected age
- NDI was not significant between lower or higher oxygenation groups.

Conclusions

- Although severe ROP was associated with higher oxygenation target levels, blindness at follow up was not significantly different between survivors at 18 to 22 months.

Neonatal Research Network Centers (2004-2009)

- Brown University
- Case Western Reserve University
- Cincinnati Children's Medical Center
- Duke University
- Emory University
- Indiana University
- RTI International
- Stanford University
- Tufts Medical Center
- University of Alabama at Birmingham
- University of California – San Diego
- University of Iowa
- University of Miami
- University of New Mexico
- University of Rochester
- University of Texas Southwestern
- University of Texas Health Science Center
- University of Utah
- Wake Forest University
- Wayne State University
- Yale University

Thanks

From: Walsh, Michele
To: Barbara Stoll; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Myriam Peralta, M.D.; Finer, Neil; Wally Carlo, M.D.; Michele Walsh; Gantz, Marie; Laptook, Abbot; Bradley Yoder; Roger Faix; ""Abhik Das (<Adas@rti.org>, " "Rich@ws-mr1.cc.emory.edu; Wade"" <wrich@ucsd.edu>, ""; nancy newman; Vohr, Betty; Susan Hintz; Kim Yolton; Roy Heyne; "" (b)(6) @aol.com>, ""; "" <Michael.Acarregui@providence.org>, " "Evans@ws-mr1.cc.emory.edu; Patricia.W" " <Patricia.W.Evans@uth.tmc.edu>, " "Adams-Chapman@ws-mr1.cc.emory.edu; Ira" " <iadamsc@emory.edu>, " "Pappas@ws-mr1.cc.emory.edu; Athina" " <apappas@med.wayne.edu>, " "Anna.M.Dusick@ws-mr1.cc.emory.edu; MD"" <adusick@pediatrics.wisc.edu>, ""; Ehrenkranz, Richard; "" <abodnar@utah.gov>, " "Bauer@ws-mr1.cc.emory.edu; Charles.R" " <CBauer@med.miami.edu>, " "JaFuller@salud.unm.edu
Subject: RE: UPDATED SUPPORT OXIMETRY PAPER
Date: Tuesday, November 29, 2011 1:08:43 PM

Very nice! Quite clear.... nothing to add. Congrats! Michele

-----Original Message-----
From: Barbara Stoll [mailto:Barbara.Stoll@oz.ped.emory.edu]
Sent: Mon 11/28/2011 8:04 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Higgins, Rosemary (NIH/NICHD) [E]; 'Myriam Peralta, M.D.'; 'Finer, Neil'; 'Wally Carlo, M.D.'; 'Michele Walsh'; 'Gantz, Marie'; 'Laptook, Abbot'; 'Bradley Yoder'; 'Roger Faix'; '"Abhik Das (<Adas@rti.org>, "'Rich@ws-mr1.cc.emory.edu; Wade'" <wrich@ucsd.edu>, "'; 'nancy newman'; 'Vohr, Betty'; 'Susan Hintz'; 'Kim Yolton'; 'Roy Heyne'; '" (b)(6) @aol.com>, "'; '" <Michael.Acarregui@providence.org>, "'Evans@ws-mr1.cc.emory.edu; Patricia.W'" <Patricia.W.Evans@uth.tmc.edu>, "'Adams-Chapman@ws-mr1.cc.emory.edu; Ira'" <iadamsc@emory.edu>, "'Pappas@ws-mr1.cc.emory.edu; Athina'" <apappas@med.wayne.edu>, "'Anna.M.Dusick@ws-mr1.cc.emory.edu; MD'" <adusick@pediatrics.wisc.edu>, "'; 'Ehrenkranz, Richard'; '" <abodnar@utah.gov>, "'Bauer@ws-mr1.cc.emory.edu; Charles.R'" <CBauer@med.miami.edu>, "'JaFuller@salud.unm.edu
Subject: Re: UPDATED SUPPORT OXIMETRY PAPER

Very nice and clearly presented paper
My edits are attached
Regards
BJS"Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> writes:
Hi

For those of you who have not yet commented, here is a revised version of the oximetry paper.

Thanks for all your input.

Rose

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From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, November 23, 2011 10:38 AM
To: 'Myriam Peralta, M.D.'; 'Finer, Neil'; 'Wally Carlo, M.D.'; 'Michele Walsh'; 'Gantz, Marie'; 'Laptook, Abbot'; 'Bradley Yoder'; 'Roger Faix'; 'Abhik Das (Adas@rti.org)'; 'Rich, Wade'; 'kurt.schibler@cchmc.org <mailto:%27kurt.schibler@cchmc.org> '; 'nancy newman'; 'Vohr, Betty'; 'Susan Hintz'; 'Kim Yolton'; 'Roy Heyne'; (b)(6) @aol.com <mailto:%1(b)(6) @aol.com> '; 'goldb008@mc.duke.edu <mailto:%27goldb008@mc.duke.edu> '; 'Michael.Acarregui@providence.org <mailto:%27Michael.Acarregui@providence.org> '; 'Evans, Patricia W'; 'Adams-Chapman, Ira'; 'Pappas, Athina'; 'Anna M. Dusick, MD'; 'emcgowan@tuftsmedicalcenter.org <mailto:%27emcgowan@tuftsmedicalcenter.org> '; 'Ehrenkranz, Richard'; 'abodnar@utah.gov <mailto:%27abodnar@utah.gov> '; 'Bauer, Charles R'; 'JaFuller@salud.unm. edu (JaFuller@salud.unm.edu)'; 'Michael O`Shea'; 'gary_myers@URMC.Rochester.edu <mailto:%27gary_myers@URMC.Rochester.edu> '
Cc: 'yvaucher@ucsd.edu <mailto:%27yvaucher@ucsd.edu> '; 'Pablo Sanchez'; 'Shankaran, Seetha'; 'Duara, Shahnaz'; 'Barbara Stoll'; 'Poindexter, Brenda B'; 'Krisa Van Meurs'; 'Kennedy, Kathleen A'; 'goldb008@mc.duke.edu <mailto:%27goldb008@mc.duke.edu> '; 'Phelps, Dale'; 'Bell, Edward (Pediatrics)'; 'Frantz, Ivan'; 'Kristi Watterberg'; Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: SUPPORT CPAP PAPER

Hi All,

Here is the SUPPORT oximetry paper and the CONSORT diagram. Please send all suggestions back to Myriam by December 6.

The papers will then go for internal NRN review.

I have also included the site PI's.

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Subject: SUPPORT CPAP PAPER
Importance: High

Hi,

Attached is the SUPPORT CPAP FU Paper for co-author input. Please send your comments to Yvonne Vaucher (yvaucher@ucsd.edu <mailto:yvaucher@ucsd.edu>) by DECEMBER 3. The paper will then go for internal NRN review and clearance. Following this, it will be submitted along with the oximetry FU paper (you will get this in the next few days) to the New England Journal of Medicine.

I have also included the steering committee PI's from the sites involved with the study. If you have any suggestions, feel free to forward them to Yvonne. Thanks to everyone for all the hard work, effort and commitment to this study!!
Rose

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: Hot Topics presentation
Date: Tuesday, November 29, 2011 11:26:00 AM
Attachments: Oximetry_slides oct.pptx

Can you insert the NRN acknowledgements slides and send back to me?

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Sent: Monday, November 28, 2011 5:05 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Wally Carlo, M.D.
Subject: RE: Hot Topics presentation

Here are the slides with tables, please send me any comments thanks

Neurodevelopmental Outcome of Extremely Preterm Infants in the SUPPORT trial Pulse Oximetry Trial

Presented for the SUPPORT study group

Eunice Kennedy Shriver NICHD Neonatal Research Network

Background

- Oxygen supplementation is vital therapy for survival in many preterm infants with respiratory disorders
- However, oxygen supplementation may increase risk of retinopathy of prematurity and BPD
- There have been concerns that restrictive oxygen practice can increase mortality and neurodevelopmental impairment

SUPPORT trial: Design

- 1316 – 24 to 27 weeks GA infants
- Randomized to lower oxygen saturation target group 85-89% vs. higher oxygen saturation group 91-95%

SUPPORT study group NEJM 2010; 362: 1959-1969

SUPPORT trial: Results

- Retinopathy of prematurity or death did not differ significantly between the two groups
- However death before discharge was higher in the lower oxygen saturation group (19.9% vs. 16.2 %, RR 1.27 95% CI, 1.01 to 1.60; P=0.04)
- Severe ROP among survivors to discharge was reduced in the lower saturation group (8.6% vs. 17.9% RR 0.53; 95% CI 0.37 to 0.73; P<0.001)

SUPPORT study group NEJM 2010; 362: 1959-1969

Hypothesis

- The composite outcome of death or neurodevelopmental impairment will be decreased in the lower saturation target oxygenation group compared to the higher oxygen saturation target group at 18 to 22 months corrected age.

Assessments at 18-22 months

- Masked neurodevelopmental examiners, certified yearly
- Bayley Scales of Infant Development 3rd edition: Cognitive Composite Score
- Modified Gross Motor Function Classification System (GMFCS)
- Neurologic examination (Amiel Tison)
- Standard questionnaires and medical history provided by parent or primary caregiver

Definitions

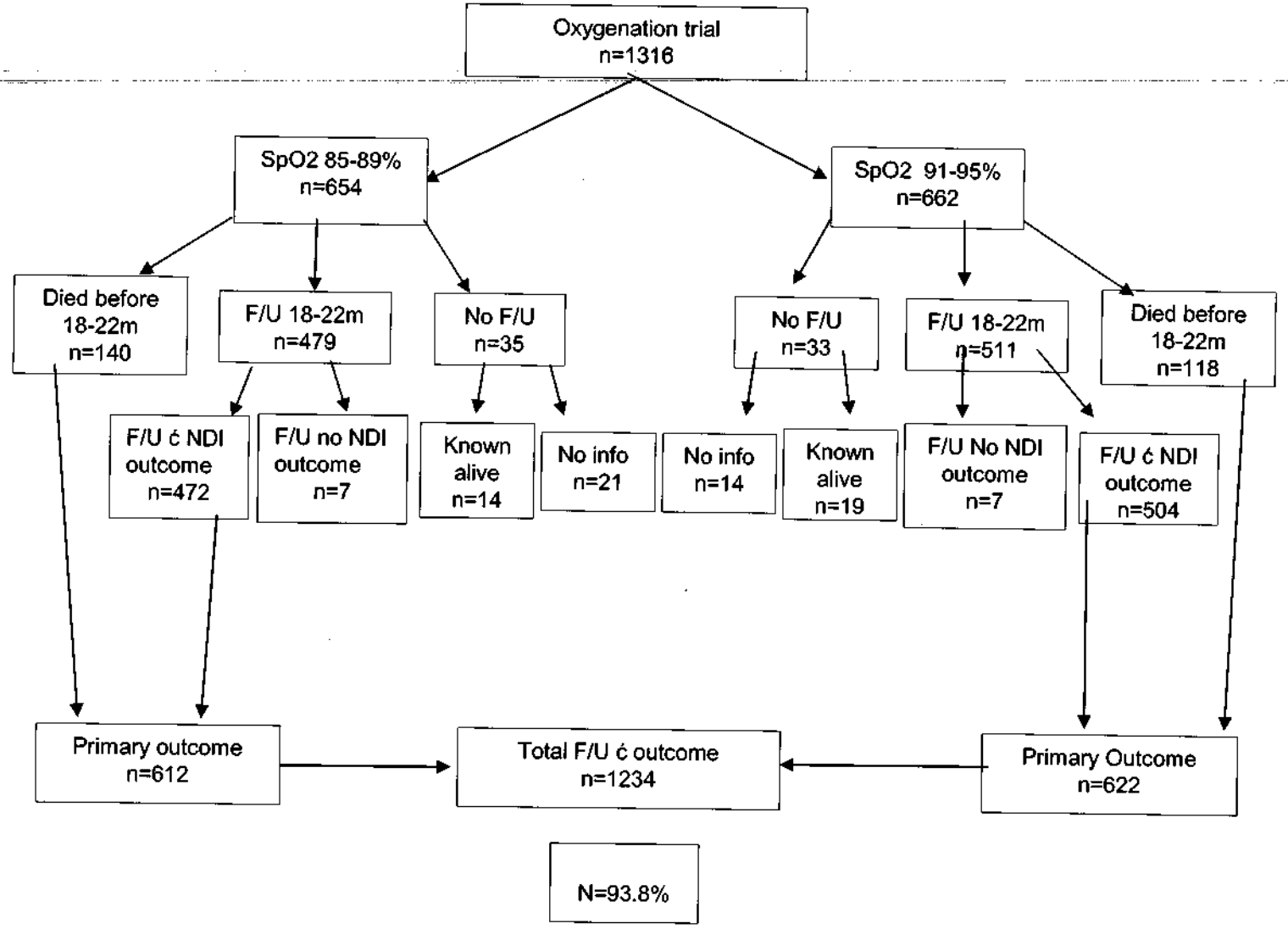
- Neurodevelopmental Impairment (NDI) defined as any of:
  - Bayley III cognitive composite score < 70
  - GMFCS $\geq$ 2
  - Moderate to Severe Cerebral Palsy (CP)
  - Hearing impairment despite amplification
  - Bilateral visual impairment (<20/200)

Outcomes

- Primary: Presence of death or NDI at 18 to 22 months adjusted age
- Other:
  - CP at 18 to 22 m adjusted age
  - Blindness at 18 to 22 m adjusted age

Data collection and analysis

- Data collected in standard forms transmitted to and analyzed by RTI International
- Analysis
  - Intention to treat
  - Adjusted for GA stratum, center, familial clustering
  - 2 sided $P < .05$
  - Adjusted relative risks and 95% CI for categorical variables were estimated using robust Poisson regression in a generalized-estimated-equation model; adjusted means and 95% CI for continues variables were estimated using linear mixed models



Baseline characteristics

	Trial Cohort		Cohort with FU visit	
Characteristic	85-89%	91-95%	85-89%	91-95%
	N=654	N=662	N=479	N=511
Birth weight - g	835.5	824.8	857.8	843.7
Gestational age - wk	26.2	26.1	26.3	26.2
SGA – (%)	6.3	8.3	3.5*	7.4*
Male sex (%)	52.1	56	50.1	55.2
Race (%)				
Non hispanic black	39.3	35	42	34.4
Non hispanic white	37	42.1	37.2	42.1
Hispanic	20.2	19.2	18	19
Maternal education < HS	24.9	27	24.4	25
Public Health Insurance	54.8	52.7	52.8	52
Mother married	43.6	46.6	46.3	47

Perinatal characteristics

	Trial Cohort		Cohort with FU visit	
Characteristic	85-89%	91-95%	85-89%	91-95%
	N=654	N=662	N=479	N=511
CPAP (%)	51.4	49.4	53	50.3
Surfactant (%)	48.6	50.6	47	49.7
Postnatal steroids (%)	9.6	10.7	8.6	9.5
BPD (%)	38	41.7	37	39
Severe ROP (%)	8.6*	17.9*	8.6*	17.4*
IVH grade 3 or 4 or PVL	15.6	15.6	11.7	11.8
NEC	11.9	10.8	8.8	8.6
LO sepsis/meningitis	36.5	35.6	32.4	32.5
Antenatal steroids	96.8	95.6	96.5	95.8
Cesarean section	67.4	66.8	69.3	65.0
Multiple births	24.6	26.6	25.9	25

Primary Oucomes at 18-22 months corrected age

Outcome (%)	85-89%	91-95%	Adjusted RR	P-value
	N=654	N=662		
Outcome determined	93.6	94	1 (0.97, 1.03)	0.79
NDI or Death	30.2	27.5	1.12 (0.94,1.32)	0.2098
Died by 18-22 mo	22.1	18.2	1.25 (1, 1.55)	0.046

Oucomes of Survivors at 18-22 months corrected age

Outcome (%)	85-89%	91-95%	Adjusted RR	P-value
	N=479	N=511		
NDI	9.5	10.5	0.87(0.6, 1.28)	0.49
Bayley III cognitive<70	7.2	7.6	0.91(0.58,1.43)	0.69
GMFCS $\geq$ 2	5.4	4.5	1.17(0.68,2.01)	0.56
Mod/severe CP	4.2	3.9	1 (0.54, 1.83)	0.99
Blindness	1	1.2	0.9 (0.28, 2.9)	0.86
Deafness	2.5	2.3	1.16 (0.54,2.49)	0.70

Bayley III cognitive composite scores among survivors at 18-22 months corrected age

Outcome (%)	85-89%	91-95%	Adjusted RR	P-value
	N=479	N=511		
Bayley III				
Cognitive composite<70	7.2	7.6	0.91(0.58,1.43)	0.69
Cognitive composite<85	22.3	26.2	0.85(0.68,1.07)	0.16
Adjusted means Cognitive composite	92.2±0.8	90.5±0.7	0.7(-1.2, 2.5)	0.48
Median cognitive composite scores	90 (85,100	90 (80, 100)		

Neurological Findings among survivors at 18-22 months corrected age

Outcome (%)	85-89%	91-95%	Adjusted RR	P-value
	N=479	N=511		
Abnormal Neuro exam	22.5	22.3	1.02(0.82,1.28)	0.84
Any CP	9	8	1.12(0.76,1.65)	0.57
Mild CP	5	4.3	1.16(0.66,2.02)	0.61
Mod CP	2.5	2.1	1.19(0.52,2.71)	0.68
Severe CP	2	2.1	0.95(0.39,2.27)	0.90

Eye findings among survivors at 18-22 months corrected age

Outcome (%)	85-89%	91-95%	Adjusted RR	P-value
	N=479	N=511		
Severe ROP	8.6	17.4		0.0001
Eye surgery	6.5	13.2	0.52(0.35,0.78)	0.001
Strabismus	9.6	8	1.2(0.8,1.8)	0.38
Nystagmus	4.6	2.4	1.81(0.89,3.69)	0.10
Tracks 180 degrees	97.1	97.2	1(0.98,1.02)	0.93
Corrective lenses	4.5	4.1	1.14(0.62,2.08)	0.65
Blind some function	0.7	0.4	1.57(0.27,8.96)	0.61
Blind no function	0.4	0.8	0.54(0.1,2.96)	0.48
Other abnormality vision	1.3	2.5	0.55(0.21,1.46)	0.23

Other medical outcomes among survivors at 18-22 months corrected age

Outcome (%)	85-89%	91-95%	Adjusted RR	P-value
	N=479	N=511		
Medications				
Bronchodilators	33.5	36.6	0.92(0.78,1.1)	0.37
Steroids	20.0	21.3	0.92(0.72,1.18)	0.51
Diuretics	3.2	2.8	1.17(0.58,2.34)	0.67
Anticonvulsants	2.5	2.3	1.08(0.49,2.37)	0.85
Readmissions	43.9	46.8	0.94(0.82,1.08)	0.40
Readmission for respiratory illness	23.4	25.2	0.93(0.74,1.16)	0.51
Readmission for growth/nutrition	2.6	2.6	1.05(0.49,2.25)	0.90

Conclusions

- There were no significant differences in the pre-specified outcome of death or neurodevelopmental impairment at 18 to 22 months corrected age
- Death remained higher in the lower target oxygenation group at 18 to 22 months corrected age
- NDI was not significant between lower or higher oxygenation groups.

Conclusions

- Although severe ROP was associated with higher oxygenation target levels, blindness at follow up was not significantly different between survivors at 18 to 22 months.

Thanks

From: Roger Faix
To: mperalta@peds.uab.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: SUPPORT CPAP PAPER
Date: Tuesday, November 29, 2011 10:59:48 AM
Attachments: Support NDI 11-20-2011.doc
Figure 1.doc

Hi Miryam!

Manuscript looks excellent. A few queries/ suggestions follow:

1) Was written informed consent sougght from only one parent or guardian or both parents and guardians (if available)?
2) Would the paragraph in Discussion that begins 'Bronchopulmonary dysplasia and longer duration of ventilation...' be better placed in the Results section?

I commend you for a very complex paper presented very clearly!

Roger

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Neurodevelopmental Outcome of Extremely Preterm Infants in a Trial of Different Oxygen Saturation Targets

Myriam Peralta-Carcelen, M.D., M.P.H.[1], Yvonne E. Vaucher, M.D., M.P.H.[2], Waldemar A. Carlo, M.D.[1], Neil N. Finer, M.D.[2], Marie G. Gantz, Ph.D.[3], Michele C. Walsh, M.D., M.S.[4], Abbott R. Laptook, M.D.[5], Bradley A. Yoder, M.D.[6], Roger G. Faix, M.D.[6], Abhik Das, Ph.D.[7], Kurt Schibler, M.D.[8], Wade Rich, R.R.T.[2], Nancy S. Newman, R.N.[4], Betty R. Vohr, M.D.[5], Kimberly Yolton, Ph.D.[8], Roy J. Heyne, M.D.[9], Deanne E. Wilson-Costello, M.D.[4], Patricia W. Evans, M.D.[10], Ricki F. Goldstein, M.D.[11], Michael J. Acarregui, M.D.[12], Ira Adams-Chapman, M.D. [13], Athina Pappas, M.D.[14], Susan R. Hintz, M.D., M.S., Epi[15], Brenda B. Poindexter, M.D., M.S.[16], Elisabeth C. McGowan, M.D.[17], Richard A. Ehrenkranz, M.D.[18], Anna Bodnar, M.D.[6], Charles R. Bauer, M.D.[19], Janell Fuller, M.D.[20], T. Michael O'Shea, M.D., M.P.H.[21], Gary J. Myers, M.D.[22], Rosemary D. Higgins, M.D.[23] for the SUPPPORT Study Group of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network.

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[7] Statistics and Epidemiology Unit, RTI International, Rockville, MD; [8] Department of Pediatrics, Cincinnati Children's Hospital Medical Center and University of Cincinnati, Cincinnati, OH; [9] Department of Pediatrics, University of Texas Southwestern Medical Center, Dallas, TX; [10] Department of Pediatrics, University of Texas Medical School at Houston, Houston, TX; [11] Department of Pediatrics, Duke University, Durham, NC; [12] Department of Pediatrics, University of Iowa, Iowa City, IA; [13] Emory University School of Medicine, Department of Pediatrics, and Children's Healthcare of Atlanta, Atlanta, GA; [14] Department of Pediatrics, Wayne State University, Detroit, MI; [15] Department of Pediatrics, Division of Neonatal and Developmental Medicine, Stanford University School of Medicine and Lucile Packard Children's Hospital, Palo Alto, CA; [16] Department of Pediatrics, Indiana University School of Medicine, Indianapolis, IN; [17] Department of Pediatrics, Division of Newborn Medicine, Floating Hospital for Children, Tufts Medical Center, Boston, MA; [18] Department of Pediatrics, Yale University School of Medicine, New Haven, CT; [19] University of Miami Miller School of Medicine, Miami, FL; [20] University of New Mexico Health Sciences Center, Albuquerque, NM; [21] Wake Forest University School of Medicine, Winston-Salem, NC; [22] Department of Pediatrics, University of Rochester Medical Center, Rochester, NY

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Word Count

Abstract: 248

Text: 1,148

ABSTRACT

BACKGROUND

Targeting lower (vs. higher) oxygen saturations in the SUPPORT Trial decreased severe retinopathy of prematurity but increased mortality before discharge. Our pre-specified hypothesis was that compared to the treatment of higher oxygen saturation, treatment with lower oxygen saturation will have a decrease in the composite outcome of death and long term neurodevelopmental impairment.

METHODS

Infants born at 24 to 27 week gestation were randomized to higher (91-95%) or lower oxygen saturation targets (85-89%) from birth to 36 weeks corrected age. The outcome of this follow up study was a composite of death or neurodevelopment impairment at 18 to 22 months corrected age. Neurodevelopmental impairment (NDI) was defined as a Bayley III cognitive composite score of less than 70, modified Gross Motor Function Classification System $\geq$2, presence of moderate to severe cerebral palsy, permanent hearing loss, and/or bilateral blindness. Results were adjusted for gestational age stratum, center and familial clustering.

RESULTS

The primary outcome was determined for 1234/1316 (93.8%) of infants enrolled in SUPPORT; 93/6% (990/1058) of survivors were evaluated at 18 to 22 months corrected age. Death or NDI occurred in 30.2% (185/612) infants in the lower oxygen saturation group and 27.5% (171/622) infants in the higher oxygen saturation group (relative risk 1.12; 95% confidence interval 0.94, 1.32; p=0.21). Death occurred in 140 (22.1%) of the children in the lower oxygen saturation

group and in 118 (18.2%) in the higher oxygen saturation group (relative risk 1.25; 95% confidence interval 1, 1.55, p=0.046). NDI was present in 9.5% (45/472) of the lower oxygen saturation group and 10.5 % (53/504) of the higher oxygen saturation group survivors (relative risk 0.87, 95% confidence interval 0.6, 1.28; p=0.49); and blindness was present in 1% (5/479) of the lower oxygen saturation group and 1.2% (6/511) of the higher oxygen saturation group (relative risk 0.9; 95% confidence interval 0.28, 2.9, p= 0.86).

CONCLUSIONS

Among extremely preterm infants targeted at different levels of oxygen saturation, no significant difference in death or neurodevelopmental impairment was observed at 18 to 22 months. Mortality remained significantly higher in the lower oxygen target group at 18 to 22 months.

BACKGROUND

Oxygen supplementation is a vital therapy for survival of many preterm infants with respiratory disorders. However, oxygen supplementation may increase the risk of retinopathy of prematurity, bronchopulmonary dysplasia, [1] periventricular leukomalacia,[2] and cerebral palsy [3] Restrictive oxygen therapy decreases retinopathy but has resulted in increased deaths in recent randomized controlled trials. [4,5,6,7]

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development SUPPORT Trial demonstrated no significant difference in a composite outcome including retinopathy of prematurity and death between a lower oxygen saturation target group (85-89%) and a higher saturation target group (91-95%). However, mortality prior to discharge was increased (19.9% of infants vs. 16.2%; relative risk 1.27; 95% CI 1.01 to 1.6; p=0.04) and severe retinopathy of prematurity among survivors was reduced (8.6% vs. 17.9%; relative risk 0.52; 95% CI 0.37 to 0.73; p<0.001) in the lower oxygen saturation target group compared to the higher saturation target group. [6] A recent meta-analysis that included the SUPPORT Trial and two other concurrent multi-center randomized controlled trials with a total of 3631 infants showed that infants randomized to an oxygen saturation target of 91-95% % had a lower mortality rate than infants randomized to oxygen saturation targets of 85-89% (14.4% versus 17.3% respectively, P=0.015). [7] The effects of oxygen on the immature brain are not clearly understood. [8] Oxidative stress injury in the premature infant may have many underlying pathophysiological processes. There has been a keen interest in determining whether higher or lower oxygen supplementation can reduce neurodevelopmental impairment. [7] However, in two non randomized studies of oxygen saturation targeting,[1,9] neurodevelopmental outcome did not differ by oxygen targets.

This study evaluated the composite outcome of death or neurodevelopmental impairment at 18 to 22 months corrected age in the subjects enrolled in the SUPPORT trial and randomized to lower (85-89%) or higher oxygen saturation targets (91-95%) from birth to 36 weeks corrected age. The pre-specified hypothesis in the SUPPORT trial was that compared to higher oxygen saturation target, the lower saturation target group will have less incidence of the composite outcome of death and neurodevelopmental impairment.

METHODS

Study Design

Extremely preterm infants (24 weeks 0 days to 27 weeks 6 days) born between February 2005 and February 2009 at 20 centers in the United States participating in the Neonatal Research Network of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development were enrolled at delivery in the prospective, randomized, controlled SUPPORT trial. Permuted block randomization was used, with stratification according to center and gestational age (24 weeks 0 days to 25 weeks 6 days or 26 weeks 0 days to 27 weeks 6 days). The infants were randomly assigned in the delivery room to a target range of oxygen saturation of 85% to 89% (the lower oxygen saturation group) or 91 to 95% (the higher oxygenation group). Using a 2-by-2 factorial design, participants were also randomly assigned to receive either CPAP immediately following delivery and a limited ventilation strategy if subsequent intubation was required or intubation with surfactant administration within an hour after birth. Procedures for enrollment, intervention and data collection have been previously reported. [6]. The study was approved by the institutional review board at each participating center and at RTI

International which is the independent data coordinating center for the Neonatal Research Network. Written informed consent was obtained from the parents or guardians of each child before delivery. Also consent was obtained for the follow up at 18-22 months corrected age.

Assessments

A comprehensive neurodevelopmental assessment was performed on survivors at 18-22 months corrected age by neurologic examiners and neurodevelopmental testers who were unaware of the treatment assignments and had been trained annually for reliability of assessments during a 2-day workshop. Developmental status was assessed using the Bayley Scales for Infant Development 3rd edition (BSID III) [10]. Cognitive Composite Scores are reported as a standardized score with a mean of 100 and a standard deviation of 15. Examiners also recorded the presence of cerebral palsy defined as a non-progressive disorder of the central nervous system and characterized by abnormal muscle tone in at least one arm or leg associated with abnormal control of movement or posture with delayed attainment of motor milestones.[11] The modified Gross Motor Function Classification System (GMFCS) [12] describes gross motor performance and has a range from 0 (normal) to 5 (most impaired). Cerebral palsy was classified depending on severity into mild (GMFCS $\leq$1), moderate (GMFCS 2 or 3) or severe (GMFCS $\geq$ 4). Hearing and visual impairment were determined based on parent report and examination.

Certified research nurses collected demographic and neonatal data using NRN definitions. Data collected included gestational age, birth weight, gender, multiple gestation, race/ethnicity, Retinopathy or prematurity (ROP) status, bronchopulmonary dysplasia (BPD), history of medical or surgical necrotizing enterocolitis (modified Bell's stage $\geq$ 2),grades 3-4 intraventricular hemorrhage (IVH) or periventricular leukomalacia (PVL), history of late onset sepsis, use of

postnatal steroids. Socioeconomic variables included insurance status, maternal marital status, maternal education, household income, language spoken at home and whether living with biological parents. Socioeconomic data from the neonatal period were used and when not available data updated at the 18-22 month visit were used. Outcomes following NICU discharge included rehospitalizations, interim medical history, surgery and medications were recorded at the 18-22 month visit.

Outcome

The composite of death or neurodevelopmental impairment at 18 to 22 months corrected age for prematurity was the pre-specified primary follow up outcome for the SUPPORT trial. This composite outcome was selected because (a) the data are available on the entire randomized trial cohort, (b) infants who died before 18 months could not be classified as having neurodevelopmental impairment and (c) death can be considered as a competing outcome to neurodevelopmental impairment among survivors. Neurodevelopmental impairment was defined as having any of the following: BSID III cognitive composite score less than 70, GMFCS $\geq$ 2, presence of moderate or severe cerebral palsy, permanent hearing loss that does not permit the child to understand directions of the examiner and communicate despite amplification with hearing aids, or bilateral visual impairment (vision < 20/200).

Analysis

Data were entered in standard forms and were transmitted to the Neonatal Research Network Data Coordinating Center at RTI International which stored, managed and analyzed the data for this study. Details regarding sample size calculations for the SUPPORT trial have been previously reported [6]. The sample size calculations were based on infants born in the year 2000 which included the rate of death or neurodevelopmental impairment at 18-22 months corrected age. All analyses were performed according to the intention to treat principle. Unadjusted comparisons of birth and demographic characteristics between treatment groups were conducted using chi-square tests for categorical variables and t tests for continuous variables. The primary analysis focused on the percentage of infants in each group for whom the primary outcome of death or NDI at 18 to 22 months corrected age could be assigned. Analysis of this and all other categorical outcomes was performed with the used of robust Poisson regression in a generalized-estimating-equation model to obtain adjusted relative risks with 95% confidence intervals. The denominator that was used to calculate the rate of each outcome was the number of infants for whom the outcome was known. Continuous outcomes were analyzed with the use of mixed-effects linear models to obtain adjusted means and standard errors. Pre-specified subgroup analyses were also conducted within each gestational age strata.

In the analysis of all neonatal and follow-up outcomes, the results were adjusted, as pre-specified, for gestational-age strata, center and familial clustering (because multiple births from the same mother were randomized to the same treatment group). Two-sided p values of less than 0.05 was considered to indicate statistical significance. For the 79 secondary outcomes analyzed according to treatment, we would expect no more than 4 tests to have p values of less than 0.05 on the basis of chance alone. Subgroup analyses were conducted within pre-specified gestational age strata for the same outcomes. Although these tests have not been adjusted for multiple

comparisons, we would expect no more than 4 tests per stratum to have p values of less than 0.05 on the basis of chance alone.

RESULTS

Characteristics of the Study Sample

The SUPPORT trial enrolled 1316 infants (see flowchart in Figure 1). Five hundred twenty four infants in the lower oxygen saturation group and 555 in the higher oxygen saturation group survived to discharge or transfer from the hospital. The baseline characteristics of the entire group have been reported previously[6] Ten children in the lower oxygen saturation group and 11 children in the higher oxygen saturation group died after discharge from the nursery and prior to the 18 to 22 month corrected age follow up visit. Thirty five children in the lower saturation group and 33 children in the higher saturation group were lost to follow up. However 14/35 in the lower saturation group and 19/33 in the higher saturation group were known to be alive at 18 to 22 months corrected age. Neurodevelopmental assessment was performed in 990/1058 infants who were not known to have died (93.6%). Of those who were evaluated at the 18 to 22 months corrected age, neurodevelopmental status was determined in 976 children. From the entire cohort the pre- specified outcome of death or neurodevelopmental impairment could be determined in 93.8% (1234/1316) of enrolled children. Compared to mothers of infants who were followed, mothers of infants who were lost to follow up were less likely to be married (31 vs. 47% p=0.01) and more likely to have only public health insurance (69 vs. 52% p=0.008). There were no other significant differences in all the other baseline characteristics of the cohort that was followed up and those lost to follow up.

Baseline characteristics of the follow up cohort and the entire trial cohort are presented in Table 1. Among children who were followed up, the percentage of infants who were small for gestational age was greater in the higher oxygen saturation target group compared to the lower saturation target group. In addition, as reported previously[6] the incidence of severe retinopathy of prematurity was higher in the higher oxygen saturation group compared to the lower saturation group but no other significant differences were found in the baseline and major hospital outcome characteristics of the infants with follow up data.

Primary Outcome

The mean corrected age for neurodevelopmental evaluation was similar between both groups (Lower oxygen saturation, 19.9 $\pm$ 2.4 months vs. higher oxygen saturation 20.2 $\pm$ 2.7 months, p=0.08). The prevalence of the composite primary outcome of death or neurodevelopmental impairment was not significantly different between the lower (185/612, 30%) and higher (171/662, 27.5%) oxygen saturation target groups (relative risk 1.12, 95% confidence interval 0.94, 1.32; p=0.21). (Table 2) In the 24 weeks to 25 weeks gestational age stratum, primary outcome data were available for 261 of 276 children in the lower saturation group and 276 of 289 in the higher saturation group. For the age stratum 26 to 27 weeks gestation outcome data were available for 351 of 378 of the lower oxygen saturation group and 346 of 373 of the higher oxygen saturation group. Similar to the entire cohort there were no significant differences in the prevalence of death or neurodevelopmental impairment within both gestational age strata as shown in table 2.

Components of the Primary Outcome

Death prior to the 18 to 22 month adjusted age visit occurred significantly more often among infants in the lower oxygen saturation target group compared to those in the higher saturation target group. (Lower oxygen saturation, 140/633, 22.1% vs. higher oxygen saturation, 118/648, 18.2%; relative risk 1.25; 95% CI 1, 1.55, p=0.046). However death at 18 to 22 months corrected age was not significantly different within either gestational age stratum (table 2)

The rate of neurodevelopmental impairment among survivors followed at the 18 to 22 month corrected age visit was similar between the lower and the higher oxygen saturation target groups (45/472, 9.5% vs 53/504, 10.5%; relative risk 0.87 95%CI 0.6, 1.28, p=0.49) Rates of neurodevelopmental impairment were not significantly different in either gestational age stratum.

Other outcomes among survivors at follow up

The percentage of children with BSID III cognitive scores below 70 was not significantly different between the lower and higher oxygen saturation group, nor was the percentage of children with cognitive scores below 85. Adjusted means of cognitive composite scores were not significantly different between the two groups and are presented in table 3.

Rates of severe retinopathy of prematurity and eye surgery among survivors to follow up were higher in the higher oxygen target group compared to the lower oxygen target group; however the rate of bilateral (1% vs 1.6%, relative risk 0.67, 95% CI 0.22, 2.02; p=0.48) or unilateral blindness were not significantly different at the 18 to 22 month corrected age visit. Other visual outcomes are presented in Table 3.

Overall readmission rates and readmission rates for respiratory problems were not significantly different between both groups. There were no significantly differences in use after discharge of bronchodilators, steroids, diuretics or any other medication. (Table 3)

DISCUSSION

In this multicenter, follow up study of infants randomized to a lower target range of oxygen saturation (85 to 89%) or to higher target oxygen saturation (91 to 95%) a significant difference was not found in the pre-specified outcome of death or neurodevelopmental impairment at 18-22 months corrected age. To our knowledge this is the only large comprehensive study in the US that has included neurodevelopmental impairment as an outcome for evaluating effects of different oxygen target saturation levels started at birth in extremely premature babies within a randomized multicenter trial. There has been concern about using lower oxygen saturation targets because of potentially increased mortality in extremely premature infants [13]. We found that death prior to discharge in the SUPPORT trial was increased among children who were assigned to lower target saturation levels, and this difference persisted at 18 to 22 months corrected age follow up.

We had reported previously that our lower saturation oxygen target was associated with a large reduction in the incidence of severe retinopathy of prematurity among survivors. [6] It has been previously reported that severe ROP may be associated with poor visual outcomes even with treatment [14,15] Although our study was not designed to collect detailed data on eye disorders or visual function at 18 to 22 months of age we found that there were no significant differences in the report of unilateral and bilateral blindness between the two groups. Eye surgery was higher in the group with a higher oxygen saturation target and was likely related to higher incidence of severe retinopathy of prematurity in this group and our criteria used to define severe retinopathy of prematurity [6]. Specific visual outcomes of eye function after the presence of retinopathy of prematurity were also not included in the outcome data collected in this trial however we did not

find a significant difference in other reported visual outcomes like nystagmus, strabismus or use of corrective lenses.

There had been concerns that lower oxygen saturation targets might increased the risk of long term neurodevelopmental impairment[5]. However NDI as defined in this study was not found to be significantly different between survivors in the lower and higher oxygen saturation groups. In addition the incidence of Cerebral Palsy did not differ between the treatment groups, though it is noteworthy that the incidence of CP was lower than previously reported in other outcome studies.[16]

It has been recognized that higher oxygen levels can be associated with chronic lung disease, however we found no difference in the use of postnatal corticosteroids or diuretics at 18 to 22 months corrected age, or persistent oxygen use at 18 to 22 months of age as well as rehospitalization between the two groups.

A limitation of this study is that it reports only follow up to 18 to 22 months corrected age, which may not been enough time to detect the presence of minor but important disabilities. It has also been reported that the BSID III may result in higher cognitive scores than an earlier vision of the Bayley Scales of Infant development (BSID-II), therefore missing developmental impairments when the 2 SD cutoff for cognitive composite scores is used[17 18]. Use of a cutoff of less than 85 for the Bayley III cognitive composite scores did not find significant differences between the groups. There is an ongoing follow up SUPPORT study that will be reporting the outcome of these children at school age. These children were cared for at tertiary care centers therefore generalizibility is a concern, however we included 20 centers around the country.

In summary we found no significant differences in death or neurodevelopmental impairment at 18 to 22 months corrected age in extremely premature infants who were randomized to a lower target oxygen saturation or higher target oxygen saturation. The increased death rate at discharge that was previously reported in the lower target oxygen saturation group was still present at 18 to 22 months corrected age. Although higher rates of retinopathy of prematurity were associated with higher oxygen saturation target levels, blindness was not significantly different among survivors at 18 to 22 months.

Acknowledgements

The National Institutes of Health, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), and the National Heart, Lung, and Blood Institute (NHLBI) provided grant support for the Neonatal Research Network's SUPPORT Trial.

Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Drs. Abhik Das (DCC Principal Investigator) and Marie Gantz (DCC Statistician) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study. The following investigators, in addition to those listed as authors, participated in this study:

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17. Anderson PJ, De Luca CR, Hutchinson E, Roberts G, Doyle LW, Group VIC. Underestimation of developmental delay by the new Bayley-III Scale. Arch Pediatr Adolesc Med 2010;164:352-6.

Table 1. Baseline characteristics of the SUPPORT group

Characteristics	Trial Cohort	
	Lower Oxygen Saturation	Higher Oxygen Saturation
	N=654	N=662
Birth weight – g	835.5± 193.4	824.8± 193
Gestational age – wk	26.2 ± 1.1	26.1 ± 1.1
Small for gestational age – no./total no. (%)	41/654 (6.3)	55/662 (8.3)
Male sex – no./total no. (%)	341/654 (52.1)	371/662 (56)
Race or ethnic group – no./total no. (%)		
Non Hispanic Black	257/654 (39.3)	232/662 (35)
Non Hispanic White	242/654 (37)	279/662 (42.1)
Hispanic	132/654 (20.2)	127/662 (19.2)
Other or unknown	23/654 (3.5)	24/662 (3.6)
Multiple births – no./total no. (%)	161/654 (24.6)	176/662 (26.6)
Maternal educational level <high school no./total no. (%)	148/594 (24.9)	165/612 (27)
Public Health Insurance only – no./total no. (%)	356/650 (54.8)	348/660 (52.7)

Mother married – no./total no. (%)	284/652 (43.6)	308/661 (46.6)
Lives with both biological parents – no./total no. (%)†	354/508 (69.7)	364/547 (66.5)
Household income < $30,000/year – no./total no.(%) †	247/474 (52.1)	291/528 (55.1)
English as primary language – no./total no. (%)‡	402/477 (84.3)	429/513 (83.6)
Cesarean section – no./total no. (%)	441/654 (67.4)	442/662 (66.8)
Antenatal steroids – no./total no. (%)	633/654 (96.8)	632/661 (95.6)
Severe retinopathy of prematurity – no./total no. (%)†	41/475 (8.6)**	91/509 (17.9)**
Bronchopulmonary dysplasia – no./total no. (%)¶	205/540 (38)	237/568 (41.7)
Intraventricular hemorrhage grade 3 or 4 or Periventricular leukomalacia – no./total no. (%)	98/630 (15.6)	100/640 (15.6)
Necrotizing enterocolitis – no./total no. (%)	76/641 (11.9)	70/649 (10.8)
Late onset sepsis/meningitis – no./total no. (%)	228/624 (36.5)	226/634 (35.6)
155/479 (32.4)	166/511 (32.5)	
Post natal steroids – no./total no. (%)	61/636 (9.6)	69/644 (10.7)
41/477 (8.6)	48/507 (9.5)	
CPAP – no./total no. (%)	336/654 (51.4)	327/662 (49.4)
254/479(53)	257/511 (50.3)	
Surfactant – no./total no. (%)	318/654 (48.6)	335/662 (50.6)
225/479 (47)	254/511 (49.7)	

*p<0.01, **p<0.001

† Available only for infant who survived to discharge or transfer

‡ Only available at 18-22 months corrected age

¶ Among survivors to 36 weeks postmenstrual age

Table 2. Primary Outcomes at 18-22 Months Corrected Age

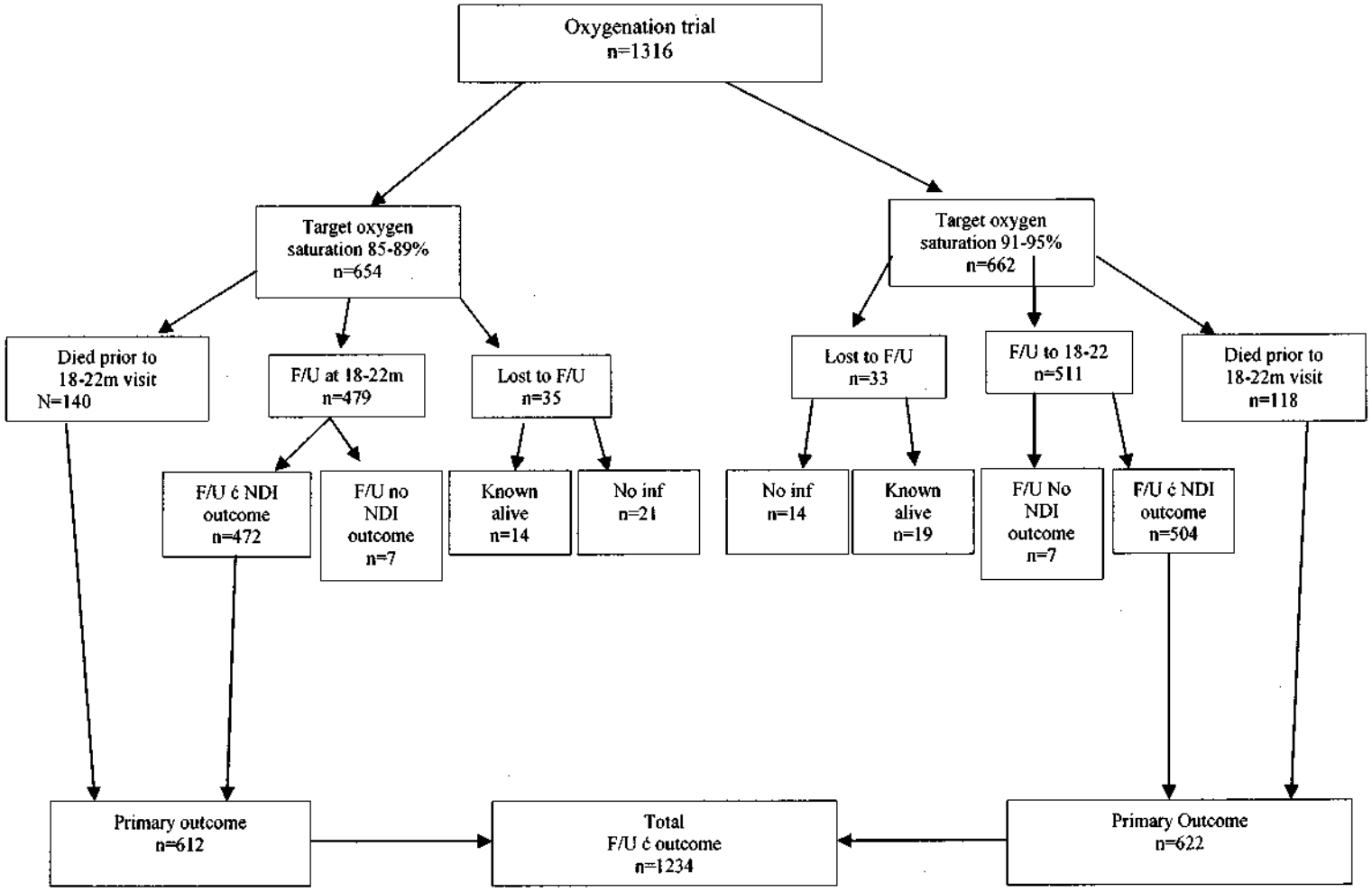
	Lower Oxygen Saturation	Higher O Satura
Lower oxygenation saturation vs higher oxygen saturation	N=654	N=6
Outcome determined for death or NDI – no./total no. (%)	612/654 (93.6)	622/66
Neurodevelopmental impairment or death – no./total no. (%)	185/612 (30.2)	171/622
Died by 18-22 months – no./total no. (%)	140/633 (22.1)	118/648
Survivors at follow-up		
Neurodevelopmental impairment – no./total no. (%)	45/472 (9.5)	53/504
Bayley III cognitive composite score < 70 – no./total no. (%)	34/471 (7.2)	38/503
Gross motor function level ≥ 2 – no./total no. (%)	26/479 (5.4)	23/511
Moderate/severe cerebral palsy – no./total no. (%)	20/479 (4.2)	20/511
Blindness – no./total no. (%)	5/479 (1)	6/511
Hearing Impairment – no./total no. (%)	12/479 (2.5)	12/511
24 0/7 to 25 6/7 weeks gestational age strata	276	28
Neurodevelopmental impairment or death – no./total no. (%)	115/261 (44.1)	112/276
Died by 18-22 months – no./total no. (%)	91/267(34.1)	79/283
Survivors at follow-up		
Neurodevelopmental impairment – no./total no. (%)	24/170 (14.1)	33/197
Bayley III cognitive composite score < 70 – no./total no. (%)	17/169 (10.1)	22/196
Gross motor function level ≥ 2 – no./total no. (%)	13/173 (7.5)	13/200
Moderate/severe cerebral palsy – no./total no. (%)	10/173 (5.8)	12/20(
Blindness – no./total no. (%)	1/173 (0.6)	3/200

Hearing Impairment – no./total no. (%)	4/173 (2.3)	10/200
26 0/7 to 27 6/7 weeks gestational age strata	378	37
Neurodevelopmental impairment or death – no./total no. (%)	70/351(19.9)	59/346
Died by 18-22 months – no./total no. (%)	49/366(13.4)	39/365
Survivors at follow-up		
Neurodevelopmental impairment – no./total no. (%)	21/302(7.0)	20/307
Bayley III cognitive composite score < 70 – no./total no. (%)	17/302 (5.6)	16/307
Gross motor function level ≥ 2 – no./total no. (%)	13/306(4.2)	10/311
Moderate/severe cerebral palsy – no./total no. (%)	10/306(3.3)	8/311
Blindness – no./total no. (%)	4/306 (1.3)	3/311
Hearing Impairment – no./total no. (%)	8/306 (2.6)	2/311

Table 3. Other Outcomes at 18 to 22 months corrected age by Group

Outcome	Lower Oxygen Saturation (N=479)	Higher Oxygen Saturation (N=510)	Relative Risk Lower vs Higher Oxy Saturatio (95% CI)
Bayley Scales of Infant Development III			
Cognitive composite < 70	34/471 (7.2)	38/503 (7.6)	0.91 (0.58, 1
Cognitive composite <85	105/471 (22.3)	132/503 (26.2)	0.85 (0.68, 1
Adjusted mean cognitive composite scores ± standard error	92.2 ± 0.8	90.5 ± 0.7	
Median cognitive composite scores (interquartile range)	90 (85, 100)	90 (80, 100)	
Neurologic findings			
Mild cerebral palsy vs. none	23/459 (5.0)	21/490 (4.3)	1.16 (0.66, 2
Moderate cerebral palsy vs. none	11/447 (2.5)	10/479 (2.1)	1.19 (0.52, 2
Severe cerebral palsy vs. none	9/445 (2.0)	10/479 (2.1)	0.95 (0.39, 2
Any cerebral palsy	43/479 (9.0)	41/510 (8.0)	1.12 (0.76, 1
Any abnormal neurologic exam	108/479 (22.5)	114/511 (22.3)	1.02 (0.82, 1
Vision/Eye findings			

Strabismus	46/478 (9.6)	41/510 (8)	1.2 (0.8, 1.
Nystagmus	22/479 (4.6)	13/510 (2.4)	1.81 (0.89, 3
Tracks 180 degrees	462/476 (97.1)	492/506 (97.2)	1 (0.98, 1.0
Corrective lenses both eyes	21/468 (4.5)	20/493 (4.1)	1.14 (0.62, 2
Blind, some function, both eyes vs. normal	3/450 (0.7)	2/475 (0.4)	1.57 (0.27, 8
Blind, no useful vision, both eyes vs. normal	2/449 (0.4)	4/477 (0.8)	0.54 (0.1, 2.
Other abnormal eye findings vs. normal	6/453 (1.3)	12/485 (2.5)	0.55 (0.21, 1
Eye surgery	31/477 (6.5)	67/509 (13.2)	0.52 (0.35, 0
Medicines			
Bronchodilators	159/475 (33.5)	185/506 (36.6)	0.92 (0.78, 1
Steroids	95/475 (20.0)	108/506 (21.3)	0.92 (0.72, 1
Diuretics	15/475 (3.2)	14/506 (2.8)	1.17 (0.58,2.
Anticonvulsants	12/478 (2.5)	12/511 (2.3)	1.08 (0.49, 2
Readmission	210/478 (43.9)	239/511 (46.8)	0.94 (0.82, 1
Readmission for respiratory reason	110/470 (23.4)	127/503 (25.2)	0.93 (0.74, 1
Readmission for growth/nutrition	12/470 (2.6)	13/503 (2.6)	1.05 (0.49, 2



From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Slaughter, Jonathan"
Subject: RE: Proposal for Secondary Analysis of Early CPAP Failure in SUPPORT Trial
Date: Tuesday, November 29, 2011 9:50:00 AM

Ok
Once you send me the updated version we will send it to the SUPPORT subcommittee and poll for the call

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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higginsr@mail.nih.gov

From: Slaughter, Jonathan [mailto:Jonathan.Slaughter@nationwidechildrens.org]
Sent: Tuesday, November 29, 2011 9:50 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Proposal for Secondary Analysis of Early CPAP Failure in SUPPORT Trial

Rose,

Absolutely. In the email to the Drs. Walsh, Finer, and Carlo I let them know it would be headed to the subcommittee in one week.

Thanks again for your help,
Jon

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]
Sent: Tuesday, November 29, 2011 9:46 AM
To: Slaughter, Jonathan
Subject: RE: Proposal for Secondary Analysis of Early CPAP Failure in SUPPORT Trial

When will this be ready for subcommittee review? 1 week? I would like to get a call set up as the holidays are usually difficult to schedule items.

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network

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From: Slaughter, Jonathan [mailto:Jonathan.Slaughter@nationwidechildrens.org]
Sent: Monday, November 28, 2011 11:51 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Proposal for Secondary Analysis of Early CPAP Failure in SUPPORT Trial

Dr. Higgins,

Attached is our protocol proposal for a secondary analysis of the SUPPORT Trial, to develop a model to predict which infants admitted to the NICU on early CPAP are at highest risk for intubation within 48 hours and also to determine the association of early CPAP failure with adverse outcomes.

I've forwarded the protocol to Dr. Carlo, Dr. Walsh, and Dr. Finer. I let them know that you would submit it to the entire SUPPORT committee in a week as we discussed.

Thanks,
Jon

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Stoll, Barbara J"; "Adams-Chapman, Ira"; "yvaucher@ucsd.edu"; "Finer, Neil"; "Wally Carlo, M.D."; "Gantz, Marie"; "Abhik Das (Adas@rti.org)"
Subject: RE: SUPPORT CPAP PAPER
Date: Tuesday, November 29, 2011 9:38:00 AM

Since this was a factorial design trial, we had decided on two separate papers both for the primary outcomes and the FU outcomes.

Thanks
Rose

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From: Stoll, Barbara J [mailto:bstoll@emory.edu]
Sent: Tuesday, November 29, 2011 12:07 AM
To: Adams-Chapman, Ira; yvaucher@ucsd.edu; Higgins, Rosemary (NIH/NICHD) [E]; 'Finer, Neil'; Wally Carlo, M.D.; Gantz, Marie; Abhik Das (Adas@rti.org)
Subject: RE: SUPPORT CPAP PAPER

Clearly presented paper. I've added my edits to Ira's
Assume these 2 f/u papers will be submitted together.
Did you consider a single f/u paper?
THANKS
BJS

From: Adams-Chapman, Ira
Sent: Monday, November 28, 2011 11:40 PM
To: yvaucher@ucsd.edu; Higgins, Rosemary (NIH/NICHD) [E]; 'Finer, Neil'; Wally Carlo, M.D.; Gantz, Marie; Abhik Das (Adas@rti.org); Stoll, Barbara J
Subject: RE: SUPPORT CPAP PAPER

Hi Yvonne,
My comments are attached in tracking changes. Information is clearly presented. Most of my comments are on page 8 of the document.
Ira

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]
Sent: Saturday, November 19, 2011 7:55 AM
To: 'Myriam Peralta, M.D.'; 'Finer, Neil'; Wally Carlo, M.D.; Michele Walsh; Gantz, Marie; 'Laptook, Abbot'; 'Bradley Yoder'; 'Roger Faix'; Abhik Das (Adas@rti.org); 'Rich, Wade'; 'kurt.schibler@cchmc.org'; nancy

newman; Vohr, Betty; Susan Hintz; 'Kim Yolton'; 'Roy Heyne'; 'drfjcmd@aol.com'; goldb008@mc.duke.edu; 'Michael.Acarregui@providence.org'; 'Evans, Patricia W'; Adams-Chapman, Ira; Pappas, Athina; 'Anna M. Dusick, MD'; 'emcgowan@tuftsmedicalcenter.org'; 'Ehrenkranz, Richard'; 'abodnar@utah.gov'; 'Bauer, Charles R'; 'JaFuller@salud. unm. edu (JaFuller@salud.unm.edu)'; 'Michael O`Shea'; 'gary_myers@URMC.Rochester.edu'
Cc: yvaucher@ucsd.edu; Pablo Sanchez; 'Shankaran, Seetha'; 'Duara, Shahnaz'; Barbara Stoll; 'Poindexter, Brenda B'; 'Krisa Van Meurs'; 'Kennedy, Kathleen A'; goldb008@mc.duke.edu; 'Phelps, Dale'; 'Bell, Edward (Pediatrics)'; 'Frantz, Ivan'; 'Kristi Watterberg'; Archer, Stephanie (NIH/NICHD) [E]
Subject: SUPPORT CPAP PAPER

Hi,

Attached is the SUPPORT CPAP FU Paper for co-author input. Please send your comments to Yvonne Vaucher (yvaucher@ucsd.edu) by **DECEMBER 3**. The paper will then go for internal NRN review and clearance. Following this, it will be submitted along with the oximetry FU paper (you will get this in the next few days) to the New England Journal of Medicine.

I have also included the steering committee PI's from the sites involved with the study. If you have any suggestions, feel free to forward them to Yvonne. Thanks to everyone for all the hard work, effort and commitment to this study!!

Rose

Rosemary D. Higgins, MD
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From: Bradley Yoder
To: Higgins, Rosemary (NIH/NICHD) [E]; "Finer, Neil"; "Rich, Wade"; Wally Carlo (wacarlo@uab.edu); "kurt.schibler@cchmc.org"; "Michele Walsh"; Roger Faix; "Laptook, Abbot"; Das, Abhik; "Gantz, Marie"; "nancy newman"
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: sct abstract1_fin_28Nov11
Date: Tuesday, November 29, 2011 9:25:13 AM

OK; agree with added data by Wally.

Brad Yoder
Division of Neonatology
University of Utah SOM

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, November 28, 2011 3:00 PM
To: 'Finer, Neil'; 'Rich, Wade'; Wally Carlo (wacarlo@uab.edu); 'kurt.schibler@cchmc.org'; 'Michele Walsh'; Roger Faix; 'Laptook, Abbot'; Bradley Yoder; Das, Abhik; 'Gantz, Marie'; 'nancy newman'
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: sct abstract1_fin_28Nov11

Hi,
Based on the prior comments, Marie has revised the abstract – let me know (if you haven't done so already) if you approve or disapprove for submission.

Thanks
Rose

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]; "yvaucher@ucsd.edu"
Cc: Myriam Peralta-Carcelen (MPeralta@peds.uab.edu)
Subject: RE: Acknowledgement slide
Date: Tuesday, November 29, 2011 9:01:00 AM

No attachment – can you resend?
Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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From: Archer, Stephanie (NIH/NICHD) [E]
Sent: Tuesday, November 29, 2011 9:01 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; 'yvaucher@ucsd.edu'
Cc: Myriam Peralta-Carcelen (MPeralta@peds.uab.edu)
Subject: RE: Acknowledgement slide

We don't normally name the people on the slides (too many to list), just the sites involved. Attached is a version for the SUPPORT FU presentations. I've also copied Myriam here, in case she wants to use it too.

Stephanie

Stephanie Wilson Archer
The Eunice Kennedy Shriver
National Institute of Child Health and Human Development
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6100 Executive Boulevard, Room 4B03
Rockville, MD 20852

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From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tuesday, November 29, 2011 6:19 AM
To: 'yvaucher@ucsd.edu'; Archer, Stephanie (NIH/NICHD) [E]
Subject: Re: Acknowledgement slide

Do we have this one? Nrn from 2004-09

From: Vaucher, Yvonne <yvaucher@ucsd.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Vaucher, Yvonne <yvaucher@ucsd.edu>
Sent: Mon Nov 28 22:36:18 2011
Subject: Acknowledgement slide

Rose,

Is there a standard acknowledgement slide I can use for the SUPPORT subcommittee, RTI and FUP PIs?

Thanks.

Yvonne

Yvonne E. Vaucher, M.D., M.P.H.
Division of Neonatal/Perinatal Medicine
Clinical Professor of Pediatrics
UCSD School of Medicine

tele: 619-543-3759
FAX: 619-543-3812

From: Roger Faix
To: Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; Rich, Wade; wacarlo@uab.edu; kurt.schibler@cchmc.org; Michele Walsh; Laptook, Abbot; Bradley Yoder; Das, Abhik; Gantz, Marie; nancy newman
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: sct abstract1_fin_28Nov11
Date: Monday, November 28, 2011 8:17:49 PM

I prefer Wally's suggested version with quantitative data/results.

Rger

From: Wally Carlo, M.D. [WCarlo@peds.uab.edu]
Sent: Monday, November 28, 2011 4:22 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; Rich, Wade; wacarlo@uab.edu; kurt.schibler@cchmc.org; Michele Walsh; Roger Faix; Laptook, Abbot; Bradley Yoder; Das, Abhik; Gantz, Marie; nancy newman
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: sct abstract1_fin_28Nov11

I approve it. Enclosed are some suggestions that include the main results as hard facts.

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
1700 6th Avenue South
176F Suite 9380R
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Phone: 205 934 4680
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Cell: 205 (b)(6)

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, November 28, 2011 4:00 PM
To: 'Finer, Neil'; 'Rich, Wade'; Wally Carlo (wacarlo@uab.edu); 'kurt.schibler@cchmc.org'; 'Michele Walsh'; 'Roger Faix'; 'Laptook, Abbot'; 'Bradley Yoder'; Das, Abhik; 'Gantz, Marie'; 'nancy newman'
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: sct abstract1_fin_28Nov11

Hi,
Based on the prior comments, Marie has revised the abstract – let me know (if you haven't done so already) if you approve or disapprove for submission.

Thanks
Rose

From: Roger Faix
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: sct abstract1_fin_28Nov11
Date: Monday, November 28, 2011 8:15:17 PM

Approve. (Provision of some qualtitatve data demonstrating the concordance of results with the two poulations would be nice, in my estimate, but is not essential at this point).

Roger

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]
Sent: Monday, November 28, 2011 3:00 PM
To: 'Finer, Neil'; 'Rich, Wade'; Wally Carlo (wacarlo@uab.edu); 'kurt.schibler@cchmc.org'; 'Michele Walsh'; Roger Faix; 'Laptook, Abbot'; Bradley Yoder; Das, Abhik; 'Gantz, Marie'; 'nancy newman'
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: sct abstract1_fin_28Nov11

Hi,

Based on the prior comments, Marie has revised the abstract – let me know (if you haven't done so already) if you approve or disapprove for submission.

Thanks

Rose

From: Barbara Stoll
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Higgins, Rosemary (NIH/NICHD) [E]; "Myriam Peralta, M.D."; "Finer, Neil"; "Wally Carlo, M.D."; "Michele Walsh"; "Gantz, Marie"; "Laptook, Abbot"; "Bradley Yoder"; "Roger Faix"; ""Abhik Das (<Adas@rti.org>, " "Rich@ws-mr1.cc.emory.edu; Wade"" <wrich@ucsd.edu>, ""; "nancy newman"; "Vohr, Betty"; "Susan Hintz"; "Kim Yolton"; "Roy Heyne"; "" <drficmd@aol.com>, ""; "" <Michael.Acarregui@providence.org>, " "Evans@ws-mr1.cc.emory.edu; Patricia.W" " <Patricia.W.Evans@uth.tmc.edu>, " "Adams-Chapman@ws-mr1.cc.emory.edu; Ira" " <iadamsc@emory.edu>, " "Pappas@ws-mr1.cc.emory.edu; Athina" " <apappas@med.wayne.edu>, " "Anna.M.Dusick@ws-mr1.cc.emory.edu; MD"" <adusick@pediatrics.wisc.edu>, ""; "Ehrenkranz, Richard"; "" <abodnar@utah.gov>, " "Bauer@ws-mr1.cc.emory.edu; Charles.R" " <CBauer@med.miami.edu>, " "JaFuller@salud.unm.edu
Subject: Re: UPDATED SUPPORT OXIMETRY PAPER
Date: Monday, November 28, 2011 8:05:23 PM
Attachments: Support O2 NDI_11-20-2011 bjs.doc

Very nice and clearly presented paper
My edits are attached
Regards
BJS"Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> writes:
Hi

For those of you who have not yet commented, here is a revised version of the oximetry paper.

Thanks for all your input.

Rose

Rosemary D. Higgins, MD

Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network

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From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, November 23, 2011 10:38 AM
To: 'Myriam Peralta, M.D.'; 'Finer, Neil'; 'Wally Carlo, M.D.'; 'Michele Walsh'; Gantz, Marie; 'Laptook, Abbot'; 'Bradley Yoder'; 'Roger Faix'; 'Abhik Das (Adas@rti.org)'; 'Rich, Wade'; 'kurt.schibler@cchmc.org'; 'nancy newman'; 'Vohr, Betty'; 'Susan Hintz'; 'Kim Yolton'; 'Roy Heyne'; (b)(6) @aol.com'; 'goldb008@mc.duke.edu'; 'Michael.Acarregui@providence.org'; 'Evans, Patricia'; 'Adams-Chapman, Ira'; 'Pappas, Athina'; 'Anna M. Dusick, MD'; 'emcgowan@tuftsmedicalcenter.org'; 'Ehrenkranz, Richard'; 'abodnar@utah.gov'; 'Bauer, Charles R'; 'JaFuller@salud.unm.edu (JaFuller@salud.unm.edu)'; 'Michael O' Shea'; 'gary_myers@URMC.Rochester.edu'
Cc: 'vvaucher@ucsd.edu'; 'Pablo Sanchez'; 'Shankaran, Seetha'; 'Dusira, Shahnaz'; 'Barbara Stoll'; 'Poindexter, Brenda B'; 'Krisa Van Meurs'; 'Kennedy, Kathleen A'; goldb008@mc.duke.edu; 'Phelps, Dale'; 'Bell, Edward (Pediatrics)'; 'Frantz, Ivan'; 'Kristi Wetterberg'; Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: SUPPORT CPAP PAPER

Hi All,

Here is the SUPPORT oximetry paper and the CONSORT diagram. Please send all suggestions back to Myriam by **December 6.**

The papers will then go for internal NRN review.

I have also included the site PI's.

Thanks for all the hard work and effort!
Rdse

Rosemary D. Higgins, MD

Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network

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Subject: SUPPORT CPAP PAPER
Importance: High

Hi,

Attached is the SUPPORT CPAP FU Paper for co-author input. Please send your comments to Yvonne Vaucher (yvaucher@ucsd.edu) by **DECEMBER 3**. The paper will then go for internal NRN review and clearance. Following this, it will be submitted along with the oximetry FU paper (you will get this in the next few days) to the New England Journal of Medicine.

I have also included the steering committee PI's from the sites involved with the study. If you have any suggestions, feel free to forward them to Yvonne. Thanks to everyone for all the hard work, effort and commitment to this study!!
Rose

Rosemary D. Higgins, MD

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Neurodevelopmental Outcome of Extremely Preterm Infants in a Trial of Different Oxygen Saturation Targets

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Word Count

Abstract: 248

Text: 1,148

ABSTRACT

BACKGROUND

Targeting lower (vs. higher) oxygen saturations in the SUPPORT Trial decreased severe retinopathy of prematurity but increased mortality before discharge. Our pre-specified hypothesis was that compared to higher oxygen saturation targets, lower oxygen saturation targeting would~~ill~~ decrease the risk of the composite outcome of death or long term neurodevelopmental impairment.

METHODS

Infants born at 24 to 27 week gestation were randomized to higher (91-95%) or lower oxygen saturation targets (85-89%) from birth to 36 weeks corrected age. The primary outcome of the follow up study was a composite of death or neurodevelopment impairment at 18 to 22 months corrected age. Neurodevelopmental impairment (NDI) was defined as a Bayley III cognitive composite score of less than 70, modified Gross Motor Function Classification System ≥2, moderate to severe cerebral palsy, permanent hearing loss, and/or bilateral blindness. Analyses~~Results~~ were adjusted for gestational age stratum, center and familial clustering.

Comment [WC1]: Should this say "Analyses" instead of Results? Ask Abhik/Marie

RESULTS

The primary outcome was determined for 1234/1316 (93.8%) of infants enrolled in SUPPORT; 93.6% (990/1058) of survivors were evaluated at 18 to 22 months corrected age. Death or NDI occurred in 30.2% (185/612) infants in the lower oxygen saturation group and 27.5% (171/622) infants in the higher oxygen saturation group (relative risk 1.12; 95% confidence interval 0.94, 1.32; p=0.21). Death occurred in 140 (22.1%) of the children in the lower oxygen saturation

group and in 118 (18.2%) in the higher oxygen saturation group (relative risk 1.25; 95% confidence interval 1, 1.55, p=0.046). NDI was present in 9.5% (45/472) of the lower oxygen saturation group and 10.5 % (53/504) of the higher oxygen saturation group survivors (relative risk 0.87, 95% confidence interval 0.6, 1.28; p=0.49.

CONCLUSIONS

Among extremely preterm infants targeted at different levels of oxygen saturation, no significant difference in death or neurodevelopmental impairment was observed at 18 to 22 months. Mortality at 18 to 22 months was increased in the lower oxygen saturation target group.

BACKGROUND

~~Oxygen supplementation is a vital therapy for survival of many~~ For many preterm infants with respiratory disorders, oxygen supplementation is vital for survival. However, oxygen supplementation may increase the risk of retinopathy of prematurity, bronchopulmonary dysplasia, [1] periventricular leukomalacia,[2] and cerebral palsy [3] Restrictive oxygen therapy decreases retinopathy but has resulted in increased deaths in recent randomized controlled trials. [4,5,6,7]

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development SUPPORT Trial demonstrated no significant difference in a composite outcome of severe retinopathy of prematurity or death before discharge between a lower oxygen saturation target group (85-89%) and a higher oxygen saturation target group (91-95%). However, death before discharge was increased (19.9% vs. 16.2%; relative risk 1.27; 95% CI 1.01 to 1.6; p=0.04) and severe retinopathy of prematurity among survivors was decreased (8.6% vs. 17.9%; relative risk 0.52; 95% CI 0.37 to 0.73; p<0.001) in the lower oxygen saturation target group compared to the higher saturation target group. [6] A recent meta-analysis that included the SUPPORT Trial and three other subsequently completed multi-center randomized controlled trials with a total of 3631 infants, showed that infants randomized to an oxygen saturation target of 91-95% % had a lower mortality rate than infants randomized to oxygen saturation targets of 85-89% (14.4% versus 17.3% respectively, P=0.015). [7] The effects of oxygen on the immature brain are not clearly understood. [8] Oxidative stress injury in the premature infant may have many underlying pathophysiological processes. There has been a keen interest in determining whether higher or lower oxygen supplementation can reduce neurodevelopmental impairment. [7] However, in two

non randomized studies of oxygen saturation targeting,[1, 9] neurodevelopmental outcome did not differ by oxygen targets.

This study evaluated the composite outcome of death or neurodevelopmental impairment at 18 to 22 months corrected age in the subjects enrolled in the SUPPORT trial and randomized to lower (85-89%) or higher oxygen saturation targets (91-95%) from birth to 36 weeks corrected age. The pre-specified hypothesis in the SUPPORT trial was that compared to a higher oxygen saturation target, a lower saturation target decreases the risk of the composite outcome of death or neurodevelopmental impairment.

METHODS

Study Design

Extremely preterm infants (24 weeks 0 days to 27 weeks 6 days) born between February 2005 and February 2009 at 20 centers in the United States participating in the Neonatal Research Network of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development were enrolled at delivery in the randomized controlled SUPPORT trial. Permuted block randomization was used, with stratification according to center and gestational age (24 weeks 0 days to 25 weeks 6 days or 26 weeks 0 days to 27 weeks 6 days). The infants were randomly assigned in the delivery room to a target range of oxygen saturation of 85% to 89% (the lower oxygen saturation group) or 91 to 95% (the higher oxygenation group). Using a 2-by-2 factorial design, participants were also randomly assigned to receive either CPAP immediately following delivery and a limited ventilation strategy if subsequent intubation was required or intubation with surfactant administration within an hour after birth. Procedures for enrollment,

intervention and data collection have been previously reported. [6]. The study was approved by the institutional review board at each participating center and at RTI International which is the independent data coordinating center for the Neonatal Research Network. Written informed consent was obtained from the parents or guardians of each child before delivery. Also consent was obtained for the follow up at 18-22 months corrected age.

Assessments

A comprehensive neurodevelopmental assessment was performed on survivors at 18-22 months corrected age by neurologic examiners and neurodevelopmental testers who were unaware of the treatment assignments~~, and had been trained annually for reliability of assessments during a 2-day workshop.~~ Developmental status was assessed using the Bayley Scales of Infant and Toddler Development 3rd edition (BSID III) [10]. Cognitive Composite Scores are reported as a standardized score with a mean of 100 and a standard deviation of 15. Examiners also recorded the presence of cerebral palsy defined as a non-progressive disorder of the central nervous system and characterized by abnormal muscle tone in at least one arm or leg associated with abnormal control of movement or posture with delayed attainment of motor milestones.[11] The modified Gross Motor Function Classification System (GMFCS) [12] was used to classify gross motor performance using a range from 0 (normal) to 5 (most impaired). Cerebral palsy was classified depending on severity into mild (GMFCS $\leq$1), moderate (GMFCS 2 or 3) or severe (GMFCS $\geq$ 4). Hearing and visual impairment were determined based on parent report and examination. A 2-day workshop was held annually to train examiners and ensure reliability of assessments.

Certified research nurses collected demographic and neonatal data using NRN definitions. Data collected included gestational age, birth weight, sex~~gender~~, multiple gestation, race/ethnicity, retinopathy or prematurity status, bronchopulmonary dysplasia, history of medical or surgical necrotizing enterocolitis (modified Bell's stage $\geq$ 2),grades 3-4 intraventricular hemorrhage or periventricular leukomalacia, history of late onset sepsis, use of postnatal steroids. Socioeconomic variables included insurance status, maternal marital status, maternal education, household income, language spoken at home, and whether living with biological parents. Socioeconomic data from the neonatal period were used and when not available, data updated at the 18-22 month visit were used. Outcomes following NICU discharge includ~~ed~~inged rehospitalizations, interim medical history, surgery, and medications were recorded at the 18-22 month visit.

Outcome

The pre-specified primary follow-up outcome of the SUPPORT trial was the composite of death or neurodevelopmental impairment at 18 to 22 months corrected age. ~~for prematurity was the pre-specified primary follow-up outcome for the SUPPORT trial.~~ This composite outcome was selected because (a) the data are available on the entire randomized trial cohort, (b) infants who died before 18 months could not be classified as having neurodevelopmental impairment and (c) death can be considered as a competing outcome to neurodevelopmental impairment among survivors. Neurodevelopmental impairment was defined as having any of the following: BSID III cognitive composite score less than 70, GMFCS $\geq$ 2, presence of moderate or severe cerebral palsy, permanent hearing loss that does not permit the child to understand directions of the

Comment [WC2]: Are these two not the same thing? It appears like that from your description of the methods.

examiner and communicate despite amplification with hearing aids, or bilateral visual impairment (vision < 20/200).

Analysis

Data were entered in standard forms and were transmitted to the Neonatal Research Network Data Coordinating Center at RTI International which stored, managed and analyzed the data for this study. Details regarding sample size calculations for the SUPPORT trial have been previously reported [6]. The sample size calculations were based on infants born in the year 2000 which included the rate of death or neurodevelopmental impairment at 18-22 months corrected age. All analyses were performed according to the intention to treat principle. Unadjusted comparisons of birth and demographic characteristics between treatment groups were conducted using chi-square tests for categorical variables and t tests for continuous variables. The primary analysis focused on the percentage of infants in each group for whom the primary outcome of death or NDI at 18 to 22 months corrected age could be assigned. Analysis of all~~this and all other~~ categorical outcomes was performed using~~with the used of~~ robust Poisson regression in a generalized-estimating-equation model to obtain adjusted relative risks with 95% confidence intervals. The denominator ~~that was~~ used to calculate the rate of each outcome was the number of infants for whom the outcome was known. Continuous outcomes were analyzed using~~with the use of~~ mixed-effects linear models to obtain adjusted means and standard errors. Pre-specified subgroup analyses were also conducted within each gestational age strata.

In the analysis of all neonatal and follow-up outcomes, ~~the~~ results were adjusted, as pre-specified, for gestational-age strata, center, and familial clustering (because multiple births from

the same mother were randomized to the same treatment group). Two-sided p values of less than 0.05 were considered ~~to indicate~~ statistically significance. For the 79 secondary outcomes analyzed according to treatment, we would expect no more than 4 tests to have p values of less than 0.05 on the basis of chance alone. Subgroup analyses were conducted within pre-specified gestational age strata for the same outcomes. Although these tests have not been adjusted for multiple comparisons, we would expect no more than 4 tests per stratum to have p values of less than 0.05 on the basis of chance alone.

RESULTS

Characteristics of the Study Sample

The SUPPORT trial enrolled 1316 infants (Figure 1). The baseline characteristics and hospital outcomes of the entire group have been reported.[6] Five hundred twenty four infants in the lower oxygen saturation group and 555 in the higher oxygen saturation group survived to discharge or transfer from the hospital. Ten children in the lower oxygen saturation group and 11 children in the higher oxygen saturation group died after discharge from the nursery and prior to the 18 to 22 month corrected age follow up visit. Thirty five children in the lower saturation group and 33 children in the higher saturation group were not evaluated in the follow up visit. However, 14/35 in the lower saturation group and 19/33 in the higher saturation group were known to be alive at 18 to 22 months corrected age. Neurodevelopmental assessment was performed in 990/1058 infants who were thought to be alive (93.6%). Of those who were evaluated at the 18 to 22 months corrected age, neurodevelopmental status was determined for~~in~~ 976 children. ~~From the entire cohort, t~~The pre-specified outcome of death or neurodevelopmental impairment could be determined for~~in~~ 93.8% (1234/1316) of enrolled children. Compared to mothers of infants who

were followed, mothers of infants who were lost to follow up were less likely to be married (31 vs. 47% p=0.01) and more likely to have only public health insurance (69 vs. 52% p=0.008). There were no ~~other~~ significant differences in ~~any of the o~~other baseline characteristics of the cohort that was followed up compared to~~and~~ those lost to follow up. The mean corrected age for neurodevelopmental evaluation was similar between both study groups (lower oxygen saturation, 19.9 ± 2.4 months vs. higher oxygen saturation 20.2 ± 2.7 months, p=0.08).

Comment [WC3]: Use decimals for %s as the denominators are generally more than 100

Baseline characteristics of the follow up cohort and the entire trial cohort are presented in Table 1. Among children who were followed, the percentage of infants who were small for gestational age was greater in the higher oxygen saturation target group compared to the lower saturation target group. In addition, as reported previously[6] the incidence of severe retinopathy of prematurity was higher in the higher oxygen saturation group compared to the lower saturation group but no other significant differences were found in the baseline characteristics or major hospital outcomes of the infants with follow up data.

Primary Outcome

The prevalence of the composite primary outcome of death or neurodevelopmental impairment was not significantly different between the lower (185/612, 30.2%) and higher (171/662, 27.5%) oxygen saturation target groups (relative risk 1.12, 95% confidence interval 0.94, 1.32; p=0.21). (Table 2) In the 24 to 25 weeks gestational age stratum, primary outcome data were available for 261 of 276 children in the lower saturation group and 276 of 289 in the higher saturation group. For the age stratum 26 to 27 weeks gestation, outcome data were available for 351 of 378 of the lower oxygen saturation group and 346 of 373 of the higher oxygen saturation group. Similar to

the entire cohort there were no significant differences in the prevalence of death or neurodevelopmental impairment within both gestational age strata as shown in table 2.

Components of the Primary Outcome

Death prior to the 18 to 22 month adjusted age visit occurred significantly more often among infants in the lower oxygen saturation target group compared to those in the higher saturation target group (lower oxygen saturation, 140/633, 22.1% vs. higher oxygen saturation, 118/648, 18.2%; relative risk 1.25; 95% CI 1, 1.55, p=0.046). ~~The rate of n~~Neurodevelopmental impairment among survivors examined~~followed~~ at the 18 to 22 month corrected age visit was similar between the lower and the higher oxygen saturation target groups (45/472, 9.5% vs. 53/504, 10.5%; relative risk 0.87 95%CI 0.6, 1.28, p=0.49)

Other outcomes among survivors at follow up

The percentage of children with BSID III cognitive scores below 70 was not significantly different between the lower and higher oxygen saturation group, nor was the percentage of children with cognitive scores below 85. Adjusted means of cognitive composite scores were not significantly different between the two groups and are presented in table 3.

The rates of severe retinopathy of prematurity and eye surgery among survivors to follow up were increased~~higher~~ in the higher oxygen target group compared to the lower oxygen target group; however the rate of bilateral (lower oxygen saturation, 1% vs higher oxygen saturation, 1.6%, relative risk 0.67, 95% CI 0.22, 2.02; p=0.48) or unilateral blindness were not significantly different at the 18 to 22 month corrected age visit. Other visual outcomes are presented in Table 3.

Comment [WC4]: Give decimal

Comment [WC5]: Maybe the data exact data should not be presented for either of should be presented for both

Overall readmission rates and readmission rates for respiratory problems were not significantly different between ~~both~~ groups. There were no significantly differences in post-~~after~~ discharge use of bronchodilators, steroids, diuretics or ~~any~~ other medications. (Table 3)

DISCUSSION

In this multicenter follow up study of infants randomized to a lower target range of oxygen saturation (85 to 89%) or to higher target oxygen saturation (91 to 95%), a significant difference between treatment groups was not found in the pre-specified outcome of death or neurodevelopmental impairment at 18-22 months corrected age. To our knowledge this is the only large comprehensive study that has included neurodevelopmental impairment as an outcome for evaluating effects of different oxygen target saturation levels started at birth in extremely premature babies within a randomized multicenter trial, but outcomes of other similarly designed trials will be reported[7]. The results of recent trials have raised concerns about using lower oxygen saturation targets because of potentially increased mortality in extremely premature infants [6,7,13]. In these trials, it was found that death prior to discharge in the SUPPORT trial was increased among children randomized to lower target saturation levels, and this difference persisted at 18 to 22 months corrected age in the current follow up study.

We had reported previously that the lower saturation oxygen target was associated with a large reduction in the incidence of severe retinopathy of prematurity among survivors. [6] It has been previously reported that severe ROP may be associated with poor visual outcomes even with treatment [14,15] Although our study was not designed to collect detailed data on eye disorders or visual function at 18 to 22 months of age we found that there were no significant differences in the report of unilateral and bilateral blindness between the two groups. Eye surgery was higher in

the group with a higher oxygen saturation target and was likely related to higher incidence of severe retinopathy of prematurity in this group and our criteria used to define severe retinopathy of prematurity [6]. Specific visual outcomes of eye function after the presence of retinopathy of prematurity were also not included in the outcome data collected in this trial. However, there were no differences~~we did not find a significant difference~~ in other reported visual outcomes, including ~~like~~ nystagmus, strabismus or use of corrective lenses.

Concerns have been raised~~There had been concerns~~ that lower oxygen saturation targets might increased the risk of long term neurodevelopmental impairment[5]. However, NDI as defined in this study was not found to be significantly different between survivors in the lower and higher oxygen saturation groups. In addition the incidence of cerebral palsy did not differ between the treatment groups, though it is noteworthy that the incidence of cerebral palsy was lower than previously reported in other outcome studies.[16]

It has been recognized that higher oxygen saturation levels can be associated with chronic lung disease. In this study~~However~~, we found no difference in the use of persistent oxygen, postnatal corticosteroids or diuretics at 18 to 22 months corrected age or in ~~the persistent oxygen use at 18 to 22 months of age or in~~ rehospitalizations between the two groups.

Although the SUPPORT cohort will be followed to school age, the present study reports~~A limitation of this study is that~~ results of a single follow up visit at~~it reports only follow up to~~ 18 to 22 months corrected age, which may not been enough time to detect the presence of minor but important disabilities. Another limitation of the study is ~~It has also been reported~~ that the BSID III may result in higher cognitive scores than an earlier vision of the Bayley Scales of Infant development (BSID-II); and a lower sensitivity if a cognitive composite score of less than 70 is

used as the criterion for impairment[17 18]. ~~Use of~~ Use of a cutoff of less than 85 for the Bayley III cognitive composite scores, did not reveal significant differences between groups.. ~~did not find significant differences between the groups. There is an ongoing follow up SUPPORT study that will be reporting the outcome of these children at school age.~~ Although we included 20 centers scattered throughout the US, all were tertiary care centers, which might limit the generalizibility of our conclusions.

In summary, we found no significant differences in death or neurodevelopmental impairment at 18 to 22 months corrected age in extremely premature infants who were randomized to a lower target oxygen saturation or higher target oxygen saturation. The increased death rate at discharge, ~~that was~~ previously reported in the lower target oxygen saturation group, was still present at 18 to 22 months corrected age. Although higher rates of retinopathy of prematurity were associated with higher oxygen saturation target levels, blindness was not significantly different among survivors at 18 to 22 months.

Acknowledgements

The National Institutes of Health, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), and the National Heart, Lung, and Blood Institute (NHLBI) provided grant support for the Neonatal Research Network's SUPPORT Trial.

Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Drs. Abhik Das (DCC Principal Investigator) and Marie Gantz (DCC Statistician) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study. The following investigators, in addition to those listed as authors, participated in this study:

NRN Steering Committee Chairs: Alan H. Jobe, MD PhD, University of Cincinnati (2003-2006); Michael S. Caplan, MD, University of Chicago, Pritzker School of Medicine (2006-2011).

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Case Western Reserve University, Rainbow Babies & Children's Hospital (U10 HD21364, M01 RR80) – Avroy A. Fanaroff, MD; Bonnie S. Siner, RN; Arlene Zadell RN; Julie DiFiore, BS; Monika Bhola, MD; Harriet G. Friedman, MA; Gulgun Yalcinkaya, MD.

Cincinnati Children's Hospital Medical Center, University of Cincinnati Hospital, and Good Samaritan Hospital (U10 HD27853, M01 RR8084) – Edward F. Donovan, MD; Vivek Narendran, MD MRCP; Kate Bridges, MD; Barbara Alexander, RN; Cathy Grisby, BSN CCRC; Marcia Worley Mersmann, RN CCRC; Holly L. Mincey, RN BSN; Jody Hessling, RN; Teresa L. Gratton, PA.

Duke University School of Medicine, University Hospital, Alamance Regional Medical Center, and Durham Regional Hospital (U10 HD40492, M01 RR30) – Ronald N. Goldberg, MD; C. Michael Cotten, MD MHS; Patricia Ashley, MD; Kathy J. Auten, MSHS; Kimberley A. Fisher, PhD FNP-BC IBCLC; Katherine A. Foy, RN; Sharon F. Freedman, MD; Kathryn E. Gustafson, PhD; Melody B. Lohmeyer, RN MSN; William F. Malcolm, MD; David K. Wallace, MD MPH.

Emory University, Children's Healthcare of Atlanta, Grady Memorial Hospital, and Emory Crawford Long Hospital (U10 HD27851, RR25008, M01 RR39) – Barbara J. Stoll, MD; Susie Buchter, MD; Anthony J. Piazza, MD; David P. Carlton, MD; Linda Black, MD; Ann M. Blackwelder, RNC BS MS; Sheena Carter, PhD; Elisabeth Dinkins, PNP; Sobha Fritz, PhD; Ellen C. Hale, RN BS CCRC; Amy K. Hutchinson, MD; Maureen Mulligan LaRossa, RN; Gloria V. Smikle, PNP MSN.

Eunice Kennedy Shriver National Institute of Child Health and Human Development – Stephanie Wilson Archer, MA.

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National Heart, Lung, and Blood Institute – Mary Anne Berberich, PhD; Carol J. Blaisdell, MD; Dorothy B. Gail, PhD; James P. Kiley, PhD.

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Stanford University and Lucile Packard Children's Hospital (U10 HD27880, UL1 RR25744, M01 RR70) – Krisa P. Van Meurs, MD; David K. Stevenson, MD; M. Bethany Ball, BS CCRC; Barbara Bentley, PsychD MSEd; Elizabeth F. Bruno, PhD; Alexis S. Davis, MD MS; Maria Elena DeAnda, PhD; Anne M. DeBattista, RN, PNP; Jean G. Kohn, MD MPH; Melinda S. Proud, RCP; Renee P. Pyle, PhD; Nicholas H. St. John, PhD; Hali E. Weiss, MD.

Tufts Medical Center, Floating Hospital for Children (U10 HD53119, M01 RR54) – Ivan D. Frantz III, MD; John M. Fiascone, MD; Anne Furey, MPH; Brenda L. MacKinnon, RNC; Ellen Nylen, RN BSN; Ana Brussa, MS OTR/L; Cecelia Sibley, PT MHA.

University of Alabama at Birmingham Health System and Children's Hospital of Alabama (U10 HD34216, M01 RR32) – Namasivayam Ambalavanan, MD; Monica V. Collins, RN BSN MaEd; Shirley S. Cosby, RN BSN. Vivien A. Phillips, RN BSN; Kirstin J. Bailey, PhD; Fred J. Biasini, PhD; Maria Hopkins, PhD; Kristen C. Johnston, MSN CRNP; Sara Krzywanski, MS; Kathleen G. Nelson, MD; Cryshelle S. Patterson, PhD; Richard V. Rector, PhD; Leslie Rodriguez, PhD; Amanda Soong, MD; Sally Whitley, MA OTR-L FAOTA; Sheree York, PT DPT MS PCS.

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University of Miami, Holtz Children's Hospital (U10 HD21397, M01 RR16587) – Shahnaz Duara, MD; Ruth Everett-Thomas, RN MSN; Maria Calejo, MEd; Alexis N. Diaz, BA; Silvia M. Frade Eguaras, BA; Andrea Garcia, MA; Kasey Hamlin-Smith, PhD; Michelle Harwood Berkowits, PhD; Sylvia Hiriart-Fajardo, MD; Elaine O. Mathews, RN; Helina Pierre, BA; Arielle Riguard, MD; Alexandra Stroerger, BA.

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University of Rochester Medical Center, Golisano Children's Hospital (U10 HD40521, M01 RR44) – Nirupama Laroia, MD; Dale L. Phelps, MD; Gary David Markowitz, MD; Linda J. Reubens, RN CCRC; Diane Hust, MS RN CS; Lisa Augostino; Julie Babish Johnson, MSW; Erica Burnell, RN; Rosemary L. Jensen; Emily Kushner, MA; Joan Merzbach, LMSW; Kelley Yost, PhD.

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University of Texas Health Science Center at Houston Medical School and Children's Memorial Hermann Hospital (U10 HD21373) – Kathleen A. Kennedy, MD MPH; Jon E. Tyson, MD MPH; Nora I. Alaniz, BS; Patricia Evans, MD; Beverly Foley Harris, RN BSN; Charles Green, PhD; Margarita Jiminez, MD MPH; Anna E. Lis, RN BSN; Sarah Martin, RN BSN; Georgia E. McDavid, RN; Brenda H. Morris, MD; Margaret L. Poundstone, RN BSN; Stacy Reddoch, BA; Saba Siddiki, MD; Patti L. Pierce Tate, RCP; Laura L. Whitely, MD; Sharon L. Wright, MT (ASCP).

University of Utah Medical Center, Intermountain Medical Center, LDS Hospital, and Primary Children's Medical Center (U10 HD53124, M01 RR64) – Shawna Baker, RN; Karie Bird, RN; Jill Burnett, RN; Laura Cole, RN; Karen A. Osborne, RN BSN CCRC; Cynthia Spencer, RNC; Mike Steffens, PhD; Kimberlee Weaver-Lewis, RN BSN; Karen Zanetti, RN.

Wake Forest University, Baptist Medical Center, Brenner Children's Hospital, and Forsyth Medical Center (U10 HD40498, M01 RR7122) – Robert G. Dillard, MD; Lisa K. Washburn, MD; Nancy J. Peters, RN CCRP; Barbara G. Jackson, RN BSN; Korinne Chiu, MA; Deborah Evans Allred, MA LPA; Donald J. Goldstein, PhD; Raquel Halfond, MA; Carroll Peterson, MA; Ellen L. Waldrep, MS; Cherrie D. Welch, MD MPH; Melissa Whalen Morris, MA; Gail Wiley Hounshell, PhD.

Wayne State University, Hutzel Women's Hospital, and Children's Hospital of Michigan (U10 HD21385) – Seetha Shankaran, MD; Beena G. Sood, MD MS; Rebecca Bara, RN BSN; Elizabeth Billian, RN MBA; Laura A. Goldston, MA; Mary Johnson, RN BSN.

Yale University, Yale-New Haven Children's Hospital, and Bridgeport Hospital (U10 HD27871, UL1 RR24139, MO1 RR125) – Vineet Bhandari, MD DM; Harris C. Jacobs, MD; Pat Cervone, RN; Patricia Gettner, RN; Monica Konstantino, RN BSN; JoAnn Poulsen, RN; Janet Taft, RN BSN; Christine G. Butler, MD; Nancy Close, PhD; Walter Gilliam, PhD; Sheila Greisman, RN; Elaine Romano, MSN; Joanne Williams, RN BSN.

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Gail, PhD, National Heart, Lung, and Blood Institute; Carl Hunt, MD, National Heart, Lung, and Blood Institute; Martin Keszler, MD, Georgetown University Hospital; W. Kenneth Poole (ex officio), PhD, RTI International; Carol K. Redmond, ScD, University of Pittsburg; Michael G. Ross, MD, MPH; UCLA School of Medicine and Public Health; Merran A. Thomson, MD, Hammersmith Hospital, UK; Steven J. Weiner, MS, The George Washington University; Marian Willinger (ex officio), PhD, Eunice Kennedy Shriver National Institute of Child Health and Human Development.

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Comment [WC6]: This is published in NEJM 2011. Ben Stenson is the first author

Comment [WC7]: I would not reference old abstracts like this. See if the paper was ever published

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Table 1. Baseline characteristics of the SUPPORT group

Characteristic	Trial Cohort		Cohort with Follow-up Visit	
	Lower Oxygen Saturation	Higher Oxygen Saturation	Lower Oxygen Saturation	Higher O: Saturat
	N=654	N=662	N=479	N=51
Birth weight – g	835.5 ± 193.4	824.8± 193	857.8 ± 186.3	843.7± 1
Gestational age – wk	26.2 ± 1.1	26.1 ± 1.1	26.3 ± 1.1	26.2 ±
Small for gestational age – no./total no. (%)	41/654 (6.3)	55/662 (8.3)	17/479 (3.5)*	38/511 (
Male sex – no./total no. (%)	341/654 (52.1)	371/662 (56.0)	240/479 (50.1)	282/511 (
Race or ethnic group – no./total no. (%)				
Non Hispanic Black	257/654 (39.3)	232/662 (35.0)	201/479 (42.0)	176/511 (
Non Hispanic White	242/654 (37.0)	279/662 (42.1)	178/479 (37.2)	218/511 (
Hispanic	132/654 (20.2)	127/662 (19.2)	86/479 (18.0)	97/511 (
Other or unknown	23/654 (3.5)	24/662 (3.6)	14/479 (2.9)	20/511 (
Multiple births – no./total no. (%)	161/654 (24.6)	176/662 (26.6)	124/479 (25.9)	128/511
Maternal educational level <high school no./total no. (%)	148/594 (24.9)	165/612 (27.0)	115/471 (24.4)	129/504 (
Public health insurance only – no./total no. (%)	356/650 (54.8)	348/660 (52.7)	253/479 (52.8)	266/511 (

Mother married – no./total no. (%)	284/652 (43.6)	308/661 (46.6)	222/479 (46.3)	243/511 (
Lives with both biological parents – no./total no. (%)†	354/508 (69.7)	364/547 (66.5)	332/478 (69.5)	345/511 (
Household income < $30,000/year – no./total no.(%) †	247/474 (52.1)	291/528 (55.1)	239/456 (52.4)	272/498 (
English as primary language – no./total no. (%)‡	402/477 (84.3)	429/513 (83.6)	402/477 (84.3)	427/511 (
Cesarean section – no./total no. (%)	441/654 (67.4)	442/662 (66.8)	332/479 (69.3)	335/511 (
Antenatal steroids – no./total no. (%)	633/654 (96.8)	632/661 (95.6)	462/479 (96.5)	487/511 (
Severe retinopathy of prematurity – no./total no. (%)†	41/475 (8.6)**	91/509 (17.9)**	38/442 (8.6)**	82/471 (1'
Bronchopulmonary dysplasia – no./total no. (%)¶	205/540 (38.0)	237/568 (41.7)	177/479 (37.0)	203/511 (
Intraventricular hemorrhage grade 3 or 4 or Periventricular leukomalacia – no./total no. (%)	98/630 (15.6)	100/640 (15.6)	56/478 (11.7)	60/510 (
Necrotizing enterocolitis – no./total no. (%)	76/641 (11.9)	70/649 (10.8)	42/479 (8.8)	44/511 (
Late onset sepsis/meningitis – no./total no. (%)	228/624 (36.5)	226/634 (35.6)		
155/479 (32.4)	166/511 (32.5)			
Post natal steroids – no./total no. (%)	61/636 (9.6)	69/644 (10.7)		
41/477 (8.6)	48/507 (9.5)			
CPAP – no./total no. (%)	336/654 (51.4)	327/662 (49.4)		
254/479(53.0)	257/511 (50.3)			
Surfactant – no./total no. (%)	318/654 (48.6)	335/662 (50.6)		
225/479 (47.0)	254/511 (49.7)			

*p<0.01, **p<0.001

† Available only for infant who survived to discharge or transfer

‡ Only available at 18-22 months corrected age

¶ Among survivors to 36 weeks postmenstrual age

Table 2. Primary Outcomes at 18-22 Months Corrected Age

Outcome	Lower Oxygen Saturation N=654	Higher Oxygen Saturation N=662	Adjusted Relative Risk
Outcome determined for death or NDI – no./total no. (%)	612/654 (93.6)	622/662 (94)	1 (0.97, 1.03)
Neurodevelopmental impairment or death – no./total no. (%)	185/612 (30.2)	171/622 (27.5)	1.12 (0.94, 1.32)
Died by 18-22 months – no./total no. (%)	140/633 (22.1)	118/648 (18.2)	1.25 (1, 1.55)
Survivors at follow-up			
Neurodevelopmental impairment – no./total no. (%)	45/472 (9.5)	53/504 (10.5)	0.87 (0.6, 1.28)
Bayley III cognitive composite score < 70 – no./total no. (%)	34/471 (7.2)	38/503 (7.6)	0.91 (0.58, 1.43)
Gross motor function level ≥ 2 – no./total no. (%)	26/479 (5.4)	23/511 (4.5)	1.17 (0.68, 2.01)
Moderate/severe cerebral palsy – no./total no. (%)	20/479 (4.2)	20/511 (3.9)	1 (0.54, 1.83)
Blindness – no./total no. (%)	5/479 (1)	6/511 (1.2)	0.9 (0.28. 2.9)
Hearing Impairment – no./total no. (%)	12/479 (2.5)	12/511 (2.3)	1.16 (0.54, 2.49)
24 0/7 to 25 6/7 weeks gestational age strata	276	289	
Neurodevelopmental impairment or death – no./total no. (%)	115/261 (44.1)	112/276 (40.6)	1.09 (0.89, 1.32)
Died by 18-22 months – no./total no. (%)	91/267(34.1)	79/283 (27.9)	1.23 (0.95, 1.59)
Survivors at follow-up			
Neurodevelopmental impairment – no./total no. (%)	24/170 (14.1)	33/197 (16.8)	0.8 (0.49, 1.3)
Bayley III cognitive composite score < 70 – no./total no. (%)	17/169 (10.1)	22/196 (11.2)	0.86 (0.47, 1.56)
Gross motor function level ≥ 2 – no./total no. (%)	13/173 (7.5)	13/200 (6.5)	1.07 (0.53, 2.17)
Moderate/severe cerebral palsy – no./total no. (%)	10/173 (5.8)	12/200(6.0)	0.86(0.39, 1.88)
Blindness – no./total no. (%)	1/173 (0.6)	3/200 (1.5)	0.39 (0.04, 3.69)

Hearing Impairment – no./total no. (%)	4/173 (2.3)	10/200 (5.0)	0.5 (0.16, 1.53)
26 0/7 to 27 6/7 weeks gestational age strata	378	373	
Neurodevelopmental impairment or death – no./total no. (%)	70/351(19.9)	59/346 (17.1)	1.17 (0.85, 1.6)
Died by 18-22 months – no./total no. (%)	49/366(13.4)	39/365(10.7)	1.28 (0.86, 1.89)
Survivors at follow-up			
Neurodevelopmental impairment – no./total no. (%)	21/302(7.0)	20/307(6.5)	0.99(0.54, 1.84)
Bayley III cognitive composite score < 70 – no./total no. (%)	17/302 (5.6)	16/307(5.2)	0.98 (0.49, 1.97)
Gross motor function level ≥ 2 – no./total no. (%)	13/306(4.2)	10/311 (3.2)	1.32(0.57, 3.01)
Moderate/severe cerebral palsy – no./total no. (%)	10/306(3.3)	8/311(2.6)	1.22(0.47, 3.2)
Blindness – no./total no. (%)	4/306 (1.3)	3/311(1.0)	1.38 (0.31, 6.05)
Hearing Impairment – no./total no. (%)	8/306 (2.6)	2/311 (0.6)	4.18(0.88, 19.87)

Table 3. Other Outcomes at 18 to 22 months corrected age by Group

Outcome	Lower Oxygen Saturation (N=479)	Higher Oxygen Saturation (N=510)	Relative Risk for Lower vs. Higher Oxygen Saturation (95% CI)	Adjusted difference in means (95% CI)	Adj P-v
Bayley Scales of Infant Development III					
Cognitive composite < 70	34/471 (7.2)	38/503 (7.6)	0.91 (0.58, 1.43)		0.
Cognitive composite <85	105/471 (22.3)	132/503 (26.2)	0.85 (0.68, 1.07)		0.
Adjusted mean cognitive composite scores ± standard error	92.2 ± 0.8	90.5 ± 0.7		0.7 (-1.2, 2.5)	0.
Median cognitive composite scores (interquartile range)	90 (85, 100)	90 (80, 100)			
Neurologic findings					
Mild cerebral palsy vs. none	23/459 (5.0)	21/490 (4.3)	1.16 (0.66, 2.02)		0.
Moderate cerebral palsy vs. none	11/447 (2.5)	10/479 (2.1)	1.19 (0.52, 2.71)		0.
Severe cerebral palsy vs. none	9/445 (2.0)	10/479 (2.1)	0.95 (0.39, 2.27)		0.
Any cerebral palsy	43/479 (9.0)	41/510 (8.0)	1.12 (0.76, 1.65)		0.
Any abnormal neurologic exam	108/479 (22.5)	114/511 (22.3)	1.02 (0.82, 1.28)		0.
Vision/Eye findings					

Strabismus	46/478 (9.6)	41/510 (8)	1.2 (0.8, 1.8)	0.
Nystagmus	22/479 (4.6)	13/510 (2.4)	1.81 (0.89, 3.69)	0.
Tracks 180 degrees	462/476 (97.1)	492/506 (97.2)	1 (0.98, 1.02)	0.
Corrective lenses both eyes	21/468 (4.5)	20/493 (4.1)	1.14 (0.62, 2.08)	0.
Blind, some function, both eyes vs. normal	3/450 (0.7)	2/475 (0.4)	1.57 (0.27, 8.96)	0.
Blind, no useful vision, both eyes vs. normal	2/449 (0.4)	4/477 (0.8)	0.54 (0.1, 2.96)	0.
Other abnormal eye findings vs. normal	6/453 (1.3)	12/485 (2.5)	0.55 (0.21, 1.46)	0.
Eye surgery	31/477 (6.5)	67/509 (13.2)	0.52 (0.35, 0.78)	0.(
Medicines				
Bronchodilators	159/475 (33.5)	185/506 (36.6)	0.92 (0.78, 1.1)	0.
Steroids	95/475 (20.0)	108/506 (21.3)	0.92 (0.72, 1.18)	0.
Diuretics	15/475 (3.2)	14/506 (2.8)	1.17 (0.58,2.34)	0.
Anticonvulsants	12/478 (2.5)	12/511 (2.3)	1.08 (0.49, 2.37)	0.
Readmission	210/478 (43.9)	239/511 (46.8)	0.94 (0.82, 1.08)	0.
Readmission for respiratory reason	110/470 (23.4)	127/503 (25.2)	0.93 (0.74, 1.16)	0.
Readmission for growth/nutrition	12/470 (2.6)	13/503 (2.6)	1.05 (0.49, 2.25)	0.

From: Finer, Neil
To: Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade; Wally Carlo (wacarlo@uab.edu); "kurt.schibler@cchmc.org"; "Michele Walsh"; "Roger Faix"; "Laptook, Abbot"; "Bradley Yoder"; Das, Abhik; "Gantz, Marie"; "nancy newman"
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: sct abstract1_fin_28Nov11
Date: Monday, November 28, 2011 7:36:25 PM

This is fine.
Thanks Marie
Neil

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
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Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: sct abstract1_fin_28Nov11

Hi,
Based on the prior comments, Marie has revised the abstract – let me know (if you haven't done so already) if you approve or disapprove for submission.

Thanks
Rose

From: Higgins, Rosemary (NIH/NICHD) [E]
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Subject: Fw: sct abstract1_fin_28Nov11
Date: Monday, November 28, 2011 6:29:50 PM
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I approve it. Enclosed are some suggestions that include the main results as hard facts.

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Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: sct abstract1_fin_28Nov11

Hi,
Based on the prior comments, Marie has revised the abstract – let me know (if you haven't done so already) if you approve or disapprove for submission.

Thanks
Rose

Enrollment propensity weighting to assess the generalizability of a randomized clinical trial

Marie Gantz, Darryl Creel, Wade Rich, Rosemary Higgins and Abhik Das for the SUPPORT Trial Subcommittee of the Eunice Kennedy Shriver NICHD Neonatal Research Network (NRN)

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Randomized trials typically enroll a convenience sample of eligible patients without regard to formal probability sampling. However, trial results often substantively change clinical practice for the population at large, without systematic evaluation of the generalizability of results.

The Surfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT) used a 2X2 factorial design to test different ventilation and oxygenation strategies for respiratory management of extremely premature babies. This influential and largest of its kind trial demonstrated that a less invasive ventilator strategy may be safe to use and indicated increased mortality at lower oxygen saturation.

Because the interventions started at ~~upon~~ delivery or within the first two hours after birth, antenatal consent was required, restricting the ability to enroll some eligible infants, including those who were born precipitously following the mother's admission. Enrolled babies had significantly higher socioeconomic status and greater exposure to antenatal steroids compared to the non-enrolled, which raised questions about the generalizability of the trial results. We conducted a sensitivity analysis by incorporating enrollment propensity weights so the analysis would better reflect the eligible population.

We used Classification and Regression Trees to model enrollment based on maternal and infant characteristics at delivery. Using the groups created by the trees, we constructed enrollment propensity weights. Then we analyzed the weighted data using models that reduced the variance based on a finite population correction. The results were largely similar to the original unweighted analysis (RR 0.91, 95% CI 0.83, 1.01 pre-weighting, RR 0.89, 95% CI 0.79, 0.99 post-weighting for death/chronic lung disease and RR 1.27, 95% 1.01, 1.60 pre-weighting, RR 1.26, 95% CI 0.98, 1.62 post-weighting for death) ~~.~~

Although weighting to reflect the characteristics of the larger population is common in survey statistics, to our knowledge the approach has not been used to explore the generalizability of results from randomized trials conducted on convenience samples of eligible patients. When adequate data on the eligible population are available and enrolled individuals are known to differ from those not enrolled, these methods provide a means to assess the sensitivity of trial results to such differences.

From: Rich, Wade
To: Gantz, Marie; Wally Carlo, M.D.; Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Creel, Darryl; Das, Abhik
Subject: RE: SUPPORT weighted analysis
Date: Monday, November 28, 2011 6:09:22 PM

Hi Marie,

Does the data table you provided previously get included with this abstract, or is the line about data being largely similar to the original trial the only reporting of the results?
Wade

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Monday, November 28, 2011 1:50 PM
To: Rich, Wade; Wally Carlo, M.D.; Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Creel, Darryl; Das, Abhik
Subject: RE: SUPPORT weighted analysis

Hello again,

Neil and I had a good discussion on the phone today. In response to that discussion, I am sending a revision of the abstract that I hope better reflects our intention to do a sensitivity analysis to explore the possible impact of enrolling a more representative population in SUPPORT. This analysis was originally discussed at a conference call about the antenatal consent analysis that compared the outcomes of enrolled and non-enrolled infants, during which Abhik suggested using weighting as an exploratory means of looking at the data. It is not meant to undermine the findings of the antenatal consent papers or to suggest that the original SUPPORT results require defending. Rather, it was meant to take advantage of the fact that we do have data on the non-enrolled infants and to see if there was any signal that our results would have differed greatly if the enrolled population had been different. We did not find such a signal (which we find reassuring) but, as Neil wisely points out, there is truly no way of knowing what would have happened if we had enrolled different infants. Please note that this abstract was written for submission for the annual meeting of the Society for Clinical Trials, which is a meeting of biostatisticians and focuses on methods for clinical trial research.

Please let me know if you have any remaining concerns about us submitting the abstract for the SCT meeting. And, if we are to go forward, Wade, please let me know if you are interested in being listed as an author. Either way, we appreciate your input.

Marie

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From: Gantz, Marie
Sent: Monday, November 28, 2011 11:29 AM

To: 'Rich, Wade'; Wally Carlo, M.D.; Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Creel, Darryl; Das, Abhik
Subject: RE: SUPPORT weighted analysis

Hi all,

First, I want to apologize for causing such dissention within this group. Neil and Wade, I was surprised by your reactions to the abstract, but as I read through your emails I understand where you are coming from, and I certainly respect your point of view. After reading your concerns, I also think we could have been clearer about the intent and conclusions of this abstract, and so I want to clarify a few points.

In no way did we intend to undermine either the results of the antenatal consent study or the original analysis of the SUPPORT data. The antenatal consent papers have clearly pointed out the pitfalls of the antenatal consent requirement for SUPPORT and the consequence that the enrolled infants were healthier than the eligible population. Once concern is that that result might cause readers to question the generalizability of the SUPPORT study. That is not a criticism of SUPPORT, nor do I think we need to defend SUPPORT, which I think was a very valuable and well-executed study.

That being said, this analysis was motivated by the fact that, unlike most clinical trials, we had access to data on the entire eligible population. That put us in the unique position of being able to do some exploratory analysis of the possible differences in the results we could have seen if the enrolled population had been more representative of the eligible population. In the analysis, we gave more weight to the less-healthy infants to explore whether the results might have changed if more infants like them (with respect not only to demographics but also everything else that happened to them in the hospital, including DR and other interventions) had been enrolled. As we expected, giving the less-healthy infants more weight resulted in a higher estimated rate of BPD. However, it did not substantially change the estimates of the impact of the SUPPORT interventions on reducing BPD. This is reassuring because it does not provide evidence that the SUPPORT results are not generalizable. Nor does it prove that they are generalizable. As Neil pointed out, we cannot truly know how the results would have changed if our enrolled population had been different. We fully agree with that statement and should have made that more clear in the abstract. This analysis was intended only as one possible sensitivity analysis to explore the robustness of the SUPPORT results, and should not be taken as anything else. This approach is not typically used in clinical trials, in part because most trials do not have the extent of data on the eligible, non-enrolled population that we did. However, these methods are widely used in survey analysis, including political opinion and exit polls which always adjust their sample to reflect the national likely voter population.

I hope that this helps clarify what we were intending to do with this analysis. We would never intend to shrug-off or undermine the work of any of the studies of the NRN. Like you, our intention is to do the best studies we can to improve the outcomes of a very vulnerable population of infants. I have the greatest respect for those of you who work with those patients in person every day. I don't think I would have the strength to do so, but I am happy to be in the background lending my support to those efforts in whatever way I can. I have truly enjoyed working with you all on SUPPORT and on other studies, and I look forward to continuing to do so.

Marie

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From: Rich, Wade [mailto:wrich@ucsd.edu]
Sent: Thursday, November 24, 2011 2:07 PM
To: Wally Carlo, M.D.; Finer, Neil; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Creel, Darryl; Das, Abhik
Subject: RE: SUPPORT weighted analysis

If the intent of this analysis is to shrug off the outcome data from the antenatal consent studies and suggest what they found is not valid, I am not interested in participating. I do not believe the this analysis provides "reassurance that the trial results are broadly applicable to the eligible NICU population." The truth is, we enrolled a population that was overall healthier than the group that was eligible which we did not enroll. That is not a knock on the trial, or the centers, or the coordinators. It simply shows that the process of antenatal consent effects trial enrollment. This may be an interesting intellectual exercise, but I do not think it in any way shows that the results of the SUPPORT trial would have been the same if the infants who were eligible but not enrolled had been included. That is information we just do not know, and cannot find out mathematically. If you all feel you should continue with this, please know that you are doing so against my wishes.
Wade

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Wednesday, November 23, 2011 5:54 PM
To: Finer, Neil; Gantz, Marie; Rich, Wade; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Creel, Darryl; Das, Abhik
Subject: RE: SUPPORT weighted analysis

Dear Neil:

I hear your concerns. This is complex modeling that if it is hard for us, imagine for the usual clinical neonatologist.

However, the SUPPORT trial results have been undermined by the concerns raised by some that the results are not generalizable because of high ANS steroid use and high non enrollment rates of eligible subjects.

We need to do this analysis and publish it. I actually do not think the analysis is so complex and the importance of the results overwhelmingly overrides all concerns as far as I understand but maybe I am missing something.

I think this is an extremely important study. Otherwise, other may have the last word on the issue of

generalizability of our study.

Wally

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Sent: Wednesday, November 23, 2011 5:10 PM
To: Gantz, Marie; Rich, Wade; Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Creel, Darryl; Das, Abhik
Subject: RE: SUPPORT weighted analysis

Hi Marie and Abhik
I have reviewed what you did for this analysis
I have a number of comments
First the analysis is anything but simple and would not be easily understood by many
It is not clear to me that the subsequent occurrence of death and IVH was exclusively related to the antenatal factors
These were the significant differences between the groups which probably requires a more detailed look at the initial level of illness, DR intervention, occurrence of hypotension
In addition How do we know what the effect of either Surf or CPAP would be on the non-enrolled infants
We know they were likely more compromised at birth, but we do not know how such infants would have responded to these interventions
I do not see how your analyses accounted for this – nor do I know how you would do this
I have a great concern that this group – the non-enrolled would most likely have required more DR interventions, needed perhaps more Epi, more DR intubation for resusc etc. These could all reduce the likelihood that you would find a difference between the 2 interventions
I am NOT a statistician
I am a clinician – so what I say probably does not measure up as a P value or a regression
But I remain concerned that this analyses is a problem
Neil

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Monday, November 21, 2011 8:54 AM
To: Rich, Wade; Finer, Neil; Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Creel, Darryl; Das, Abhik
Subject: SUPPORT weighted analysis

Importance: High

Attached are two items: (1) results of the weighted analysis of SUPPORT data (in which the enrolled infants are weighted to reflect the characteristics of the eligible population), and (2) an abstract for the Society for Clinical Trials meeting in May on the statistical methods used for this analysis. Wade is listed as a coauthor on the abstract, which we would like to submit for SUPPORT subcommittee and Steering Committee approval this week (the abstract deadline is December 1). Please let us know if you have any comments on the abstract. We would like to send it to the subcommittee today so that we can request SC approval on the call tomorrow afternoon.

If you have any questions about the weighted analysis, please let Darryl and I know. Darryl does survey analysis at RTI, and he performed the weighting and weighted analyses presented in the attached.

Thanks,
Marie

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]; "Myriam Peralta, M.D."; "Finer, Neil"; "Wally Carlo, M.D."; "Michele Walsh"; "Gantz, Marie"; "Laptook, Abbot"; "Bradley Yoder"; "Roger Faix"; "Abhik Das (Adas@rti.org)"; "Rich, Wade"; "kurt.schibler@cchmc.org"; "nancy newman"; "Vohr, Betty"; "Susan Hintz"; "Kim Yolton"; "Roy Heyne"; (b)(6) @aol.com"; "goldb008@mc.duke.edu"; "Michael.Acarregui@providence.org"; "Evans, Patricia W"; "Adams-Chapman, Ira"; "Pappas, Athina"; "Anna M. Dusick, MD"; "emcgowan@tuftsmedicalcenter.org"; "Ehrenkranz, Richard"; "abodnar@utah.gov"; "Bauer, Charles R"; "JaFuller@salud. unm. edu (JaFuller@salud.unm.edu)"; "Michael O`Shea"; "gary_myers@URMC.Rochester.edu"
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Subject: UPDATED SUPPORT OXIMETRY PAPER
Date: Monday, November 28, 2011 2:35:00 PM
Attachments: Support O2 NDI 11-20-2011wc (3).doc
Importance: High

Hi
For those of you who have not yet commented, here is a revised version of the oximetry paper.

Thanks for all your input.

Rose

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Cc: 'yvaucher@ucsd.edu'; 'Pablo Sanchez'; 'Shankaran, Seetha'; 'Duara, Shahnaz'; 'Barbara Stoll'; 'Poindexter, Brenda B'; 'Krisa Van Meurs'; 'Kennedy, Kathleen A'; 'goldb008@mc.duke.edu'; 'Phelps, Dale'; 'Bell, Edward (Pediatrics)'; 'Frantz, Ivan'; 'Kristi Watterberg'; Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: SUPPORT CPAP PAPER

Hi All,
Here is the SUPPORT oximetry paper and the CONSORT diagram. Please send all suggestions back to Myriam by **December 6**.
The papers will then go for internal NRN review.

I have also included the site PI's.

Thanks for all the hard work and effort!
Rose

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From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Saturday, November 19, 2011 7:55 AM
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Cc: yvaucher@ucsd.edu; Pablo Sanchez; 'Shankaran, Seetha'; 'Duara, Shahnaz'; Barbara Stoll; 'Poindexter, Brenda B'; 'Krisa Van Meurs'; 'Kennedy, Kathleen A'; goldb008@mc.duke.edu; 'Phelps, Dale'; 'Bell, Edward (Pediatrics)'; 'Frantz, Ivan'; 'Kristi Watterberg'; Archer, Stephanie (NIH/NICHD) [E]
Subject: SUPPORT CPAP PAPER
Importance: High

Hi,
Attached is the SUPPORT CPAP FU Paper for co-author input. Please send your comments to Yvonne Vaucher (yvaucher@ucsd.edu) by **DECEMBER 3**. The paper will then go for internal NRN review and clearance. Following this, it will be submitted along with the oximetry FU paper (you will get this in the next few days) to the New England Journal of Medicine.
I have also included the steering committee PI's from the sites involved with the study. If you have any suggestions, feel free to forward them to Yvonne. Thanks to everyone for all the hard work, effort and commitment to this study!!
Rose

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Neurodevelopmental Outcome of Extremely Preterm Infants in a Trial of Different Oxygen Saturation Targets

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Word Count

Abstract: 248

Text: 1,148

ABSTRACT

BACKGROUND

Targeting lower (vs. higher) oxygen saturations in the SUPPORT Trial decreased severe retinopathy of prematurity but increased mortality before discharge. Our pre-specified hypothesis was that compared to higher oxygen saturation targets, lower oxygen saturation targeting will decrease the risk of the composite outcome of death or long term neurodevelopmental impairment.

METHODS

Infants born at 24 to 27 week gestation were randomized to higher (91-95%) or lower oxygen saturation targets (85-89%) from birth to 36 weeks corrected age. The primary outcome of the follow up study was a composite of death or neurodevelopment impairment at 18 to 22 months corrected age. Neurodevelopmental impairment (NDI) was defined as a Bayley III cognitive composite score of less than 70, modified Gross Motor Function Classification System ≥2, moderate to severe cerebral palsy, permanent hearing loss, and/or bilateral blindness. Results were adjusted for gestational age stratum, center and familial clustering.

RESULTS

The primary outcome was determined for 1234/1316 (93.8%) of infants enrolled in SUPPORT; 93.6% (990/1058) of survivors were evaluated at 18 to 22 months corrected age. Death or NDI occurred in 30.2% (185/612) infants in the lower oxygen saturation group and 27.5% (171/622) infants in the higher oxygen saturation group (relative risk 1.12; 95% confidence interval 0.94, 1.32; p=0.21). Death occurred in 140 (22.1%) of the children in the lower oxygen saturation

Comment [WC1]: Should this say "Analyses" instead of Results? Ask Abhik/Marie

group and in 118 (18.2%) in the higher oxygen saturation group (relative risk 1.25; 95% confidence interval 1, 1.55, p=0.046). NDI was present in 9.5% (45/472) of the lower oxygen saturation group and 10.5 % (53/504) of the higher oxygen saturation group survivors (relative risk 0.87, 95% confidence interval 0.6, 1.28; p=0.49.

CONCLUSIONS

Among extremely preterm infants targeted at different levels of oxygen saturation, no significant difference in death or neurodevelopmental impairment was observed at 18 to 22 months. Mortality at 18 to 22 months was increased in the lower oxygen saturation target group.

BACKGROUND

Oxygen supplementation is a vital therapy for survival of many preterm infants with respiratory disorders. However, oxygen supplementation may increase the risk of retinopathy of prematurity, bronchopulmonary dysplasia, [1] periventricular leukomalacia,[2] and cerebral palsy [3] Restrictive oxygen therapy decreases retinopathy but has resulted in increased deaths in recent randomized controlled trials. [4,5,6,7]

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development SUPPORT Trial demonstrated no significant difference in a composite outcome of severe retinopathy of prematurity or death before discharge between a lower oxygen saturation target group (85-89%) and a higher oxygen saturation target group (91-95%). However, death before discharge was increased (19.9% vs. 16.2%; relative risk 1.27; 95% CI 1.01 to 1.6; p=0.04) and severe retinopathy of prematurity among survivors was decreased (8.6% vs. 17.9%; relative risk 0.52; 95% CI 0.37 to 0.73; p<0.001) in the lower oxygen saturation target group compared to the higher saturation target group. [6] A recent meta-analysis that included the SUPPORT Trial and three other subsequently completed multi-center randomized controlled trials with a total of 3631 infants showed that infants randomized to an oxygen saturation target of 91-95% % had a lower mortality rate than infants randomized to oxygen saturation targets of 85-89% (14.4% versus 17.3% respectively, P=0.015). [7] The effects of oxygen on the immature brain are not clearly understood. [8] Oxidative stress injury in the premature infant may have many underlying pathophysiological processes. There has been a keen interest in determining whether higher or lower oxygen supplementation can reduce neurodevelopmental impairment. [7] However, in two non randomized studies of oxygen saturation targeting,[1,9] neurodevelopmental outcome did not differ by oxygen targets.

This study evaluated the composite outcome of death or neurodevelopmental impairment at 18 to 22 months corrected age in the subjects enrolled in the SUPPORT trial and randomized to lower (85-89%) or higher oxygen saturation targets (91-95%) from birth to 36 weeks corrected age. The pre-specified hypothesis in the SUPPORT trial was that compared to a higher oxygen saturation target, a lower saturation target decreases the risk of the composite outcome of death or neurodevelopmental impairment.

METHODS

Study Design

Extremely preterm infants (24 weeks 0 days to 27 weeks 6 days) born between February 2005 and February 2009 at 20 centers in the United States participating in the Neonatal Research Network of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development were enrolled at delivery in the randomized controlled SUPPORT trial. Permuted block randomization was used, with stratification according to center and gestational age (24 weeks 0 days to 25 weeks 6 days or 26 weeks 0 days to 27 weeks 6 days). The infants were randomly assigned in the delivery room to a target range of oxygen saturation of 85% to 89% (the lower oxygen saturation group) or 91 to 95% (the higher oxygenation group). Using a 2-by-2 factorial design, participants were also randomly assigned to receive either CPAP immediately following delivery and a limited ventilation strategy if subsequent intubation was required or intubation with surfactant administration within an hour after birth. Procedures for enrollment, intervention and data collection have been previously reported. [6]. The study was approved by the institutional review board at each participating center and at RTI International which is the

independent data coordinating center for the Neonatal Research Network. Written informed consent was obtained from the parents or guardians of each child before delivery. Also consent was obtained for the follow up at 18-22 months corrected age.

Assessments

A comprehensive neurodevelopmental assessment was performed on survivors at 18-22 months corrected age by neurologic examiners and neurodevelopmental testers who were unaware of the treatment assignments and had been trained annually for reliability of assessments during a 2-day workshop. Developmental status was assessed using the Bayley Scales of Infant and Toddler Development 3rd edition (BSID III) [10]. Cognitive Composite Scores are reported as a standardized score with a mean of 100 and a standard deviation of 15. Examiners also recorded the presence of cerebral palsy defined as a non-progressive disorder of the central nervous system and characterized by abnormal muscle tone in at least one arm or leg associated with abnormal control of movement or posture with delayed attainment of motor milestones.[11] The modified Gross Motor Function Classification System (GMFCS) [12] was used to classify gross motor performance using a range from 0 (normal) to 5 (most impaired). Cerebral palsy was classified depending on severity into mild (GMFCS $\leq$1), moderate (GMFCS 2 or 3) or severe (GMFCS $\geq$ 4). Hearing and visual impairment were determined based on parent report and examination.

Certified research nurses collected demographic and neonatal data using NRN definitions. Data collected included gestational age, birth weight, gender, multiple gestation, race/ethnicity, retinopathy or prematurity status, bronchopulmonary dysplasia, history of medical or surgical necrotizing enterocolitis (modified Bell's stage $\geq$ 2),grades 3-4 intraventricular hemorrhage or

periventricular leukomalacia, history of late onset sepsis, use of postnatal steroids. Socioeconomic variables included insurance status, maternal marital status, maternal education, household income, language spoken at home, and whether living with biological parents. Socioeconomic data from the neonatal period were used and when not available, data updated at the 18-22 month visit were used. Outcomes following NICU discharge included rehospitalizations, interim medical history, surgery, and medications were recorded at the 18-22 month visit.

Outcome

The composite of death or neurodevelopmental impairment at 18 to 22 months corrected age for prematurity was the pre-specified primary follow up outcome for the SUPPORT trial. This composite outcome was selected because (a) the data are available on the entire randomized trial cohort, (b) infants who died before 18 months could not be classified as having neurodevelopmental impairment and (c) death can be considered as a competing outcome to neurodevelopmental impairment among survivors. Neurodevelopmental impairment was defined as having any of the following: BSID III cognitive composite score less than 70, GMFCS $\geq$ 2, presence of moderate or severe cerebral palsy, permanent hearing loss that does not permit the child to understand directions of the examiner and communicate despite amplification with hearing aids, or bilateral visual impairment (vision < 20/200).

Comment [WC2]: Are these two not the same thing? It appears like that from your description of the methods.

Analysis

Data were entered in standard forms and were transmitted to the Neonatal Research Network Data Coordinating Center at RTI International which stored, managed and analyzed the data for this study. Details regarding sample size calculations for the SUPPORT trial have been previously reported [6]. The sample size calculations were based on infants born in the year 2000 which included the rate of death or neurodevelopmental impairment at 18-22 months corrected age. All analyses were performed according to the intention to treat principle. Unadjusted comparisons of birth and demographic characteristics between treatment groups were conducted using chi-square tests for categorical variables and t tests for continuous variables. The primary analysis focused on the percentage of infants in each group for whom the primary outcome of death or NDI at 18 to 22 months corrected age could be assigned. Analysis of this and all other categorical outcomes was performed with the used of robust Poisson regression in a generalized-estimating-equation model to obtain adjusted relative risks with 95% confidence intervals. The denominator that was used to calculate the rate of each outcome was the number of infants for whom the outcome was known. Continuous outcomes were analyzed with the use of mixed-effects linear models to obtain adjusted means and standard errors. Pre-specified subgroup analyses were also conducted within each gestational age strata.

In the analysis of all neonatal and follow-up outcomes, the results were adjusted, as pre-specified, for gestational-age strata, center, and familial clustering (because multiple births from the same mother were randomized to the same treatment group). Two-sided p values of less than 0.05 were considered to indicate statistical significance. For the 79 secondary outcomes analyzed according to treatment, we would expect no more than 4 tests to have p values of less than 0.05 on the basis of chance alone. Subgroup analyses were conducted within pre-specified gestational age strata for the same outcomes. Although these tests have not been adjusted for multiple

comparisons, we would expect no more than 4 tests per stratum to have p values of less than 0.05 on the basis of chance alone.

RESULTS

Characteristics of the Study Sample

The SUPPORT trial enrolled 1316 infants (Figure 1). The baseline characteristics and hospital outcomes of the entire group have been reported.[6] Five hundred twenty four infants in the lower oxygen saturation group and 555 in the higher oxygen saturation group survived to discharge or transfer from the hospital. Ten children in the lower oxygen saturation group and 11 children in the higher oxygen saturation group died after discharge from the nursery and prior to the 18 to 22 month corrected age follow up visit. Thirty five children in the lower saturation group and 33 children in the higher saturation group were not evaluated in the follow up visit. However, 14/35 in the lower saturation group and 19/33 in the higher saturation group were known to be alive at 18 to 22 months corrected age. Neurodevelopmental assessment was performed in 990/1058 infants who were thought to be alive (93.6%). Of those who were evaluated at the 18 to 22 months corrected age, neurodevelopmental status was determined in 976 children. From the entire cohort, the pre-specified outcome of death or neurodevelopmental impairment could be determined in 93.8% (1234/1316) of enrolled children. Compared to mothers of infants who were followed, mothers of infants who were lost to follow up were less likely to be married (31 vs. 47% p=0.01) and more likely to have only public health insurance (69 vs. 52% p=0.008). There were no other significant differences in any of the other baseline characteristics of the cohort that was followed up and those lost to follow up. The mean corrected age for

Comment [WC3]: Use decimals for %s as the denominators are generally more than 100

neurodevelopmental evaluation was similar between both groups (lower oxygen saturation, 19.9 ± 2.4 months vs. higher oxygen saturation 20.2 ± 2.7 months, p=0.08).

Baseline characteristics of the follow up cohort and the entire trial cohort are presented in Table 1. Among children who were followed, the percentage of infants who were small for gestational age was greater in the higher oxygen saturation target group compared to the lower saturation target group. In addition, as reported previously[6] the incidence of severe retinopathy of prematurity was higher in the higher oxygen saturation group compared to the lower saturation group but no other significant differences were found in the baseline characteristics or major hospital outcomes of the infants with follow up data.

Primary Outcome

The prevalence of the composite primary outcome of death or neurodevelopmental impairment was not significantly different between the lower (185/612, 30.2%) and higher (171/662, 27.5%) oxygen saturation target groups (relative risk 1.12, 95% confidence interval 0.94, 1.32; p=0.21). (Table 2) In the 24 to 25 weeks gestational age stratum, primary outcome data were available for 261 of 276 children in the lower saturation group and 276 of 289 in the higher saturation group. For the age stratum 26 to 27 weeks gestation, outcome data were available for 351 of 378 of the lower oxygen saturation group and 346 of 373 of the higher oxygen saturation group. Similar to the entire cohort there were no significant differences in the prevalence of death or neurodevelopmental impairment within both gestational age strata as shown in table 2.

Components of the Primary Outcome

Death prior to the 18 to 22 month adjusted age visit occurred significantly more often among infants in the lower oxygen saturation target group compared to those in the higher saturation

target group (lower oxygen saturation, 140/633, 22.1% vs. higher oxygen saturation, 118/648, 18.2%; relative risk 1.25; 95% CI 1, 1.55, p=0.046). The rate of neurodevelopmental impairment among survivors followed at the 18 to 22 month corrected age visit was similar between the lower and the higher oxygen saturation target groups (45/472, 9.5% vs. 53/504, 10.5%; relative risk 0.87 95%CI 0.6, 1.28, p=0.49)

Other outcomes among survivors at follow up

The percentage of children with BSID III cognitive scores below 70 was not significantly different between the lower and higher oxygen saturation group, nor was the percentage of children with cognitive scores below 85. Adjusted means of cognitive composite scores were not significantly different between the two groups and are presented in table 3.

The rates of severe retinopathy of prematurity and eye surgery among survivors to follow up were higher in the higher oxygen target group compared to the lower oxygen target group; however the rate of bilateral (lower oxygen saturation, 1% vs higher oxygen saturation, 1.6%, relative risk 0.67, 95% CI 0.22, 2.02; p=0.48) or unilateral blindness were not significantly different at the 18 to 22 month corrected age visit. Other visual outcomes are presented in Table 3.

Comment [WC4]: Give decimal

Comment [WC5]: Maybe the data exact data should not be presented for either of should be presented for both

Overall readmission rates and readmission rates for respiratory problems were not significantly different between both groups. There were no significantly differences in after discharge use of bronchodilators, steroids, diuretics or any other medication. (Table 3)

DISCUSSION

In this multicenter follow up study of infants randomized to a lower target range of oxygen saturation (85 to 89%) or to higher target oxygen saturation (91 to 95%), a significant difference between treatment groups was not found in the pre-specified outcome of death or neurodevelopmental impairment at 18-22 months corrected age. To our knowledge this is the only large comprehensive study that has included neurodevelopmental impairment as an outcome for evaluating effects of different oxygen target saturation levels started at birth in extremely premature babies within a randomized multicenter trial but outcomes of other similarly designed trials will be reported[7]. The results of recent trials have raised concerns about using lower oxygen saturation targets because of potentially increased mortality in extremely premature infants [6,7,13]. In these trials, it was found that death prior to discharge in the SUPPORT trial was increased among children randomized to lower target saturation levels, and this difference persisted at 18 to 22 months corrected age in the current follow up study.

We had reported previously that the lower saturation oxygen target was associated with a large reduction in the incidence of severe retinopathy of prematurity among survivors. [6] It has been previously reported that severe ROP may be associated with poor visual outcomes even with treatment [14,15] Although our study was not designed to collect detailed data on eye disorders or visual function at 18 to 22 months of age we found that there were no significant differences in the report of unilateral and bilateral blindness between the two groups. Eye surgery was higher in the group with a higher oxygen saturation target and was likely related to higher incidence of severe retinopathy of prematurity in this group and our criteria used to define severe retinopathy of prematurity [6]. Specific visual outcomes of eye function after the presence of retinopathy of prematurity were also not included in the outcome data collected in this trial. However, we did

not find a significant difference in other reported visual outcomes like nystagmus, strabismus or use of corrective lenses.

There had been concerns that lower oxygen saturation targets might increased the risk of long term neurodevelopmental impairment[5]. However, NDI as defined in this study was not found to be significantly different between survivors in the lower and higher oxygen saturation groups. In addition the incidence of cerebral palsy did not differ between the treatment groups, though it is noteworthy that the incidence of cerebral palsy was lower than previously reported in other outcome studies.[16]

It has been recognized that higher oxygen levels can be associated with chronic lung disease. However, we found no difference in the use of postnatal corticosteroids or diuretics at 18 to 22 months corrected age or in the persistent oxygen use at 18 to 22 months of age or in rehospitalizations between the two groups.

A limitation of this study is that it reports only follow up to 18 to 22 months corrected age, which may not been enough time to detect the presence of minor but important disabilities. It has also been reported that the BSID III may result in higher cognitive scores than an earlier vision of the Bayley Scales of Infant development (BSID-II); and a lower sensitivity if a cognitive composite score of less than 70 is used as the criterion for impairment[17 18]. Use of a cutoff of less than 85 for the Bayley III cognitive composite scores did not find significant differences between the groups. There is an ongoing follow up SUPPORT study that will be reporting the outcome of these children at school age. Although we included 20 centers scattered throughout the US, all were tertiary care centers, which might limit the generalizibility of our conclusions.

In summary, we found no significant differences in death or neurodevelopmental impairment at 18 to 22 months corrected age in extremely premature infants who were randomized to a lower target oxygen saturation or higher target oxygen saturation. The increased death rate at discharge that was previously reported in the lower target oxygen saturation group was still present at 18 to 22 months corrected age. Although higher rates of retinopathy of prematurity were associated with higher oxygen saturation target levels, blindness was not significantly different among survivors at 18 to 22 months.

Acknowledgements

The National Institutes of Health, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), and the National Heart, Lung, and Blood Institute (NHLBI) provided grant support for the Neonatal Research Network's SUPPORT Trial.

Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Drs. Abhik Das (DCC Principal Investigator) and Marie Gantz (DCC Statistician) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study. The following investigators, in addition to those listed as authors, participated in this study:

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Comment [WC6]: This is published in NEJM 2011. Ben Stenson is the first author

Comment [WC7]: I would not reference old abstracts like this. See if the paper was ever published

Table 1. Baseline characteristics of the SUPPORT group

Characteristic	Trial Cohort		Cohort with Follow-up Visit	
	Lower Oxygen Saturation	Higher Oxygen Saturation	Lower Oxygen Saturation	Higher O: Saturat
	N=654	N=662	N=479	N=51
Birth weight – g	835.5 ± 193.4	824.8± 193	857.8 ± 186.3	843.7± 1
Gestational age – wk	26.2 ± 1.1	26.1 ± 1.1	26.3 ± 1.1	26.2 ±
Small for gestational age – no./total no. (%)	41/654 (6.3)	55/662 (8.3)	17/479 (3.5)*	38/511 (
Male sex – no./total no. (%)	341/654 (52.1)	371/662 (56.0)	240/479 (50.1)	282/511 (
Race or ethnic group – no./total no. (%)				
Non Hispanic Black	257/654 (39.3)	232/662 (35.0)	201/479 (42.0)	176/511 (
Non Hispanic White	242/654 (37.0)	279/662 (42.1)	178/479 (37.2)	218/511 (
Hispanic	132/654 (20.2)	127/662 (19.2)	86/479 (18.0)	97/511 (
Other or unknown	23/654 (3.5)	24/662 (3.6)	14/479 (2.9)	20/511 (
Multiple births – no./total no. (%)	161/654 (24.6)	176/662 (26.6)	124/479 (25.9)	128/511
Maternal educational level <high school no./total no. (%)	148/594 (24.9)	165/612 (27.0)	115/471 (24.4)	129/504 (
Public health insurance only – no./total no. (%)	356/650 (54.8)	348/660 (52.7)	253/479 (52.8)	266/511 (

Mother married – no./total no. (%)	284/652 (43.6)	308/661 (46.6)	222/479 (46.3)	243/511 (
Lives with both biological parents – no./total no. (%)†	354/508 (69.7)	364/547 (66.5)	332/478 (69.5)	345/511 (
Household income < $30,000/year – no./total no.(%) †	247/474 (52.1)	291/528 (55.1)	239/456 (52.4)	272/498 (
English as primary language – no./total no. (%)‡	402/477 (84.3)	429/513 (83.6)	402/477 (84.3)	427/511 (
Cesarean section – no./total no. (%)	441/654 (67.4)	442/662 (66.8)	332/479 (69.3)	335/511 (
Antenatal steroids – no./total no. (%)	633/654 (96.8)	632/661 (95.6)	462/479 (96.5)	487/511 (
Severe retinopathy of prematurity – no./total no. (%)†	41/475 (8.6)**	91/509 (17.9)**	38/442 (8.6)**	82/471 (1'
Bronchopulmonary dysplasia – no./total no. (%)¶	205/540 (38.0)	237/568 (41.7)	177/479 (37.0)	203/511 (
Intraventricular hemorrhage grade 3 or 4 or Periventricular leukomalacia – no./total no. (%)	98/630 (15.6)	100/640 (15.6)	56/478 (11.7)	60/510 (
Necrotizing enterocolitis – no./total no. (%)	76/641 (11.9)	70/649 (10.8)	42/479 (8.8)	44/511 (
Late onset sepsis/meningitis – no./total no. (%)	228/624 (36.5)	226/634 (35.6)		
155/479 (32.4)	166/511 (32.5)			
Post natal steroids – no./total no. (%)	61/636 (9.6)	69/644 (10.7)		
41/477 (8.6)	48/507 (9.5)			
CPAP – no./total no. (%)	336/654 (51.4)	327/662 (49.4)		
254/479(53.0)	257/511 (50.3)			
Surfactant – no./total no. (%)	318/654 (48.6)	335/662 (50.6)		
225/479 (47.0)	254/511 (49.7)			

*p<0.01, **p<0.001

† Available only for infant who survived to discharge or transfer

‡ Only available at 18-22 months corrected age

¶ Among survivors to 36 weeks postmenstrual age

Table 2. Primary Outcomes at 18-22 Months Corrected Age

Outcome	Lower Oxygen Saturation N=654	Higher Oxygen Saturation N=662	Adjusted Relative Risk
Outcome determined for death or NDI – no./total no. (%)	612/654 (93.6)	622/662 (94)	1 (0.97, 1.03)
Neurodevelopmental impairment or death – no./total no. (%)	185/612 (30.2)	171/622 (27.5)	1.12 (0.94, 1.32)
Died by 18-22 months – no./total no. (%)	140/633 (22.1)	118/648 (18.2)	1.25 (1, 1.55)
Survivors at follow-up			
Neurodevelopmental impairment – no./total no. (%)	45/472 (9.5)	53/504 (10.5)	0.87 (0.6, 1.28)
Bayley III cognitive composite score < 70 – no./total no. (%)	34/471 (7.2)	38/503 (7.6)	0.91 (0.58, 1.43)
Gross motor function level ≥ 2 – no./total no. (%)	26/479 (5.4)	23/511 (4.5)	1.17 (0.68, 2.01)
Moderate/severe cerebral palsy – no./total no. (%)	20/479 (4.2)	20/511 (3.9)	1 (0.54, 1.83)
Blindness – no./total no. (%)	5/479 (1)	6/511 (1.2)	0.9 (0.28. 2.9)
Hearing Impairment – no./total no. (%)	12/479 (2.5)	12/511 (2.3)	1.16 (0.54, 2.49)
24 0/7 to 25 6/7 weeks gestational age strata	276	289	
Neurodevelopmental impairment or death – no./total no. (%)	115/261 (44.1)	112/276 (40.6)	1.09 (0.89, 1.32)
Died by 18-22 months – no./total no. (%)	91/267(34.1)	79/283 (27.9)	1.23 (0.95, 1.59)
Survivors at follow-up			
Neurodevelopmental impairment – no./total no. (%)	24/170 (14.1)	33/197 (16.8)	0.8 (0.49, 1.3)
Bayley III cognitive composite score < 70 – no./total no. (%)	17/169 (10.1)	22/196 (11.2)	0.86 (0.47, 1.56)
Gross motor function level ≥ 2 – no./total no. (%)	13/173 (7.5)	13/200 (6.5)	1.07 (0.53, 2.17)
Moderate/severe cerebral palsy – no./total no. (%)	10/173 (5.8)	12/200(6.0)	0.86(0.39, 1.88)
Blindness – no./total no. (%)	1/173 (0.6)	3/200 (1.5)	0.39 (0.04, 3.69)

Hearing Impairment – no./total no. (%)	4/173 (2.3)	10/200 (5.0)	0.5 (0.16, 1.53)
26 0/7 to 27 6/7 weeks gestational age strata	378	373	
Neurodevelopmental impairment or death – no./total no. (%)	70/351(19.9)	59/346 (17.1)	1.17 (0.85, 1.6)
Died by 18-22 months – no./total no. (%)	49/366(13.4)	39/365(10.7)	1.28 (0.86, 1.89)
Survivors at follow-up			
Neurodevelopmental impairment – no./total no. (%)	21/302(7.0)	20/307(6.5)	0.99(0.54, 1.84)
Bayley III cognitive composite score < 70 – no./total no. (%)	17/302 (5.6)	16/307(5.2)	0.98 (0.49, 1.97)
Gross motor function level ≥ 2 – no./total no. (%)	13/306(4.2)	10/311 (3.2)	1.32(0.57, 3.01)
Moderate/severe cerebral palsy – no./total no. (%)	10/306(3.3)	8/311(2.6)	1.22(0.47, 3.2)
Blindness – no./total no. (%)	4/306 (1.3)	3/311(1.0)	1.38 (0.31, 6.05)
Hearing Impairment – no./total no. (%)	8/306 (2.6)	2/311 (0.6)	4.18(0.88, 19.87)

Table 3. Other Outcomes at 18 to 22 months corrected age by Group

Outcome	Lower Oxygen Saturation (N=479)	Higher Oxygen Saturation (N=510)	Relative Risk for Lower vs. Higher Oxygen Saturation (95% CI)	Adjusted difference in means (95% CI)	Adj P-v
Bayley Scales of Infant Development III					
Cognitive composite < 70	34/471 (7.2)	38/503 (7.6)	0.91 (0.58, 1.43)		0.
Cognitive composite <85	105/471 (22.3)	132/503 (26.2)	0.85 (0.68, 1.07)		0.
Adjusted mean cognitive composite scores ± standard error	92.2 ± 0.8	90.5 ± 0.7		0.7 (-1.2, 2.5)	0.
Median cognitive composite scores (interquartile range)	90 (85, 100)	90 (80, 100)			
Neurologic findings					
Mild cerebral palsy vs. none	23/459 (5.0)	21/490 (4.3)	1.16 (0.66, 2.02)		0.
Moderate cerebral palsy vs. none	11/447 (2.5)	10/479 (2.1)	1.19 (0.52, 2.71)		0.
Severe cerebral palsy vs. none	9/445 (2.0)	10/479 (2.1)	0.95 (0.39, 2.27)		0.
Any cerebral palsy	43/479 (9.0)	41/510 (8.0)	1.12 (0.76, 1.65)		0.
Any abnormal neurologic exam	108/479 (22.5)	114/511 (22.3)	1.02 (0.82, 1.28)		0.
Vision/Eye findings					

Strabismus	46/478 (9.6)	41/510 (8)	1.2 (0.8, 1.8)	0.
Nystagmus	22/479 (4.6)	13/510 (2.4)	1.81 (0.89, 3.69)	0.
Tracks 180 degrees	462/476 (97.1)	492/506 (97.2)	1 (0.98, 1.02)	0.
Corrective lenses both eyes	21/468 (4.5)	20/493 (4.1)	1.14 (0.62, 2.08)	0.
Blind, some function, both eyes vs. normal	3/450 (0.7)	2/475 (0.4)	1.57 (0.27, 8.96)	0.
Blind, no useful vision, both eyes vs. normal	2/449 (0.4)	4/477 (0.8)	0.54 (0.1, 2.96)	0.
Other abnormal eye findings vs. normal	6/453 (1.3)	12/485 (2.5)	0.55 (0.21, 1.46)	0.
Eye surgery	31/477 (6.5)	67/509 (13.2)	0.52 (0.35, 0.78)	0.(
Medicines				
Bronchodilators	159/475 (33.5)	185/506 (36.6)	0.92 (0.78, 1.1)	0.
Steroids	95/475 (20.0)	108/506 (21.3)	0.92 (0.72, 1.18)	0.
Diuretics	15/475 (3.2)	14/506 (2.8)	1.17 (0.58,2.34)	0.
Anticonvulsants	12/478 (2.5)	12/511 (2.3)	1.08 (0.49, 2.37)	0.
Readmission	210/478 (43.9)	239/511 (46.8)	0.94 (0.82, 1.08)	0.
Readmission for respiratory reason	110/470 (23.4)	127/503 (25.2)	0.93 (0.74, 1.16)	0.
Readmission for growth/nutrition	12/470 (2.6)	13/503 (2.6)	1.05 (0.49, 2.25)	0.

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "wcarlo@peds.uab.edu"
Subject: Re: SUPPORT CPAP PAPER
Date: Monday, November 28, 2011 12:57:56 PM

Thanks
Rose

From: Wally Carlo, M.D. <WCarlo@peds.uab.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Mon Nov 28 12:57:21 2011
Subject: FW: SUPPORT CPAP PAPER

Rose:

I am trying to help Myriam to expedite this paper. She has a lot of clinical commitments on her plate.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
1700 6th Avenue South
176F Suite 9380R
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From: Myriam Peralta, M.D.
Sent: Monday, November 28, 2011 11:44 AM
To: Wally Carlo, M.D.
Cc: 'Rosemary Higgins'
Subject: RE: SUPPORT CPAP PAPER

Thank you that it will be fine if you want to send the draft to everyone. I will get with Becky to help me with the references she may have more experience than people here thank you again.

From: Wally Carlo, M.D.
Sent: Wednesday, November 23, 2011 7:52 PM
To: Myriam Peralta, M.D.
Cc: Rosemary Higgins
Subject: RE: SUPPORT CPAP PAPER

Hi Myriam:

Excellent job. I have made tracked changes. You may prefer me to send this draft to all so they do not have to make the same suggestions. I usually prefer it that way. You could also remove the

changes you do not like and you or I can send it still with tracked changes so other improve on it. Let me know what you prefer to do.

I am concerned with the emphasis on the subgroup analysis although I think just eliminating a few statements (as I did) may be the easy solution.

You should improve the reference list. Also, Becky can help with all the secretarial support before you send out the next draft.

Wally

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From: Bell, Edward (Pediatrics) [mailto:edward-bell@uiowa.edu]
Sent: Wednesday, November 23, 2011 12:39 PM
To: Myriam Peralta, M.D.
Cc: Rosemary Higgins; Wally Carlo, M.D.
Subject: FW: SUPPORT CPAP PAPER

There's a typo in the Abstract (Results section). It should be 93.6% (not 93/6%).

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, November 23, 2011 9:38 AM
To: 'Myriam Peralta, M.D.'; 'Finer, Neil'; 'Wally Carlo, M.D.'; 'Michele Walsh'; 'Gantz, Marie'; 'Laptook, Abbot'; 'Bradley Yoder'; 'Roger Faix'; 'Abhik Das (Adas@rti.org)'; 'Rich, Wade'; 'kurt.schibler@cchmc.org'; 'nancy newman'; 'Vohr, Betty'; 'Susan Hintz'; 'Kim Yolton'; 'Roy Heyne'; (b)(6) @aol.com'; 'goldb008@mc.duke.edu'; 'Michael.Acarregui@providence.org'; 'Evans, Patricia W'; 'Adams-Chapman, Ira'; 'Pappas, Athina'; 'Anna M. Dusick, MD'; 'emcgowan@tuftsmedicalcenter.org'; 'Ehrenkranz, Richard'; 'abodnar@utah.gov'; 'Bauer, Charles R'; 'JaFuller@salud. unm. edu (JaFuller@salud.unm.edu)'; 'Michael O`Shea'; 'gary_myers@URMC.Rochester.edu'
Cc: 'yvaucher@ucsd.edu'; 'Pablo Sanchez'; 'Shankaran, Seetha'; 'Duara, Shahnaz'; 'Barbara Stoll'; 'Poindexter, Brenda B'; 'Krisa Van Meurs'; 'Kennedy, Kathleen A'; 'goldb008@mc.duke.edu'; 'Phelps, Dale'; Bell, Edward (Pediatrics); 'Frantz, Ivan'; 'Kristi Watterberg'; Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: SUPPORT CPAP PAPER

Hi All,
Here is the SUPPORT oximetry paper and the CONSORT diagram. Please send all suggestions back to Myriam by **December 6**.
The papers will then go for internal NRN review.

I have also included the site PI's.

Thanks for all the hard work and effort!
Rose

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From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Saturday, November 19, 2011 7:55 AM
To: 'Myriam Peralta, M.D.'; 'Finer, Neil'; Wally Carlo, M.D.; Michele Walsh; Gantz, Marie; 'Laptook, Abbot'; 'Bradley Yoder'; 'Roger Faix'; Abhik Das (Adas@rti.org); 'Rich, Wade'; 'kurt.schibler@cchmc.org'; nancy newman; Vohr, Betty; Susan Hintz; 'Kim Yolton'; 'Roy Heyne'; (b)(6) @aol.com'; goldb008@mc.duke.edu; 'Michael.Acarregui@providence.org'; 'Evans, Patricia W'; 'Adams-Chapman, Ira'; Pappas, Athina; 'Anna M. Dusick, MD'; 'emcgowan@tuftsmedicalcenter.org'; 'Ehrenkranz, Richard'; 'abodnar@utah.gov'; 'Bauer, Charles R'; 'JaFuller@salud. unm. edu (JaFuller@salud.unm.edu)'; 'Michael O`Shea'; 'gary_myers@URMC.Rochester.edu'
Cc: yvaucher@ucsd.edu; Pablo Sanchez; 'Shankaran, Seetha'; 'Duara, Shahnaz'; Barbara Stoll; 'Poindexter, Brenda B'; 'Krisa Van Meurs'; 'Kennedy, Kathleen A'; goldb008@mc.duke.edu; 'Phelps, Dale'; 'Bell, Edward (Pediatrics)'; 'Frantz, Ivan'; 'Kristi Watterberg'; Archer, Stephanie (NIH/NICHD) [E]
Subject: SUPPORT CPAP PAPER
Importance: High

Hi,
Attached is the SUPPORT CPAP FU Paper for co-author input. Please send your comments to Yvonne Vaucher (yvaucher@ucsd.edu) by **DECEMBER 3**. The paper will then go for internal NRN review and clearance. Following this, it will be submitted along with the oximetry FU paper (you will get this in the next few days) to the New England Journal of Medicine.
I have also included the steering committee PI's from the sites involved with the study. If you have any suggestions, feel free to forward them to Yvonne. Thanks to everyone for all the hard work, effort and commitment to this study!!
Rose

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Barbara Stoll"; "Luc Brion"
Cc: "Michele Walsh"; "JACLYN LEVAN"
Subject: RE: FW: Question about the SUPPORT
Date: Monday, November 28, 2011 9:30:00 AM

The updated proposal can be submitted at any time

Thanks
Rose

Rosemary D. Higgins, MD
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From: Barbara Stoll [mailto:Barbara.Stoll@oz.ped.emory.edu]
Sent: Sunday, November 27, 2011 10:10 PM
To: Luc Brion; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Michele Walsh; JACLYN LEVAN
Subject: Re: FW: Question about the SUPPORT

Luc

I would think this newer question should be included in the same study

I thought that we had decided to postpone this analysis to next year's PAS

BJSLuc Brion <Luc.Brion@utsouthwestern.edu> writes:
Barbara and Michele:

Thanks again for the subcommittee's comments about the proposal entitled: "Changes in Therapy and Outcomes Associated with The SUPPORT Trial."

Since the subcommittee requested to delay resubmission to 2012, Jackie and I wonder when you would like us to submit.

In addition, we would like to consider to analyze whether the time between intubation and surfactant administration could potentially be an important predictor of outcome in babies initially on CPAP (instead of time between birth and intubation for babies intubated in the DR, which is now one of the quality outcomes used by the National Quality Forum). Could you please advise whether we should consider presenting this in another study, or instead include this variable in the revised version of the above study.

Best regards,

Luc

Luc P. Brion, MD

Professor of Pediatrics

Director, Fellowship Training Program in Neonatal-Perinatal Medicine

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lucbrion@utsouthwestern.edu

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, November 21, 2011 9:11 AM
To: Lilo Brion
Cc: JACLYN LEVAN; Barbara Stoll; Michele Walsh
Subject: RE: Question about the SUPPORT

I.he subcommittee and you can decide after if this warrants a second report.

Thanks

Rbse

Rosemary D. Higgins, MD

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From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]
Sent: Saturday, November 19, 2011 9:34 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: JACLYN LEVAN
Subject: FW: Question about the SUPPORT

Rose,[Marker]

I have other SUPPORT-related questions for you.

Re: "Changes in Therapy and Outcomes Associated with The SUPPORT Trial"

The response of the subcommittee to Jackie LeVan's proposal was to resubmit in 2012.

"It was suggested the subcommittee approves but the analysis should start with data somewhat in 2012"

I need some guidance from you. Which 2012 session would you suggest us to submit the revision to the committee?

We would consider suggesting to analyze whether the time between intubation and surfactant administration could potentially be an important predictor of outcome in babies initially on CPAP (instead of time between birth and intubation for babies intubated in the DR). Would you suggest this to be presented in another study, or merged with the above study?

Luc P. Brion, MD

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luc.brion@utsouthwestern.edu

From: Luc Brion
Sent: Thursday, November 10, 2011 11:21 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Question about the SUPPORT

Rose:

Did the SUPPORT trial database collect information on postnatal age at the time of intubation in the CPAP arm? Unless I missed it, I cannot find it in the NEJM manuscript.

If that information was collected, may I ask Neil Finer directly or ask the subcommittee? Who should I contact?

Thanks

Luc

Luc P. Brion, MD

Professor of Pediatrics

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "adas@rti.org"
Subject: Re: SUPPORT weighted analysis
Date: Saturday, November 26, 2011 6:41:49 AM

Abhik-
Did this explanation go to Neil?
Thanks
Rose

----- Original Message -----
From: Das, Abhik <adas@rti.org>
To: Wally Carlo, M.D. <WCarlo@peds.uab.edu>; Gantz, Marie <mgantz@rti.org>; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Wallace, Dennis <dwallace@rti.org>
Sent: Wed Nov 23 23:18:25 2011
Subject: RE: SUPPORT weighted analysis

I agree. I think Neil may be over interpreting things here. All we tried to do was make the distribution of key baseline features in the enrolled population more reflective of the total eligible population by weighting the data appropriately, and then seeing whether that altered the treatment effect. This is an exploratory secondary analysis that is not meant to take away from the original trial results, just help us understand how generalizeable they may be. Unlike many other trials, we could do this here because the GDB provided us with rich baseline data on the entire eligible population. I am cc ing Dennis here to get his independent statistical opinion because he was not involved in this analysis. I am fine with also getting an opinion from Ambal.

Rose: Have you heard from others on the subcommittee on this abstract?

Thanks

Abhik

-----Original Message-----
From: Wally Carlo, M.D. [WCarlo@peds.uab.edu]
Sent: Wednesday, November 23, 2011 10:17 PM Eastern Standard Time
To: Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik
Subject: RE: SUPPORT weighted analysis

Hi Marie, Rose, and Abhik:

I think we are at an impasse with Neil.

I love this type of work. To me, this type of modeling is straight forward (although I do not claim to know how to do the analysis). This is very similar to related research by Ambal, Tyson, and others in the NRN.

Maybe we should get an independent opinion from someone at RTI and maybe a clinician such as Ambal.

Wally

Wally Carlo, M.D.

Edwin M. Dixon Professor of Pediatrics

University of Alabama at Birmingham

Director, Division of Neonatology

Director, Newborn Nurseries

1700 6th Avenue South

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From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Monday, November 21, 2011 10:54 AM
To: Rich, Wade; Finer, Neil; Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Creel, Darryl; Das, Abhik
Subject: SUPPORT weighted analysis
Importance: High

Attached are two items: (1) results of the weighted analysis of SUPPORT data (in which the enrolled infants are weighted to reflect the characteristics of the eligible population), and (2) an abstract for the Society for Clinical Trials meeting in May on the statistical methods used for this analysis. Wade is listed as a coauthor on the abstract, which we would like to submit for SUPPORT subcommittee and Steering Committee approval this week (the abstract deadline is December 1). Please let us know if you have any comments on the abstract. We would like to send it to the subcommittee today so that we can request SC approval on the call tomorrow afternoon.

If you have any questions about the weighted analysis, please let Darryl and I know. Darryl does survey analysis at RTI, and he performed the weighting and weighted analyses presented in the attached.

Thanks,

Marie

Marie Gantz, Ph.D.

Senior Research Statistician

RTI International

mgantz@rti.org

828-254-6255

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "adas@rti.org"
Subject: Re: SUPPORT weighted analysis
Date: Friday, November 25, 2011 2:37:28 PM

Do you want me to set up a brief call with neil, wally you and I?

----- Original Message -----
From: Das, Abhik <adas@rti.org>
To: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Fri Nov 25 11:08:46 2011
Subject: RE: SUPPORT weighted analysis

Thanks. I just dont understand the almost hostile response from Wade and Neil. By their token, there is no value to any predictive modeling or imputation in any situation (from the Tyson estimator to climate model or economic projections)! How do you suggest we handle this?
Abhik

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]
Sent: Friday, November 25, 2011 10:49 AM Eastern Standard Time
To: Das, Abhik; 'wcarlo@peds.uab.edu'; Gantz, Marie
Cc: Wallace, Dennis
Subject: Re: SUPPORT weighted analysis

Most of the subcommittee is in favor

Rose

----- Original Message -----
From: Das, Abhik <adas@rti.org>
To: Wally Carlo, M.D. <WCarlo@peds.uab.edu>; Gantz, Marie <mgantz@rti.org>; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Wallace, Dennis <dwallace@rti.org>
Sent: Wed Nov 23 23:18:25 2011
Subject: RE: SUPPORT weighted analysis

I agree. I think Neil may be over interpreting things here. All we tried to do was make the distribution of key baseline features in the enrolled population more reflective of the total eligible population by weighting the data appropriately, and then seeing whether that altered the treatment effect. This is an exploratory secondary analysis that is not meant to take away from the original trial results, just help us understand how generalizeable they may be. Unlike many other trials, we could do this here because the GDB provided us with rich baseline data on the entire eligible population. I am cc ing Dennis here to get his independent statistical opinion because he was not involved in this analysis. I am fine with also getting an opinion from Ambal.

Rose: Have you heard from others on the subcommittee on this abstract?

Thanks

Abhik

-----Original Message-----

From: Wally Carlo, M.D. [WCarlo@peds.uab.edu]
Sent: Wednesday, November 23, 2011 10:17 PM Eastern Standard Time
To: Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik
Subject: RE: SUPPORT weighted analysis

Hi Marie, Rose, and Abhik:

I think we are at an impasse with Neil.

I love this type of work. To me, this type of modeling is straight forward (although I do not claim to know how to do the analysis). This is very similar to related research by Ambal, Tyson, and others in the NRN.

Maybe we should get an independent opinion from someone at RTI and maybe a clinician such as Ambal.

Wally

Wally Carlo, M.D.

Edwin M. Dixon Professor of Pediatrics

University of Alabama at Birmingham

Director, Division of Neonatology

Director, Newborn Nurseries

1700 6th Avenue South

176F Suite 9380R

Birmingham, AL 35233-7335

Phone: 205 934 4680

FAX: 205 934 3100

Cell: 205 (b)(6)

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Monday, November 21, 2011 10:54 AM
To: Rich, Wade; Finer, Neil; Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Creel, Darryl; Das, Abhik
Subject: SUPPORT weighted analysis
Importance: High

Attached are two items: (1) results of the weighted analysis of SUPPORT data (in which the enrolled infants are weighted to reflect the characteristics of the eligible population), and (2) an abstract for the Society for Clinical Trials meeting in May on the statistical methods used for this analysis. Wade is listed as a coauthor on the abstract, which we would like to submit for SUPPORT subcommittee and Steering Committee approval this week (the abstract deadline is December 1). Please let us know if you have any comments on the abstract. We would like to send it to the subcommittee today so that we can request SC approval on the call tomorrow afternoon.

If you have any questions about the weighted analysis, please let Darryl and I know. Darryl does survey analysis at RTI, and he performed the weighting and weighted analyses presented in the attached.

Thanks,

Marie

Marie Gantz, Ph.D.

Senior Research Statistician

RTI International

mgantz@rti.org

828-254-6255

From: Finer, Neil
To: Wally Carlo, M.D.; Gantz, Marie; Rich, Wade; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Creel, Darryl; Das, Abhik
Subject: RE: SUPPORT weighted analysis
Date: Wednesday, November 23, 2011 9:12:59 PM

Hi Wally
I do not think that SUPPORT is any less generalizeable than any other published trial
Rather we have demonstrated the importance of the limitations of antenatal consent
I have no fear that the results will be undermined
I think they are as good as you can get
However the analyses using antenatal factors etc cannot predict how potentially more sick and compromised infants would have responded to the 2 interventions
If the population as a whole was sicker they overall may have needed more DR interventions and thus the differences between the groups for intubation etc may have fallen to a less significant level.
The same can be argued for many of the outcomes
I am worried that simple analysis will suggest that we would have had the same results on a more compromised population. We have no information to rationally make such a suggestion
I think it is over simplifying a very complex question
I do not feel the need to overly defend our studies. Rather we need to think for future studies how to include such infants and not try to suggest that we do not need to do this because we can analyze away any differences
My own shortcomings are legion
I am a basic, simple, honest laborer, more a gunfighter and certainly not a scientist, and live in the clinical arena, especially the DR.
I don't know how to predict how any given population will respond to randomized interventions, if I did we would not need the studies.
I remain unconvinced of the value of this approach – it to me is overly defensive and misplaced.
We don't need to defend what we did. We just reported more about the non-enrolled than anyone before us, and that does not in any way devalue the Trials
With respect
Neil

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Wednesday, November 23, 2011 5:54 PM
To: Finer, Neil; Gantz, Marie; Rich, Wade; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Creel, Darryl; Das, Abhik
Subject: RE: SUPPORT weighted analysis

Dear Neil:

I hear your concerns. This is complex modeling that if it is hard for us, imagine for the usual clinical neonatologist.

However, the SUPPORT trial results have been undermined by the concerns raised by some that the results are not generalizable because of high ANS steroid use and high non enrollment rates of eligible subjects.

We need to do this analysis and publish it. I actually do not think the analysis is so complex and the importance of the results overwhelmingly overrides all concerns as far as I understand but maybe I am missing something.

I think this is an extremely important study. Otherwise, other may have the last word on the issue of generalizability of our study.

Wally

Wally Carlo, M.D.
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From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Wednesday, November 23, 2011 5:10 PM
To: Gantz, Marie; Rich, Wade; Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Creel, Darryl; Das, Abhik
Subject: RE: SUPPORT weighted analysis

Hi Marie and Abhik
I have reviewed what you did for this analysis
I have a number of comments
First the analysis is anything but simple and would not be easily understood by many
It is not clear to me that the subsequent occurrence of death and IVH was exclusively related to the antenatal factors
These were the significant differences between the groups which probably requires a more detailed look at the initial level of illness, DR intervention, occurrence of hypotension
In addition How do we know what the effect of either Surf or CPAP would be on the non-enrolled infants
We know they were likely more compromised at birth, but we do not know how such infants would have responded to these interventions
I do not see how your analyses accounted for this – nor do I know how you would do this
I have a great concern that this group – the non-enrolled would most likely have required more DR interventions, needed perhaps more Epi, more DR intubation for resusc etc. These could all reduce the likelihood that you would find a difference between the 2 interventions
I am NOT a statistician
I am a clinician – so what I say probably does not measure up as a P value or a regression
But I remain concerned that this analyses is a problem

Neil

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Monday, November 21, 2011 8:54 AM
To: Rich, Wade; Finer, Neil; Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Creel, Darryl; Das, Abhik
Subject: SUPPORT weighted analysis
Importance: High

Attached are two items: (1) results of the weighted analysis of SUPPORT data (in which the enrolled infants are weighted to reflect the characteristics of the eligible population), and (2) an abstract for the Society for Clinical Trials meeting in May on the statistical methods used for this analysis. Wade is listed as a coauthor on the abstract, which we would like to submit for SUPPORT subcommittee and Steering Committee approval this week (the abstract deadline is December 1). Please let us know if you have any comments on the abstract. We would like to send it to the subcommittee today so that we can request SC approval on the call tomorrow afternoon.

If you have any questions about the weighted analysis, please let Darryl and I know. Darryl does survey analysis at RTI, and he performed the weighting and weighted analyses presented in the attached.

Thanks,
Marie

Marie Gantz, Ph.D.
Senior Research Statistician
RTI International
mgantz@rti.org
828-254-0255

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: SUPPORT weighted analysis
Date: Wednesday, November 23, 2011 2:34:00 PM

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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higginsr@mail.nih.gov

From: Laptook, Abbot [mailto:ALaptook@WIHRI.org]
Sent: Wednesday, November 23, 2011 2:27 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT weighted analysis

Yes, AL

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, November 21, 2011 2:36 PM
To: Wally Carlo, M.D.; Finer, Neil; 'kurt.schibler@cchmc.org'; Michele Walsh; 'Roger Faix'; Laptook, Abbot; 'Bradley Yoder'; Abhik Das (adas@rti.org); 'Gantz, Marie'; nxs5@cwru.edu; Rich, Wade
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: SUPPORT weighted analysis
Importance: High

Hi
Attached are two items: (1) results of the weighted analysis of SUPPORT data (in which the enrolled infants are weighted to reflect the characteristics of the eligible population), and (2) an abstract for the Society for Clinical Trials meeting in May on the statistical methods used for this analysis. Wade is listed as a coauthor on the abstract, which we would like to submit for SUPPORT subcommittee and Steering Committee approval this week (the abstract deadline is December 1). Please let us know if you have any comments on the abstract. If you have any questions about the weighted analysis, please let Darryl and Marie know. Darryl does survey analysis at RTI, and he performed the weighting and weighted analyses presented in the attached.

The meeting info is:
Society for Clinical Trials, 33rd Annual Meeting
May 20-23, 2011
Miami, FL

Please send me a yes/no vote by November 25 for Marie to submit the abstract.

Thanks

Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Vaucher, Yvonne
To: Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik; Vaucher, Yvonne
Subject: RE: NRN PAS 2012.pdf - Adobe Acrobat Professional
Date: Wednesday, November 23, 2011 12:22:27 PM

Marie,

According to the detailed individual data sheets you sent me, two children with unilateral HI (# 19 and # 22) appeared to be among the 11 children with HI but without amplification . Did we exclude them from the analysis? Even if they were excluded we are left with 5 unamplified children judged to have clinical HI who had not had post-discharge diagnostic studies so we don't know the actual hearing status, one child with "equivocal" post-diagnostic results and two who failed their post-diagnostic hearing tests but for whom we don't know if the loss was permanent. The cleanest would be to include the kids with amplification only-we do know those are permanent. I know this is such a small number of children and we can try to sort them out by contacting their centers again later-the question is what to use now for the paper and Hot Topics. Questions about HI are likely to arise at Hot Topics even though this will obviously have any influence on the primary outcome.

Abhik, I really don't want to dissect more as this is such a small group, but I do want to be a straightforward as possible and use the most reliable data. Does it change anything if we use only those who were amplified? Hopefully not though one child more or less on either treatment arm may change the significance of hearing impairment between groups. I do think the present data for the unamplified children is uncertain though in the end it may turn out that we should use them after all.

Yvonne

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Wednesday, November 23, 2011 8:55 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Vaucher, Yvonne
Cc: Das, Abhik
Subject: RE: NRN PAS 2012.pdf - Adobe Acrobat Professional

Bilateral (not unilateral) hearing loss was used in the definition of NDI. Some children did not have amplification, but that is also part of the our NDI definition (impairment plus or minus amplification). We could look at NDI defined with hearing loss that requires amplification, but it would be a secondary outcome since it is not our official NDI definition (and it would add to our count of outcomes that we have tested).

Marie

Marie Gantz, Ph.D.
Senior Research Statistician
RTI International
mgantz@rti.org
919-254-6255

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, November 23, 2011 7:13 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; (suhas.kallapur@cchmc.org); Abbot Laptook (alaptook@wihri.org); Abhik Das (adas@rti.org); Ambal (ambal@uab.edu); Anna Maria Hibbs (AnnaMaria.hibbs@cwru.edu); barbara_stoll@oz.ped.emory.edu; bpoindex@iupui.edu; carl_dangio@urmc.rochester.edu; Carlton, David P; cotte010@mc.duke.edu; dstevenson@stanford.edu; dwallace@rti.org; Ed Bell (edward-bell@uiowa.edu); goldb008@mc.duke.edu; Greg Sokol (gsokol@iupui.edu); Haresh Kirpalani (KIRPALANIH@email.chop.edu); 'John Barks'; Jon.E.Tyson@uth.tmc.edu; Kennedy, Kathleen A; Krisa Van Meurs (vanmeurs@stanford.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); Kurt Schibler [kurt.schibler@cchmc.org]; Luc Brion (luc.brion@utsouthwestern.edu); Martin Keszler (mkeszler@wihri.org); mcw3@po.cwru.edu; Meena Garg (mgarg@mednet.ucla.edu); Nelin, Leif; Pablo.Sanchez@UTSouthwestern.edu; Polin, Richard; Robin Ohls (rohls@salud.unm.edu); ronnie_guillet@urmc.rochester.edu; Satyan Lakshminrusimha; Schmidt, Barbara (Neonatology); Seetha Shankaran ; Sood, Beena [bsood@med.wayne.edu]; Truog, William (MD); Uday Devaskar (UDEVASKAR@MEDNET.UCLA.EDU); Wally Carlo (wacarlo@uab.edu); (apappas@med.wayne.edu); (EMcGowan@tufts-nemc.org); Andrea Duncan (AFDuncan@salud.unm.edu); Betty Vohr (bvohr@wihri.org); (b)(6) @aol.com; Gary Myers (gary_myers@URMC.Rochester.edu); golds005@mc.duke.edu; Hallam Hurt (hurt@email.chop.edu); Howard Kilbride (hkilbride@cmh.edu); 'ira adams-chapman'; Isabell Purdy (ipurdy@mednet.ucla.edu); JaFuller@salud. unm. edu (JaFuller@salud.unm.edu); Jean Steichen (steichjj@uc.edu); Keith Yeates (Keith.Yeates@nationwidechildrens.org); 'Kim Yolton'; Marsha Gerdes (gerdes@email.chop.edu); Myriam Peralta-Carcelen (MPeralta@peds.uab.edu); 'Patrick Jones'; richard.ehrenkranz@yale.edu; 'Roy Heyne'; Soraya Abbasi (soraya.abbasi@uphs.upenn.edu); 'Susan Hintz'; Tarah Colaizy (tarah-colaizy@uiowa.edu); Vaucher, Yvonne
Cc: Archer, Stephanie (NIH/NICHD) [E]; 'Zaterka-Baxter, Kristin'; 'Cunningham, Meg'; 'Huitema, Carolyn Petrie'; 'Gabrio, Jenna'; 'Newman, Jamie'
Subject: RE: NRN PAS 2012.pdf - Adobe Acrobat Professional

Only was PAS abstract was included on the prior email – try this one and you should be able to click on the left side of the file for each pdf.

Thanks for your patience

Rose

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From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, November 23, 2011 9:44 AM
To: (suhas.kallapur@cchmc.org); Abbot Laptook (alaptook@wihri.org); Abhik Das (adas@rti.org); Ambal (ambal@uab.edu); Anna Maria Hibbs (AnnaMaria.hibbs@cwru.edu); barbara_stoll@oz.ped.emory.edu; bpoindex@iupui.edu; carl_dangio@urmc.rochester.edu; Carlton, David P; cotte010@mc.duke.edu; dstevenson@stanford.edu; dwallace@rti.org; Ed Bell (edward-bell@uiowa.edu); goldb008@mc.duke.edu; Greg Sokol (gsokol@iupui.edu); Haresh Kirpalani

(KIRPALANIH@email.chop.edu); John Barks; Jon.E.Tyson@uth.tmc.edu; Kennedy, Kathleen A; Krisa Van Meurs (vanmeurs@stanford.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); Kurt Schibler [kurt.schibler@cchmc.org]; Luc Brion (luc.brion@utsouthwestern.edu); Martin Keszler (mkeszler@wihri.org); mcw3@po.cwru.edu; Meena Garg (mgarg@mednet.ucla.edu); Nelin, Leif; Pablo.Sanchez@UTSouthwestern.edu; Polin, Richard; Robin Ohls (rohls@salud.unm.edu); ronnie_guillet@urmc.rochester.edu; Satyan Lakshminrusimha; Schmidt, Barbara (Neonatology); Seetha Shankaran ; Sood, Beena [bsood@med.wayne.edu]; Truog, William (MD); Uday Devaskar (UDEVASKAR@MEDNET.UCLA.EDU); Wally Carlo (wacarlo@uab.edu); (apappas@med.wayne.edu); (EMcGowan@tufts-nemc.org); Andrea Duncan (AFDuncan@salud.unm.edu); Betty Vohr (bvohr@wihri.org); (b)(6) @aol.com; Gary Myers (gary_myers@URMC.Rochester.edu); golds005@mc.duke.edu; Hallam Hurt (hurt@email.chop.edu); Howard Kilbride (hkilbride@cmh.edu); ira adams-chapman; Isabell Purdy (ipurdy@mednet.ucla.edu); JaFuller@salud. unm. edu (JaFuller@salud.unm.edu); Jean Steichen (steichjj@uc.edu); Keith Yeates (Keith.Yeates@nationwidechildrens.org); Kim Yolton; Marsha Gerdes (gerdes@email.chop.edu); Myriam Peralta-Carcelen (MPeralta@peds.uab.edu); Patrick Jones; richard.ehrenkranz@yale.edu; Roy Heyne; Soraya Abbasi (soraya.abbasi@uphs.upenn.edu); Susan Hintz; Tarah Colaizy (tarah-colaizy@uiowa.edu); Yvonne Vaucher

Cc: Archer, Stephanie (NIH/NICHD) [E]; 'Zaterka-Baxter, Kristin'; Cunningham, Meg; Huitema, Carolyn Petrie; 'Gabrio, Jenna'; 'Newman, Jamie'

Subject: NRN PAS 2012.pdf - Adobe Acrobat Professional

Hi,

Here is the set of PAS submitted abstracts. Thanks to everyone for all the hard work and effort!!

Rose

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Blaisdell, Carol (NIH/NHLBI) [E]; Gail, Dorothy (NIH/NHLBI) [E]
Subject: RE: PAS SUPPORT abstracts
Date: Wednesday, November 23, 2011 11:32:00 AM

We don't have pulmonary hypertension data collected systematically for the patients. The BPD outcomes are likely to be evaluated in the breathing outcomes study – we may have a late breaker but we haven't seen the data analysis as yet as data are still being cleaned.

Happy Thanksgiving

Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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higginsr@mail.nih.gov

From: Blaisdell, Carol (NIH/NHLBI) [E]
Sent: Wednesday, November 23, 2011 10:36 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Gail, Dorothy (NIH/NHLBI) [E]
Subject: RE: PAS SUPPORT abstracts

Thanks for sharing these Rose,
Peralta's abstract isn't part of the attachment—

Any sense if incidence of pulmonary hypertension was different between groups?
Do you know if the severity of BPD differed by group? (ie. Either mild/mod/severe or Need for oxygen after 40 wk corrected age)?

Appreciate the updates, Happy Thanksgiving,

Carol

Carol J. Blaisdell M.D.
Medical Officer
Lung Development and Pediatrics
Lung Biology and Diseases Branch
Division of Lung Diseases
NHLBI, NIH
301-435-0222

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, November 23, 2011 9:46 AM
To: Blaisdell, Carol (NIH/NHLBI) [E]; Gail, Dorothy (NIH/NHLBI) [E]
Subject: PAS SUPPORT abstracts

Carol and Dorothy,
Attached are the SUPPORT Trial abstracts submitted for potential presentation to PAS 2012. I will let you know the status once decisions for presentation are made in February 2012.

Thanks for all your help with this study.

Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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From: Vaucher, Yvonne
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: NRN PAS 2012.pdf - Adobe Acrobat Professional
Date: Wednesday, November 23, 2011 11:24:04 AM

Two were unilateral but coded as hearing impaired without amplification.

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, November 23, 2011 8:21 AM
To: Vaucher, Yvonne
Cc: 'Gantz, Marie'; 'Abhik Das (Adas@rti.org)'
Subject: RE: NRN PAS 2012.pdf - Adobe Acrobat Professional

Yvonne
Did all of these children have unilateral (not our definition) or bilateral (is our definition) of hearing loss?? I am fine with looking at this as long as Marie and Abhik agree.

Thanks
Rose

Rosemary D. Higgins, MD
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From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]
Sent: Wednesday, November 23, 2011 11:06 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: NRN PAS 2012.pdf - Adobe Acrobat Professional

PS. Betty and I have been conversing via e-mail about the hearing loss question. I would like to ask Marie to rerun the NDI outcomes using only the children with amplification since which would be the cleanest run since these are the only ones we actually are sure have permanent hearing loss. Only 2 of the hearing impaired/not amplified children failed their post-discharge hearing screen but we don't know whether their loss is permanent or not. If we deleted "permanent" we could use the whole group but even then two had only unilateral loss (2 of the non-amplified) which is not considered to be HI and it would not conform to the NRN definition of NDI..

Thanks Rose. Am doing the Hot Topic Slides. Hope to have them for your review next Monday.

Yvonne

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, November 23, 2011 7:13 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; (suhas.kallapur@cchmc.org); Abbot Laptook (alaptook@wihri.org); Abhik Das (adas@rti.org); Ambal (ambal@uab.edu); Anna Maria Hibbs (AnnaMaria.hibbs@cwru.edu); barbara_stoll@oz.ped.emory.edu; bpoindex@iupui.edu; carl_dangio@urmc.rochester.edu; Carlton, David P; cotte010@mc.duke.edu; dstevenson@stanford.edu; dwallace@rti.org; Ed Bell (edward-bell@uiowa.edu); goldb008@mc.duke.edu; Greg Sokol (gsokol@iupui.edu); Haresh Kirpalani (KIRPALANIH@email.chop.edu); 'John Barks'; Jon.E.Tyson@uth.tmc.edu; Kennedy, Kathleen A; Krisa Van Meurs (vanmeurs@stanford.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); Kurt Schibler [kurt.schibler@cchmc.org]; Luc Brion (luc.brion@utsouthwestern.edu); Martin Keszler (mkeszler@wihri.org); mcw3@po.cwru.edu; Meena Garg (mgarg@mednet.ucla.edu); Nelin, Leif; Pablo.Sanchez@UTSouthwestern.edu; Polin, Richard; Robin Ohls (rohls@salud.unm.edu); ronnie_guillet@urmc.rochester.edu; Satyan Lakshminrusimha; Schmidt, Barbara (Neonatology); Seetha Shankaran ; Sood, Beena [bsood@med.wayne.edu]; Truog, William (MD); Uday Devaskar (UDEVASKAR@MEDNET.UCLA.EDU); Wally Carlo (wacarlo@uab.edu); (apappas@med.wayne.edu); (EMcGowan@tufts-nemc.org); Andrea Duncan (AFDuncan@salud.unm.edu); Betty Vohr (bvohr@wihri.org); (b)(6) @aol.com; Gary Myers (gary_myers@URMC.Rochester.edu); golds005@mc.duke.edu; Hallam Hurt (hurt@email.chop.edu); Howard Kilbride (hkilbride@cmh.edu); 'ira adams-chapman'; Isabell Purdy (ipurdy@mednet.ucla.edu); JaFuller@salud. unm. edu (JaFuller@salud.unm.edu); Jean Steichen (steichjj@uc.edu); Keith Yeates (Keith.Yeates@nationwidechildrens.org); 'Kim Yolton'; Marsha Gerdes (gerdes@email.chop.edu); Myriam Peralta-Carcelen (MPeralta@peds.uab.edu); 'Patrick Jones'; richard.ehrenkranz@yale.edu; 'Roy Heyne'; Soraya Abbasi (soraya.abbasi@uphs.upenn.edu); 'Susan Hintz'; Tarah Colaizy (tarah-colaizy@uiowa.edu); Vaucher, Yvonne
Cc: Archer, Stephanie (NIH/NICHD) [E]; 'Zaterka-Baxter, Kristin'; 'Cunningham, Meg'; 'Huitema, Carolyn Petrie'; 'Gabrio, Jenna'; 'Newman, Jamie'
Subject: RE: NRN PAS 2012.pdf - Adobe Acrobat Professional

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Thanks for your patience

Rose

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From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, November 23, 2011 9:44 AM
To: (suhas.kallapur@cchmc.org); Abbot Laptook (alaptook@wihri.org); Abhik Das (adas@rti.org); Ambal (ambal@uab.edu); Anna Maria Hibbs (AnnaMaria.hibbs@cwru.edu); barbara_stoll@oz.ped.emory.edu; bpoindex@iupui.edu; carl_dangio@urmc.rochester.edu; Carlton, David P; cotte010@mc.duke.edu; dstevenson@stanford.edu; dwallace@rti.org; Ed Bell (edward-bell@uiowa.edu); goldb008@mc.duke.edu; Greg Sokol (gsokol@iupui.edu); Haresh Kirpalani (KIRPALANIH@email.chop.edu); John Barks; Jon.E.Tyson@uth.tmc.edu; Kennedy, Kathleen A; Krisa Van Meurs (vanmeurs@stanford.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); Kurt Schibler [kurt.schibler@cchmc.org]; Luc Brion (luc.brion@utsouthwestern.edu); Martin Keszler (mkeszler@wihri.org); mcw3@po.cwru.edu; Meena Garg (mgarg@mednet.ucla.edu); Nelin, Leif; Pablo.Sanchez@UTSouthwestern.edu; Polin, Richard; Robin Ohls (rohls@salud.unm.edu); ronnie_guillet@urmc.rochester.edu; Satyan Lakshminrusimha; Schmidt, Barbara (Neonatology); Seetha Shankaran ; Sood, Beena [bsood@med.wayne.edu]; Truog, William (MD); Uday Devaskar (UDEVASKAR@MEDNET.UCLA.EDU); Wally Carlo (wacarlo@uab.edu); (apappas@med.wayne.edu); (EMcGowan@tufts-nemc.org); Andrea Duncan (AFDuncan@salud.unm.edu); Betty Vohr (bvohr@wihri.org); (b)(6) @aol.com; Gary Myers (gary_myers@URMC.Rochester.edu); golds005@mc.duke.edu; Hallam Hurt (hurt@email.chop.edu); Howard Kilbride (hkilbride@cmh.edu); ira adams-chapman; Isabell Purdy (ipurdy@mednet.ucla.edu); JaFuller@salud. unm. edu (JaFuller@salud.unm.edu); Jean Steichen (steichjj@uc.edu); Keith Yeates (Keith.Yeates@nationwidechildrens.org); Kim Yolton; Marsha Gerdes (gerdes@email.chop.edu); Myriam Peralta-Carcelen (MPeralta@peds.uab.edu); Patrick Jones; richard.ehrenkranz@yale.edu; Roy Heyne; Soraya Abbasi (soraya.abbasi@uphs.upenn.edu); Susan Hintz; Tarah Colaizy (tarah-colaizy@uiowa.edu); Yvonne Vaucher
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Subject: NRN PAS 2012.pdf - Adobe Acrobat Professional

Hi,
Here is the set of PAS submitted abstracts. Thanks to everyone for all the hard work and effort!!
Rose

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Myriam Peralta, M.D."
Cc: "Gantz, Marie"
Subject: RE: SUPPORT manuscript
Date: Wednesday, November 23, 2011 10:33:00 AM

This works – thanks –I will send it out

Happy Thanksgiving!!
Rose

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From: Myriam Peralta, M.D. [mailto:MPeralta@peds.uab.edu]
Sent: Wednesday, November 23, 2011 10:19 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Gantz, Marie
Subject: RE: SUPPORT manuscript

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Cc: Gantz, Marie
Subject: RE: SUPPORT manuscript

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Thanks
Rose

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From: Myriam Peralta, M.D. [mailto:MPeralta@peds.uab.edu]
Sent: Tuesday, November 22, 2011 6:47 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT manuscript

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From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tue 11/22/2011 1:46 PM
To: Myriam Peralta, M.D.
Cc: Wally Carlo, M.D.
Subject: SUPPORT manuscript

Myriam,

Please send me the SUPPORT manuscript so that I can distribute before thanksgiving.

Thanks

Rose

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To: "Myriam Peralta, M.D."
Subject: RE: SUPPORT manuscript
Date: Wednesday, November 23, 2011 10:33:00 AM

Myriam
Thanks for getting this back – I hope (b)(6)
Best of luck (b)(6)
Rose

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Blaisdell, Carol (NIH/NHLBI) [E]; Gail, Dorothy (NIH/NHLBI) [E]
Subject: PAS SUPPORT abstracts
Date: Wednesday, November 23, 2011 9:46:00 AM
Attachments: Hintz, SUPPORT MRI CUSs, 2011-11-15.docx
Hintz, SUPPORT MRI, 2011-11-15.docx
Kennedy, ROP Natural History, 2011-11-10.pdf
Navarette, SUPPORT Growth, 2011-11-10.pdf
Peralta, SUPPORT FU Oxymetry, 2011-11-16.pdf
Vaucher, SUPPORT FU CPAP, 2011-11-16.docx

Carol and Dorothy,
Attached are the SUPPORT Trial abstracts submitted for potential presentation to PAS 2012. I will let you know the status once decisions for presentation are made in February 2012.

Thanks for all your help with this study.

Rose

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FINAL November 14th SUBMITTED

Title: Early and late cranial ultrasound (CUS) to predict 18-22 month outcomes in extremely preterm infants: The Neuroimaging and Neurodevelopmental Outcomes (NEURO) cohort

S R Hintz, MD, MS Epi[1], L A Wrage, MPH[2], D Bulas, MD[3], T L Slovis, MD[4], A Das, PhD[2], N Finer, MD[5] and R D Higgins, MD[6]. [1]Stanford University, Palo Alto, CA, United States; [2]RTI International, Research Triangle Park, NC, United States; [3]Children's National Medical Center, Washington, DC, United States; [4]Children's Hospital of Michigan, Detroit, MI, United States; [5]University of California, San Diego, CA, United States and [6]the SUPPORT subcommittee and the NICHD Neonatal Research Network (NRN), Bethesda, MD, United States.

Background: Cranial US (CUS) is routinely used to identify acute brain injury and assist in prognosis for extremely preterm (EPT) infants. Studies vary regarding the capability of neonatal CUS to predict childhood outcomes.

Objective: To determine associations and predictive value of early and late CUS findings with 18-22 months outcomes in a large contemporary EPT cohort.

Design/Methods: NEURO was a prospective study of early (4-14 days) and late (34-42 wks PMA) CUS and near-term MRI in a subcohort of 24-27+6/7 wk EGA infants in the NRN SUPPORT study. All neuroimaging was centrally read. Follow up (FU) outcomes at 18-22 mo corrected age included Bayley III Scales, cerebral palsy (CP), neurodevelopmental impairment (NDI), and unimpaired.

Results: 480 infants had all neuroimaging within protocol timing. 444 had FU (15 died, 21 lost, 95% FU rate). Rates of adverse CUS findings and impairment at FU were low. Selected results are shown.

Relation of early and late CUS to 18-22 mo outcomes

	Early CUS		Late CUS			Early or Late
Outcome	Normal (n=321)	IVH 3/4 or PVL (n=44)	Normal (n=320)	Mod/severe ventriculomegaly (VM) (n=17)	cPVL, cyst, mod/severe VM or shunt (n=26)	Any cerebellar lesions (n=7)
Cognitive score<70	16/318 (5%)	5 (11%)	13/316 (4.1%)	3 (18%)	6 (23%)	2 (29%)
Mod/severe CP	2 (0.6%)	9 (20%)	1 (0.3%)	8 (47%)	9 (35%)	6 (86%)
NDI	18/318 (5.7%)	13 (30%)	16/316 (5.1%)	10 (59%)	13 (50%)	6 (86%)
Unimpaired	154/312 (49%)	14/43 (33%)	157/310 (50%)	3 (18%)	5 (19%)	1 (14.3%)

NDI: any of Cog<70, mod/sev CP, GMFCS>=2, bilat blind or deaf; Unimpaired: all of Cog & Lang>85, no CP, blindness, or deafness

Predictive associations of CUS findings with 18-22 mo outcomes

	CUS finding*	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Cognitive<70	Early adverse	19	91	11	95
	Late adverse	23	95	23	95
Mod/severe CP	Early adverse	69	92	21	99
	Late adverse	69	96	35	99
Death or NDI	Early adverse	31	92	34	91
	Late adverse	29	97	54	91
Unimpaired	Normal both Early and Late	66	44	52	59

*Early adverse CUS: IVH grade 3/4 or PVL; Late adverse CUS: cPVL, p-cyst, mod-severe VM or shunt

Conclusions: Early and late CUS findings were associated with 18-22 mo outcomes. Sensitivity and PPV were

poor, but specificity and NPV were excellent. Having normal early and late CUS was poorly predictive of unimpaired outcome. Cerebellar lesions on CUS were rare; relation to outcomes will be further explored by MRI.

FINAL November 14th submitted

Title: Brain MRI and outcomes at 18-22 months in extremely preterm infants: The Neuroimaging and Neurodevelopmental Outcomes (NEURO) cohort

S R Hintz, MD MS Epi[1], L A Wrage, MPH[2], P D Barnes, MD[1], D Bulas, MD[3], T Slovis, MD[4], A Das, PhD[2], N Finer, MD[5] and R Higgins, MD[6]. [1]Stanford University, Palo Alto, CA, United States; [2]RTI International, Research Triangle Park, NC, United States; [3]Children's National Medical Center, Washington, DC, United States; [4]Children's Hospital of Michigan, Detroit, MI, United States; [5]UCSD, San Diego, CA, United States and [6]the SUPPORT subcommittee and the NICHD Neonatal Research Network (NRN), Bethesda, MD, United States.

Background: Extremely preterm (EPT) infants are at high risk for adverse neurodevelopmental outcomes. Cranial ultrasound (CUS) is standard practice for brain imaging, but near-term brain MRI has been reported to better predict outcomes in this population.

Objective: To assess associations of near-term brain MRI findings including severity of white matter abnormalities (WMA) and cerebellar (BEL) lesions, and early and late CUS findings, with early childhood neurodevelopmental outcomes in a large EPT cohort.

Design/Methods: NEURO was a prospective study of early (4-14 days) and late (34-42 wks PMA) CUS and near-term MRI in a subcohort of 24-27+6/7 wk EGA infants in the NRN SUPPORT study. Follow Up (FU) outcomes at 18-22 mo corrected age included Bayley III Scales, neurodevelopmental impairment (NDI) (any of Cognitive<70, mod/severe CP, GMFCS>= 2, blindness or deafness), and unimpaired. Logistic regression analysis evaluated associations of CUS and MRI with outcomes, adjusting for multiple other factors.

Results: 480 infants had both CUS, and MRI within 2 weeks of late CUS. 444 had FU (15 died; 21 lost). Outcomes by severity of WMA and BEL lesions on MRI are shown.

18-22 mo outcomes and WMA on brain MRI

	Severity of WMA (Inder TE, et al, J Peds 2003)				
	Normal (n=98)	**Mild (n=260)**	**Moderate (n=68)**	**Severe (n=18)**	**p value**
Cognitive score, mean (SD)	94 (14)	93 (13)	90 (15)	78 (15)	<.0001
Cognitive score<70	4.1%	4.3%	11%	22%	0.01
Mod/severe CP	0	1.2%	1.5%	50%	<.0001
NDI	4.1%	5.8%	11%	61%	<.0001
Unimpaired	57%	47%	43%	17%	0.01

18-22 mo outcomes and cerebellar lesions on brain MRI

	No BEL lesions (n=373)	**Any BEL lesions (n=71)**	**p value**
Cognitive score, mean (SD)	93.1 (13.5)	85.0 (14.9)	<.0001
Cognitive<70	4.1%	16%	<.0001
Mod/severe CP	1.6%	9.9%	0.002
NDI	5.7%	23%	<.0001
Unimpaired	51%	31%	0.003

In regression models including both early and late CUS, brain MRI findings (BEL) remained independently associated with outcomes including death or NDI (OR 3.1, 95%CI 1.4-7.1, p=0.008), or cognitive<70 (OR 2.6, 1.1-6.4, p=0.03). Late CUS findings also remained independently associated with adverse outcomes, but predictive accuracy of models was improved with inclusion of MRI.

Conclusions: Brain MRI abnormalities were associated with adverse outcomes, independent of multiple factors including early and late CUS findings. Near-term brain MRI may augment CUS in prediction of early childhood outcomes for EPT infants.

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2012 PAS Annual Meeting

Subspecialty: Neonatology - General
Theme: Neonatal - Patient-Oriented Research

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Pediatric Hospital Medicine: No, Do not consider this abstract for presentation at the Pediatric Hospital Medicine, July 19-22, 2012
Research Type: Clinical
Presentation Sabbath Conflict on: N/A
APA Special Interest Groups, Committees or Regions: None

AWARDS APPLIED FOR:

No awards selected

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Title:

Evaluating Retinopathy of Prematurity (ROP) Screening Guidelines for 24-27 Week Gestational Age (GA) Infants

Kathleen A Kennedy, MD, MPH[1], Lisa A Wrage, MPH[2], Dale Phelps, MD[3] and Rosemary Higgins, MD[4]. [1]Pediatrics, UT Houston Medical, Houston, TX, United States; [2]RTI International, Research Triangle Park, NC, United States; [3]University of Rochester, Rochester, NY, United States and [4]the SUPPORT Subcommittee of the NICHD Neonatal Research Network, NICHD, Rockville, MD, United States.

Background: Timely detection of treatable ROP is important for optimal outcomes. The 2006 screening guidelines are based on infants born in 1986-1997: screening should begin by 31 wks postmenstrual age (PMA) and continue until vessels have reached zone III at ≥ 35 wks or, for infants without prethreshold ROP, until 45 wks PMA. Earlier treatment of ROP (Type 1 ROP: stage 3 or plus disease in zone I or stage 2-3 with plus disease in zone II) is now recommended.

Objective: To validate current ROP screening guidelines for 24-27 wk infants.

Design/Methods:

In the NICHD Network SUPPORT trial, severe ROP (Type 1 ROP or treatment with laser, cryotherapy, or bevacizumab) or death was the primary outcome for the O_2 saturation target arm of the factorial trial. Infants 24 0/7 to 27 6/7 wks GA with consent prior to delivery were eligible. Examinations followed current screening recommendations. Exam results were collected until a study endpoint was reached: ROP treatment, full vascularization to the ora serrata, vascularization in zone III in 2 consecutive exams, or 55 wks PMA.

Results: 1316 infants were enrolled. 1091 (83%) survived to ROP determination. 997 (91%) of these infants had a definitive ROP outcome. 644 infants developed ROP (138 met criteria for severe ROP); 353 had no ROP. 128/138 (93%) with severe ROP had sufficient data (no missing or delayed exams) to determine the age of onset of ROP. Infants with severe ROP were less mature [mean(SD) 25.5(0.9) wks vs 26.8(0.9) wks, p<0.0001] and lower birth weight [mean (SD) 708(148)g vs 942(173)g, p<0.0001] than infants with no ROP. The PMAs at which selected percentiles reached diagnosis are shown below:

	Cumulative % with Diagnosis of ROP						
	1%	5%	25%	50%	75%	95%	99%
ROP type (number of infants)	Postmenstrual Age (weeks)						
Diagnosis of any ROP (n=642)	30.4	31.4	32.7	33.9	35.1	37.9	41.0

Diagnosis of Severe (Type 1/Treated) ROP (n=128)	32.7	33.9	35.1	36.4	38.6	43.3	45.0

The PMA at onset of severe ROP ranged from 32.1 to 53.1 wks. In this referral center cohort of 997 infants, 0.5% were diagnosed with severe ROP after back transfer; 1.0% (7% of infants with severe ROP) reached severe ROP after discharge.

Conclusions: Our data support the 2006 guidelines. In these 997 infants, we did not observe treatable ROP before 32 wks PMA; only 1 infant developed severe ROP after 45 wks. A limitation of this study is that infants < 24 wks GA were not enrolled; these data may not generalize to less mature infants.

Other Previews:

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Filename: 752262

2012 PAS Annual Meeting

Subspecialty: Neonatology - General
Theme: Not yet indicated

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Pediatric Hospital Medicine: No, Do not consider this abstract for presentation at the Pediatric Hospital Medicine, July 19-22, 2012
Research Type: Clinical
Presentation Sabbath Conflict on: N/A
APA Special Interest Groups, Committees or Regions: None

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No awards selected

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Society for Pediatric Research

Title: Growth Outcomes of Preterm Infants Exposed to Different Oxygen Saturation Target Ranges from Birth

Cristina Navarrete, MD[1], Shahnaz Duara, MD[1] and Rosemary Higgins, MD[2]. [1]University of Miami, Miami, FL, United States and [2]the SUPPORT Subcommittee of the NICHD Neonatal Research Network , NICHD, Rockville, MD, United States.

Background: Post-natal growth restriction is a major morbidity in preterm infants. Perturbations in oxygenation may influence

somatic growth; a recent study showed that infants exposed to higher oxygen saturation (SpO2) targets experienced poorer growth (Tin, Arch Child Dis FN 2001). The Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial (SUPPORT) showed that a lower target range of SpO2 from birth, as compared with a higher range, resulted in less retinopathy of prematurity in survivors but an increase in mortality (Carlo, NEJM 2010).

Objective: To test the hypotheses that infants kept in the low SpO2 target range from birth will have better growth trajectories and better growth at 36 weeks and at 18-22 months corrected age (fewer babies <10% for weight).

Design/Methods: A sub-cohort of 810 preterm infants enrolled in SUPPORT (n=1,316), randomized at birth to low (85-89%, n=402, GA 26.2 ± 1.1wks, BW 838.6 ± 186 gm) or high (91-95%, n=408, GA 26.2 ± 1.1wks, BW 839.6 ± 191gm) SpO2 target range was studied. Anthropometric measures were obtained at birth, postnatal days 7, 14, 21, and 28; 32 and 36 weeks post-menstrual age, and at 18-22 months corrected age. Longitudinal growth trajectories were constructed for each target group using the means of each measure per time point. Poor growth (weight, length, head circumference <10th %ile) at 36 weeks and 18-22 months was analyzed using robust Poisson regression.

Results: Growth trajectories for Wt, L, and HC showed no differences in growth between the low and high SpO2 assignment groups. There was no difference in mortality by 36 weeks and the rate of poor growth at 36 wks and at 18-22 month was not different for any measure [Table1].

Conclusions: Early oxygen saturation target assignment did not impact on growth in a large subgroup of infants enrolled in the SUPPORT Trial.

Growth Outcomes by Assigned Groups

	Low SpO2 (n=402)	High SpO2 (n=408)	p-value
n (%) death by 36wk	69 (17.2)	60 (14.7)	0.32
n /N(%) with Wt <10th %ile at 36wk	155/333 (46.6)	172/342 (50.3)	0.30
n /N(%) with Wt <10th %ile at 18-22m	48/296 (16.2)	45/313 (14.4)	0.49
n /N(%) with L <10th %ile at 36wk	203/314 (64.7)	218/315 (69.2)	0.21
n /N(%) with L <10th %ile at 18-22m	79/296 (26.7)	98/313 (31.3)	0.28
n /N(%) with HC <10th %ile at 36wk	124/319 (38.9)	130/325 (40.0)	0.87
n /N(%) with HC <10th %ile at 18-22m	46/296 (15.5)	49/313 (15.7)	0.92

Other Previews:

Abstract Disclosure Info: Disclosures

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First Author: Myriam Peralta-Carcelen, MD, MPH
Responsible Author: Myriam Peralta-Carcelen, MD, MPH
Presenting Author: Myriam Peralta-Carcelen, MD, MPH
Contact Person: Myriam Peralta-Carcelen, MD

Filename: 750268

2012 PAS Annual Meeting

Subspecialty: Neonatal Epidemiology & Follow-Up
Theme: Neonatal Medicine: Clinical Trials

Contact Author: Myriam Peralta-Carcelen, MD
Department/Institution/Address: Pediatrics, University of Alabama at Birmingham, 1600 7th Avenue South, Birmingham, AL, 35233, United States
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Responsible Author Declaration: As the responsible author, I confirm that the individual listed as the sponsor has been contacted and given the opportunity to review the abstract and has subsequently agreed to sponsor this abstract.

Presenting Author: Myriam Peralta-Carcelen, MD, MPH
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The presenting author is member of these Alliance Societies:
Is Presenting Author a Trainee? No, Not a Trainee
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QUESTIONNAIRE INFORMATION

Eastern Society for Pediatric Research: No, Do not consider this abstract for the Eastern SPR
Pediatric Hospital Medicine: No, Do not consider this abstract for presentation at the Pediatric Hospital Medicine, July 19-22, 2012
Research Type: Clinical
Presentation Sabbath Conflict on: N/A
APA Special Interest Groups, Committees or Regions: None

AWARDS APPLIED FOR:

No awards selected

SPONSOR INFORMATION

Sponsoring Member for PAS/ASPR abstract:

First Author: Yvonne E Vaucher, MD, MPH **Filename:** 750265
Responsible Author: Yvonne E Vaucher, MD, MPH
Presenting Author: Yvonne E Vaucher, MD, MPH
Contact Person: Yvonne E Vaucher, MD. MPH

2012 PAS Annual Meeting

Subspecialty: Neonatal Epidemiology & Follow-Up
Theme: Neonatal Medicine: Clinical Trials

Contact Author: Yvonne E Vaucher, MD. MPH
Department/Institution/Address: Pediatrics,Division of Neonatology, Univ California, San Diego, 200 West Arbor Drive MC 8774, San Diego, CA, 92103, United States
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Reponsible Author: Yvonne E Vaucher, MD, MPH
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Responsible Author Declaration: As the responsible author, I confirm that the individual listed as the sponsor has been contacted and given the opportunity to review the abstract and has subsequently agreed to sponsor this abstract.

Presenting Author: Yvonne E Vaucher, MD, MPH
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The presenting author is member of these Alliance Societies:
Is Presenting Author a Trainee? No, Not a Trainee
Presenter Copyright Declaration:
I certify that any material I will use, display, distribute, reproduce or have reproduced or distributed in connection with my above noted presentation for which I do not have permission to use, is my original work and/or is public information or another type of material which does not require securing permission from another party to use, display, distribute, reproduce or have reproduced or distributed.

QUESTIONNAIRE INFORMATION

Eastern Society for Pediatric Research: No, Do not consider this abstract for the Eastern SPR
Pediatric Hospital Medicine: No, Do not consider this abstract for presentation at the Pediatric Hospital Medicine, July 19-22, 2012
Research Type: Clinical
Presentation Sabbath Conflict on: N/A
APA Special Interest Groups, Committees or Regions: None

AWARDS APPLIED FOR:

No awards selected

SPONSOR INFORMATION

Sponsoring Member for PAS/ASPR abstract:
Sponsor Name: Yvonne Vaucher

Email: yvaucher@ucsd.edu
Is the Sponsor an Author? Yes
Sponsoring Societies:
Academic Pediatric Association
American Academy of Pediatrics
Global Pediatric Research Program

Title: Neurodevelopmental Outcome of Extremely Premature Infants Enrolled in the SUPPORT trial: Early CPAP versus Intubation with Surfactant Administration

Yvonne E Vaucher, MD, MPH[1], Marie G Gantz, PhD[2], Neil N Finer, MD[1] and Rosemary D Higgins, MD[3]. [1]Division of Neonatology, Department of Pediatrics, University of California,, San Diego, CA, United States; [2]Statistics and Epidemiology, RTI International, Research Triangle Park, NC, United States and [3]SUPPORT Subcommittee of the NICHD Neonatal Research Network, NICHD, Rockville, MD, United States.

Background: The multicenter SUPPORT randomized, controlled trial demonstrated that initial treatment with non-invasive CPAP is an alternative to early surfactant administration after intubation and is associated with similar rates of death or BPD in infants born at 24 to 27 weeks gestation.

Objective: We hypothesized that, compared to treatment with surfactant administration after intubation, treatment with early CPAP would decrease the composite outcome of death or neurodevelopmental impairment (NDI).

Design/Methods: The SUPPORT Trial enrolled 1316 extremely premature infants, 24 to 27 weeks gestation, randomized to receive either CPAP in the delivery room with a limited ventilation strategy for two weeks (CPAP) or intubation with surfactant administration within one hour after birth (SURF). Infants were randomized within each center by gestational age strata (24 0/7-25 6/7 and 26 0/7-27 6/7 weeks). A standardized neurodevelopmental assessment was performed at 18-22 months corrected age. The primary, pre-specified composite outcome was death or NDI including at least one of the following: BSID-III cognitive score < 70, Gross Motor Function Classification System (GMFCS) score 2, moderate/severe cerebral palsy, bilateral blindness or permanent hearing impairment. Results were adjusted for gestational age, center and familial clustering.

Results: Death or NDI was determined for 1234/1316 (93.8%) enrolled infants. Death or NDI occurred in 27.9% (173/621) of CPAP and 29.9% (183/613) of SURF infants (p=0.38). Rates of death (CPAP-18.4 vs. SURF-21.9%, p=0.10), NDI alone (CPAP-10.9 vs. SURF 9.1%, p=0.44), cognitive score < 70 (CPAP-7.2 vs. SURF-7.6%, p=0.84), moderate/severe cerebral palsy (CPAP-4.1 vs. SURF-4.0%, p=0.82), GMFCS 2 (CPAP-5.1 vs. SURF 4.8%, p=0.95); blindness (CPAP-0.8 vs. SURF 1.5%, p=0.31), and permanent hearing impairment (CPAP-3.3 vs. SURF-1.5%, p=0.06) were similar in both treatment arms. There were no significant differences in neurodevelopmental outcomes between CPAP and SURF groups within each GA stratum.

Conclusions: We found no significant difference in the composite outcome of death or neurodevelopmental impairment at 18-22 months corrected age between extremely premature infants randomized to treatment with either early CPAP or intubation and surfactant administration.

Other Previews:
Abstract Disclosure Info:

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: SUPPORT weighted analysis
Date: Tuesday, November 22, 2011 1:26:00 PM

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301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Tuesday, November 22, 2011 1:19 PM
To: Das, Abhik; Rich, Wade
Cc: Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie; wacarlo@uab.edu
Subject: RE: SUPPORT weighted analysis

I think the idea and methods are great. I have no reservations.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
1700 6th Avenue South
176F Suite 9380R
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
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From: Das, Abhik [mailto:adas@rti.org]
Sent: Tuesday, November 22, 2011 11:18 AM
To: Rich, Wade
Cc: Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie; wacarlo@uab.edu
Subject: RE: SUPPORT weighted analysis

Wade:

We did this analysis as a spin off from your antenatal consent study when Neil started asking about any impact on the treatment effect that our consent process may have caused by enrolling a specialized/atypical sample into the trial. This was the only, albeit non-traditional, way that I could think of to begin to answer that type of question. So, this work is very much a logical follow up from our work on the antenatal consent study and your work with Marie on identifying the differences between the trial sample and the GDB non enrolled but eligible sample. We will definitely work with you on developing this further into a paper. For the abstract, time was short and we targeted this more towards the expected statistical audience for this conference. However any comments you have will be more than welcome. Unless you have serious objections, we would very much like to retain both you and Rose as co-authors on this, because it will certainly be more credible to have clinical collaborators and the funding agency represented on the authorship.

Thanks a lot

Abhik

From: Rich, Wade [mailto:wrich@ucsd.edu]
Sent: Tuesday, November 22, 2011 11:57 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.; Finer, Neil; 'kurt.schibler@cchmc.org'; Michele Walsh; 'Roger Faix'; 'Laptook, Abbot'; 'Bradley Yoder'; Das, Abhik; Gantz, Marie; nxs5@cwru.edu
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: SUPPORT weighted analysis

I do not need to be an author for this abstract. I did not participate in its preparation.
Wade

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, November 21, 2011 11:36 AM
To: Wally Carlo, M.D.; Finer, Neil; 'kurt.schibler@cchmc.org'; Michele Walsh; 'Roger Faix'; 'Laptook, Abbot'; 'Bradley Yoder'; Abhik Das (adas@rti.org); 'Gantz, Marie'; nxs5@cwru.edu; Rich, Wade
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: SUPPORT weighted analysis
Importance: High

Hi

Attached are two items: (1) results of the weighted analysis of SUPPORT data (in which the enrolled infants are weighted to reflect the characteristics of the eligible population), and (2) an abstract for the Society for Clinical Trials meeting in May on the statistical methods used for this analysis. Wade is listed as a coauthor on the abstract, which we would like to submit for SUPPORT subcommittee and Steering Committee approval this week (the abstract deadline is December 1). Please let us know if you have any comments on the abstract. If you have any questions about the weighted analysis, please let Darryl and Marie know. Darryl does survey analysis at RTI, and he performed the weighting and weighted analyses presented in the attached.

The meeting info is:

Society for Clinical Trials, 33rd Annual Meeting
May 20-23, 2011
Miami, FL

Please send me a yes/no vote by November 25 for Marie to submit the abstract.

Thanks

Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: SUPPORT weighted analysis
Date: Tuesday, November 22, 2011 12:20:00 PM

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From: Newman, Nancy S [mailto:Nancy.Newman2@UHhospitals.org]
Sent: Tuesday, November 22, 2011 12:20 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT weighted analysis

I vote yes to the abstract.

Nancy

Nancy Newman, BA, RN
Case Western Reserve University
Rainbow Babies and Children's Hospital
nxs5@case.edu

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, November 21, 2011 2:36 PM
To: Wally Carlo, M.D.; Finer, Neil; 'kurt.schibler@cchmc.org'; Michele Walsh; 'Roger Faix'; 'Laptook, Abbot'; 'Bradley Yoder'; Abhik Das (adas@rti.org); 'Gantz, Marie'; nxs5@cwru.edu; Rich, Wade
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: SUPPORT weighted analysis
Importance: High

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Rich, Wade"
Subject: RE: SUPPORT weighted analysis
Date: Tuesday, November 22, 2011 12:06:00 PM

Are you ok with submission??

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From: Rich, Wade [mailto:wrich@ucsd.edu]
Sent: Tuesday, November 22, 2011 11:57 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.; Finer, Neil; 'kurt.schibler@cchmc.org'; Michele Walsh; 'Roger Faix'; 'Laptook, Abbot'; 'Bradley Yoder'; Abhik Das (adas@rti.org); 'Gantz, Marie'; nxs5@cwru.edu
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: SUPPORT weighted analysis

I do not need to be an author for this abstract. I did not participate in its preparation.
Wade

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Sent: Monday, November 21, 2011 11:36 AM
To: Wally Carlo, M.D.; Finer, Neil; 'kurt.schibler@cchmc.org'; Michele Walsh; 'Roger Faix'; 'Laptook, Abbot'; 'Bradley Yoder'; Abhik Das (adas@rti.org); 'Gantz, Marie'; nxs5@cwru.edu; Rich, Wade
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: SUPPORT weighted analysis
Importance: High

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Please send me a yes/no vote by November 25 for Marie to submit the abstract.

Thanks
Rose

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Das, Abhik"; "Gantz, Marie"
Subject: RE: SUPPORT weighted analysis
Date: Tuesday, November 22, 2011 10:54:00 AM

We can tell the SC that the subcommittee approves, I send it out asking for only objections – I can send through clearance today.

Rose

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From: Das, Abhik [mailto:adas@rti.org]
Sent: Tuesday, November 22, 2011 10:50 AM
To: Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT weighted analysis

I guess it is fine for the subcommittee to have the rest of the week.

Rose: I was thinking that if the subcommittee is fine with this, we don't necessarily need SC approval? We would need NICHD clearance before we can submit this by Dec 1.

Thanks

Abhik

From: Gantz, Marie
Sent: Tuesday, November 22, 2011 10:47 AM
To: 'Higgins, Rosemary (NIH/NICHD) [E]'
Cc: Das, Abhik
Subject: RE: SUPPORT weighted analysis

Will we be able to ask the SC for approval at the meeting today if the subcommittee still has the rest of the week to vote?

Marie

Marie Gantz, Ph.D.

Senior Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, November 21, 2011 2:42 PM
To: Gantz, Marie
Subject: RE: SUPPORT weighted analysis

This will hopefully be quick if folks are reading email

Rose

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Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Monday, November 21, 2011 2:38 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT weighted analysis

Thanks, Rose.

Marie

Marie Gantz, Ph.D.
Senior Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, November 21, 2011 2:36 PM
To: Wally Carlo, M.D.; Finer, Neil; 'kurt.schibler@cchmc.org'; Michele Walsh; 'Roger Faix'; 'Laptook, Abbot'; 'Bradley Yoder'; Das, Abhik; Gantz, Marie; nxs5@cwru.edu; Rich, Wade
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: SUPPORT weighted analysis
Importance: High

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Miami, FL

Please send me a yes/no vote by November 25 for Marie to submit the abstract.

Thanks
Rose

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Blaisdell, Carol (NIH/NHLBI) [E]
Cc: Zaterka-Baxter, Kristin; Das, Abhik
Subject: Blaisdell. thank you.pdf - Adobe Acrobat Professional
Date: Tuesday, November 22, 2011 9:20:00 AM
Attachments: Blaisdell. thank you.pdf

Carol

Thanks for serving on our DSMC for SUPPORT and THANK YOU for all the help with SUPPORT.

Best regards

Rose

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

National Institutes of Health
Eunice Kennedy Shriver National
Institute of Child Health and
Human Development
Bethesda, Maryland 20892

November 18, 2011

Carol J. Blaisdell , M.D.
Medical Officer
Division of Lung Diseases
National Heart, Lung, and Blood Institute, NIH
6701 Rockledge Dr., 10042
Bethesda MD 20892

Dear Dr. Blaisdell:

On behalf of the National Institute of Child Health and Human Development and the Neonatal Research Network, we wish to extend our sincere gratitude to you for serving on the Network's Data and Safety Monitoring Committee (DSMC) for the SUPPORT Trial. We are honored by your commitment and contributions to the Network and hope that you benefited from this important collaboration. Your strong leadership and pulmonary expertise have served the Network well by supporting its mission and the efforts of its members. Your commitment to the Network has been evident in your passion for the ideas and accomplishments.

Again, many thanks for all of your efforts on behalf of the Neonatal Research Network. We wish you continued success. For all of your efforts for the Network and, ultimately, the field of maternal and child health, we are deeply appreciative and very proud.

With warmest regards,

Rosemary D. Higgins, M.D.

Program Scientist for the Neonatal Research Network

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Langham, Amira (NIH/NICHD) [E]; Evans, Josephine (NIH/OD) [E]
Cc: "Hoult, Ben (NIH/OD) [E]"
Subject: FW: Hot Topics Speaker - Final Confirmaiton
Date: Tuesday, November 22, 2011 9:18:00 AM
Attachments: 1.4 The Program.doc
RE Panel Discussion Leader at Hot Topics Dec 4-6 2011 - Session on Follow-up..msg

Hi,
I am an invited speaker at Hot Topics in Neonatology to be held Dec. 4-6 at the Omni Shoreham Hotel in DC. They have offered to pay for incidental expenses (parking is $25-30/day). How do we do a sponsored local travel so that we can be reimbursed? Let me know and I can get the paperwork in order.
I also attached the email from Mike Rosenthal stating this was ok for official duty.

Thanks for your help
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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higginsr@mail.nih.gov

From: Bidus, Karen [mailto:kbidus@NEMOURS.ORG]
Sent: Monday, November 21, 2011 4:28 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Hot Topics Speaker - Final Confirmaiton

Dr. Higgins -

Thank you again for agreeing to participate as faculty at *Hot Topics in Neonatology*, scheduled for December 4-6, 2011, at the Omni Shoreham Hotel, in Washington, D.C.

I just wanted to confirm a few details with you before the conference.

SPEAKER READY ROOM - NEW THIS YEAR! To make your experience as a faculty member more enjoyable, we have added a Speaker Ready Room this year. You must report to the Speaker Ready Room across from the conference registration desk at least four hours prior to your talk to sign in for the conference, pick up your badge, and provide the AV team with your talk. Staff will be happy to run through your talk with you, and make any changes you deem necessary. The Speaker Ready Room is open 2-6 on Sunday, 7-5 on Monday, and 7-1:30 on Tuesday. The Speaker Ready Room will be stocked with finger foods and coffee/tea for the duration of the conference.

HOTEL RESERVATION - We do not currently have a hotel room reserved for you. If there is a problem

with your reservation, please email Jacque Pass - jpass@nemours.org - as soon as possible.

TRAVEL - We do not have a copy of your travel arrangments from our travel agent, so we are assuming you have made your own arrangments.

EXPENSES - Just a reminder that Nemours will reimburse incidental travel expenses. Please save your itemized receipts - which you can submit at the conference to either Karen Stong or Karen Bidus at the Registrar's desk, or mail in after the conference. Once we receive your speaker reimbursement form and your receipts, we will process your expenses and honoraria for payment. You will receive a check from Nemours within three weeks of submitting your paperwork. We are sorry, we will not be able to pay honoraria or reimburse expenses in cash.

MOST IMPORTANT - Please plan to keep your talk on time. The moderators have been known to take desperate measures to keep the conference on schedule! We've attached the final copy of the program for your information.

Thank you again - please don't hesitate to contact me with any questions or concerns about your participation in Hot Topics. I can be reached at the office at 302-651-6752 through December 1, or my cell phone 302-377-4974 at any time.

Karen Bidus
Director, Office of CME
Alfred I. duPont Hospital for Children
302-651-6752

Nemours has received Accreditation with Commendation from the ACCME.

Please consider the environment before printing this e-mail.

Hot Topics in Neonatology®

December 4-6, 2011

Sunday, December 4

2:00 p.m. – 6:00 p.m. Registration at West Registration Desk
6:00 p.m. – 7:00 p.m. Reception – Empire Room

Monday, December 5

7:00 a.m. Registration at West Registration Desk/ Continental Breakfast
7:45 a.m. Doors open
8:15 a.m. Welcome and Introductions – *Jerold F. Lucey, MD and Jay Greenspan, MD, MBA*

Current Interest

Moderator – Andrew R. Wilkinson, MB ChB, MRCP, DCH

8:30 a.m. Late Effects of Anesthesia in Infants – *Mary Ellen McCann, MD, MPH*
8:50 a.m. Questions
9:00 a.m. Prenatal Surgery for Spina Bifida: MOMS Trial – *N. Scott Adzick, MD*
9:20 a.m. Questions
9:30 a.m. Cord Blood Storage: Pro and Con – *Mervin C. Yoder, MD*
9:50 a.m. Questions
10:00 a.m. Coffee Break/ Poster Viewing/Exhibits**

Green Apples! Promising but?

Moderator – M. Jeffrey Maisels, MD, DSc

10:30 a.m. Neonatal Hyperbilirubinemia: Stanate® – *Simon Tulloch, MD*
10:50 a.m. Questions
11:00 a.m. Cost-effectiveness of routine bilirubin screening – *Gautham K. Suresh, MD, DM, MS*
11:10 a.m. Audience questions and comments by *M. Jeffrey Maisels, MD, DSc*
11:30 a.m. Autologous Cord Blood Cells for HIE – *Charles Michael Cotten, MD, MHSC*
11:50 a.m. Questions
Noon Lunch (on your own)/Poster Viewing/Exhibits**

Perinatology

Moderator – Jay S. Greenspan, MD, MBA

1:30 p.m. Antenatal Steroids: What has Happened Since Liggins and Howie – *Ronald Wapner, MD*
2:00 p.m. The Role of Progestogens in the Prevention of Preterm Birth – *Roberto Romero, MD*
2:30 p.m. Discussion & Audience Questions – *Roberto Romero, MD and Ronald Wapner, MD*
3:00 p.m. Coffee Break/Poster Viewing/Exhibits**

The Future

Moderator – Terrie Inder, MB ChB, MD

3:30 p.m. Oxygenation Targets: Can They be Achieved? - *Eduardo Bancalari, MD*
3:50 p.m. Questions
4:00 p.m. What's New in Imaging – *Terrie Inder, MB ChB, MD*
4:20 p.m. Questions
4:30 p.m. A Brave New World: Telemedicine and eHealth in Neonatology – *Dale C. Alverson, MD*
4:50 p.m. Questions
5:00 p.m. Adjourn
5:30 – 6:30 p.m. Reception in the Empire Room – Meet a Robot!

Tuesday, December 6

7:00 a.m. Registration at West Registration Desk/ Continental Breakfast
7:30 a.m. Doors open

Current Interest
Moderator – Alan H. Jobe, MD, PhD

8:00 a.m. Bevacizumab – Treatment for ROP – *Helen Mintz-Hittner, MD*
8:20 a.m. Point-Counterpoint – *Graham E. Quinn, MD, MSCE and Helen Mintz-Hittner, MD*
8:30 a.m. Questions
8:35 a.m. Follow-up – 7 Years of Brain Cooling NICHD Trial – *Seetha Shankaran, MD*
8:55 a.m. Questions
9:05 a.m. Long Term Follow-up: Creative Measures to Ensure Maximal Return
Panel Discussion – *Maureen Hack, MB ChB; Rosemary D. Higgins, MD; Seetha Shankaran, MD; Betty Vohr, MD*
9:30 a.m. Getting the Most Out of Follow-up Programmes – *David W.A. Milligan, MD, FRCPH*
9:50 a.m. Questions
10:00 a.m. Coffee Break/Poster Viewing/Exhibits **

Brain Cooling Plus What?
Moderator – David Edwards, DSc, FMed Sci

10:30 a.m. Update on EPO Neuroprotection- Has its Time Come? – *Sandra Juul, MD, PhD*
10:50 a.m. Questions
11:00 a.m. Review of Adult Brain Cooling - *Robert C. Tasker, MBBS, MD, FRCP*
11:20 a.m. Questions
11:30 a.m. Brain Cooling and Xenon – *Marianne Thoresen, MD, PhD*
11:50 a.m. Current Thoughts on the Future of Brain Cooling Plus Other Possible Therapies –
Panel Discussion – *David Edwards, DSc, FMedSci; Terrie Inder, MB ChB, MD; Marianne Thoresen, MD, PhD*
12:30 p.m. Lunch (on your own)/Poster Viewing/Exhibits**

Nutrition
Moderator – Avroy A. Fanaroff, MD

1:45 p.m. Early Nutrition and Long-term Risk of Obesity – *Atul Singhal, MD*
2:05 p.m. Questions
2:15 p.m. Lactoferrin in Preterm Neonates – *Paolo Manzoni, MD*
2:35 p.m. Questions
2:45 p.m. Caffeine for Apnea of Prematurity Trial: Outcomes at Age 5 Years - *Barbara Schmidt, MD*
3:05 p.m. Questions
3:15 p.m. NICHD Support Trial Follow-Up Outcomes –*Myriam Peralta Carceleen, MD, MPH; Yvonne E. Vaucher, MD, MPH*
3:55 p.m. Questions
4:15 p.m. Adjourn

** Breaks include music and slides by Sheldon Korones, MD.

ACCREDITATION

Nemours is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

Nemours designates this live activity for a maximum of 12.0 AMA PRA Category 1 Credits™. Physicians should only claim the credit commensurate with the extent of their participation in the activity.

Blansfield, Earl (NIH/NICHD) [E]

From: Rosenthal, Mike (NIH/NICHD) [C]
Sent: Friday, February 18, 2011 1:11 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Panel Discussion Leader at Hot Topics, Dec 4-6, 2011 - Session on Follow-up.

Hi Rose,

I see no ethics issues with this as an official duty activity.

Mike

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Thursday, February 17, 2011 7:54 PM
To: Spong, Catherine (NIH/NICHD) [E]; Rosenthal, Mike (NIH/NICHD) [C]
Subject: Fw: Panel Discussion Leader at Hot Topics, Dec 4-6, 2011 - Session on Follow-up.

Would this be acceptable? The meeting is in DC.

Rose

----- Original Message -----
From: Gail M. Murphy <info@hottopics.org>
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Jay Greenspan <jgreensp@nemours.org>
Sent: Thu Feb 17 19:01:29 2011
Subject: RE: Panel Discussion Leader at Hot Topics, Dec 4-6, 2011 - Session on Follow-up.

Thanks for your great suggestions for Hot Topics 2011. I'd like you to lead a panel discussion on Follow-up which I will assemble in the next few weeks.

Dr. Jay Greenspan will send you a formal invitation in a few weeks which you can use to get approval for accepting an invitation to be a speaker at Hot Topics.

Sincerely yours,

Jerold F. Lucey MD
Professor of Pediatrics- Emeritus
University of Vermont College of Medicine Editor Emeritus, Pediatrics Burlington, VT 05405

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "merran.thomson@imperial.ac.uk"
Cc: "Zaterka-Baxter, Kristin"; "Das, Abhik"
Subject: THANKS
Date: Monday, November 21, 2011 4:29:00 PM
Attachments: Thomson thank you.pdf

Merran
Thanks so much for serving on our SUPPORT DSMC. We really appreciate your commitment and dedication.

With warmest regards,
Rose

Rosemary D. Higgins, MD
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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

National Institutes of Health
Eunice Kennedy Shriver National
Institute of Child Health and
Human Development
Bethesda, Maryland 20892

November 18, 2011

Merran A. Thomson, MD
Specialty: Neonatology, Respiratory Physiology
Department of Paediatrics and Neonatal Medicine
Hammersmith Hospital,
Du Cane Road
London W12 0HS (UK)

Dear Dr. Thomson:

On behalf of the National Institute of Child Health and Human Development and the Neonatal Research Network, we wish to extend our sincere gratitude to you for serving on the Network's Data and Safety Monitoring Committee (DSMC) for the SUPPORT Trial. We are honored by your commitment and contributions to the Network and hope that you benefited from this important collaboration. Your strong leadership and neonatal pulmonary expertise have served the Network well by supporting its mission and the efforts of its members. Your commitment to the Network has been evident in your passion for the ideas and accomplishments.

Again, many thanks for all of your efforts on behalf of the Neonatal Research Network. We wish you continued success. For all of your efforts for the Network and, ultimately, the field of maternal and child health, we are deeply appreciative and very proud.

With warmest regards,

R Higgins

Rosemary D. Higgins, M.D.

Program Scientist for the Neonatal Research Network

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: SUPPORT weighted analysis
Date: Monday, November 21, 2011 2:37:00 PM

I am also a yes

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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From: Das, Abhik [mailto:adas@rti.org]
Sent: Monday, November 21, 2011 2:37 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT weighted analysis

You have my vote!

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, November 21, 2011 2:36 PM
To: Wally Carlo, M.D.; Finer, Neil; 'kurt.schibler@cchmc.org'; Michele Walsh; 'Roger Faix'; 'Laptook, Abbot'; 'Bradley Yoder'; Das, Abhik; Gantz, Marie; nxs5@cwru.edu; Rich, Wade
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: SUPPORT weighted analysis
Importance: High

Hi

Attached are two items: (1) results of the weighted analysis of SUPPORT data (in which the enrolled infants are weighted to reflect the characteristics of the eligible population), and (2) an abstract for the Society for Clinical Trials meeting in May on the statistical methods used for this analysis. Wade is listed as a coauthor on the abstract, which we would like to submit for SUPPORT subcommittee and Steering Committee approval this week (the abstract deadline is December 1). Please let us know if you have any comments on the abstract. If you have any questions about the weighted analysis, please let Darryl and Marie know. Darryl does survey analysis at RTI, and he performed the weighting and weighted analyses presented in the attached.

The meeting info is:

Society for Clinical Trials, 33rd Annual Meeting
May 20-23, 2011
Miami, FL

Please send me a yes/no vote by November 25 for Marie to submit the abstract.

Thanks

Rose

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Wally Carlo, M.D."; "Finer, Neil"; "kurt.schibler@cchmc.org"; "Michele Walsh"; "Roger Faix"; "Laptook, Abbot"; "Bradley Yoder"; "Abhik Das (adas@rti.org)"; "Gantz, Marie"; "nxs5@cwru.edu"; "Rich, Wade"
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: SUPPORT weighted analysis
Date: Monday, November 21, 2011 2:35:00 PM
Attachments: SUPPORTWeightAdjusmentFinal.docx
sct abstract1_fin.docx
Importance: High

Hi

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SUPPORT Study Enrollment Propensity Weighting

Background

The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants (SUPPORT) was a randomized, 2X2 factorial designed multi-center trial conducted by the *Eunice Kennedy Shriver* NICHD Neonatal Research Network (NRN) (Clinical Trials Gov. Number, NCT 00233324) (REF). The trial prospectively compared Continuous Positive Airway Pressure (CPAP) and a protocol driven limited ventilatory strategy begun in the delivery room and continuing in the Neonatal Intensive Care Unit with the early (< 1 hour) intratracheal administration of surfactant followed by conventional mechanical ventilation. Infants were also randomized to a prospective comparison of a lower oxygen saturation target range (85% to 89%) with a higher, more conventional target range (91% to 95%) until 36 weeks postmenstrual age or the infant was no longer requiring ventilatory support or oxygen, using purpose altered oximeters. Eligible infants were those born at NRN centers at 24 0/7 to 27 6/7 weeks gestational age (GA), without known major congenital malformations, and with full resuscitation intended. Randomization was performed in the delivery room and was stratified by study center and GA group (24 0/7 – 25 6/7 weeks and 26 0/7 – 27 6/7 weeks). Multiple births were randomized together. Antenatal consent was required for enrollment.

Comment [MG1]: This was lifted from the most recent Antenatal Consent paper.

Of the 4,369 infants who were inborn at Neonatal Research Network centers and eligible for enrollment in the SUPPORT study, 1,316 were enrolled in the trial. A comparison of enrolled and non-enrolled infants revealed statistically significant differences, including higher socioeconomic status and higher exposure to antenatal steroids in the enrolled group (REF). These differences, which were attributed to the requirement of antenatal consent, led to concern about the generalizability of the results of the SUPPORT study, and to speculation that the results might have differed if the enrolled infants had the same characteristics as the eligible population. To address these issues, we conducted a secondary analysis in which the infants enrolled in SUPPORT were weighted to reflect the characteristics of the eligible population. We refer to this type of weighting as enrollment propensity weighting.

Methods

Outcome Definitions

The primary outcome in the arm of the trial that compared CPAP to early surfactant was the composite outcome of bronchopulmonary dysplasia (BPD) or death by 36 weeks postmenstrual age (PMA). BPD was defined two ways: (1) use of supplemental oxygen (BPD1), and (2) failure of a physiologic challenge that attempted to wean the infant from supplemental oxygen (BPD2). The primary outcome in the arm of the trial that compared the higher and lower oxygen saturation targets was the composite outcome of severe retinopathy of prematurity (ROP) or death while hospitalized. Severe ROP was defined as Type 1 ROP or ROP that required treatment with surgery or bevacizumab.

Statistical Methods

Classification and Regression Trees (CART®) methods were used to model whether or not eligible infants were enrolled in SUPPORT based on study center, maternal characteristics including age, marital status, antenatal antibiotics and steroids, and infant characteristics including gender, multiple birth, weight, GA, race and Apgar scores at 1 and 5 minutes. CART® reveals complex relationships in data through a process of recursive partitioning in which a series of binary splits divide observations into homogeneous groups based on values of the independent variables that minimize the within-group variance of the dependent variable. This results in a tree structure where observations with common values of the independent variables that are most predictive of the outcome are grouped together.

SUDAAN's® WTADJUST procedure was used to adjust the enrollment propensity weights; CART® group, center, gender, race, GA, any antenatal steroids, and full course of antenatal steroids were predictors in the weight adjustment model. Prior to weighting, missing values for any antenatal steroids and full course of antenatal steroids were imputed using SUDAAN®'s HOTDECK procedure, with CART® group, center, race, and GA as predictors for any antenatal steroids and the same variables plus any antenatal steroids as predictors for full course of antenatal steroids.

SUDAAN®'s analytic procedures were used to analyze the weighted data, accounting for stratification by center and GA group, and for familial clustering; the original analysis of the SUPPORT data also adjusted for these

design factors. In addition, the SUDAAN® models incorporated the adjusted weights and, because a finite number of infants were eligible for SUPPORT, appropriately reduced the variance based on a finite population correction.

Results

CART divided the 4,369 eligible infants into 7 groups, ranging in size from 136 to 1,156 infants (Figure). The CART groups were based on values of the variables for study center, full course of antenatal steroids, antenatal antibiotics, and GA (greater than 25 1/7 weeks). The proportion of enrolled infants in each of the 7 CART groups ranged from 13% to 55%, demonstrating that there was substantial variation in the likelihood of enrollment, or the enrollment propensity, between the groups.

Fifteen enrolled infants were missing responses for both the any antenatal steroids and full course of antenatal steroids variables; an additional 27 infants were missing a response for full course of antenatal steroids. Missing values were sequentially imputed for any antenatal steroids followed by full course.

The adjusted enrollment propensity weights of the 1,316 enrolled infants summed to 4,369, the number of eligible infants. The summed weights for each predictor in the weight adjustment model matched the eligible infant count (Table 1). The largest differences between the pre- and post-weighting characteristics of the enrolled infants were in antenatal steroid exposure (96 vs. 88% for any steroids, 72 vs. 56% for full course).

In the primary analysis of SUPPORT data (REF), there was not a significant difference between the CPAP and surfactant treatment groups with respect to the primary outcome of death or BPD by 36 weeks PMA using either BPD definition, nor were there significant differences for death alone or BPD among survivors to 36 weeks PMA. Likewise, there was not a significant difference between the low and high oxygen saturation target groups for the primary outcome of death or severe ROP or for severe ROP among survivors. Death while hospitalized was more frequent in the high oxygen saturation target group (16.2 vs. 19.9%, Relative risk (RR) 1.27, 95% Confidence interval (CI) 1.01, 1.6).

In the analysis of the weighted SUPPORT data, the results were similar to the primary analysis. The largest difference was in the percent of infants with BPD1 or death by 36 weeks PMA in the CPAP and surfactant groups (48.7 vs. 54.1% for CPAP vs. surfactant pre-weighting, 51.9 vs. 58.6% post-weighting). Although there was a slightly greater incidence of BPD1 or death in both groups after weighting, the relative risk remained nearly the same (RR 0.91, 95% CI 0.83, 1.01 pre-weighting, RR 0.89, 95% CI 0.79, 0.99 post-weighting). Likewise, rates of BPD1 and BPD2 among survivors and BPD2 or death by 36 weeks PMA were higher in the weighted data but the relative risks did not change substantially from the original analysis results. Results for the death and severe ROP outcomes were very similar in the pre- and post-weighting analyses; percentages of infants with the outcomes changed by less than one percent, and the relative risks were nearly identical.

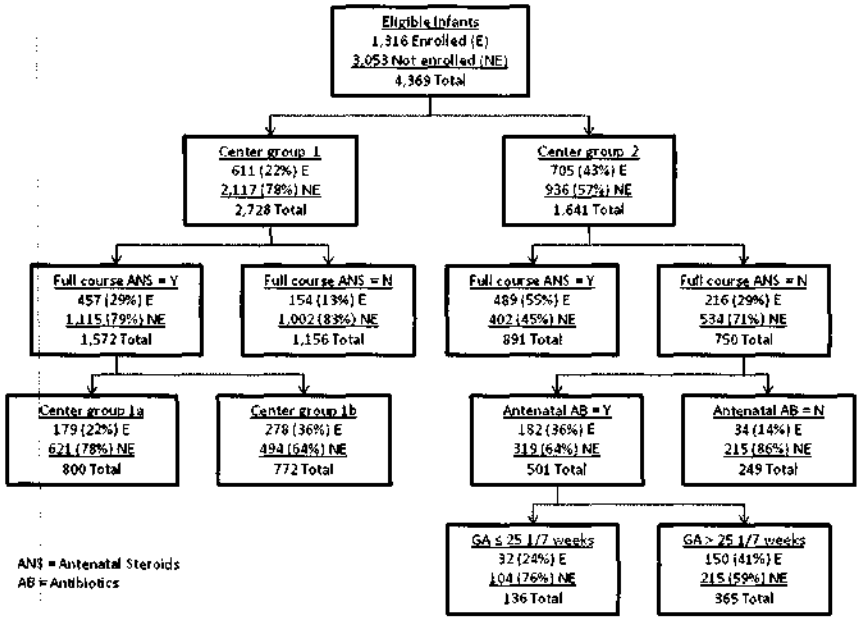

Figure. CART® Tree

Variable	Pre-Weighting Total=1316 Sum (%)	Post-Weighting Total=4369 Sum (%)
CART group		
1	154 (12)	1,156 (26)
2	179 (14)	800 (18)
3	278 (21)	772 (18)
4	34 (3)	249 (6)
5	32 (2)	136 (3)
6	150 (11)	365 (8)
7	489 (37)	891 (20)
Center		
A	184 (14)	438 (10)
B	124 (9)	268 (6)
C	107 (8)	199 (5)
D	90 (7)	458 (10)
E	86 (7)	255 (6)
F	85 (6)	348 (8)
G	74 (6)	303 (7)
H	74 (6)	142 (3)
I	73 (6)	201 (5)
J	68 (5)	263 (6)
K	65 (5)	247 (6)
L	57 (4)	138 (3)
M	56 (4)	191 (4)
N	52 (4)	272 (6)
O	37 (3)	240 (5)
P	29 (2)	112 (3)
Q	21 (2)	99 (2)
R	17 (1)	75 (2)
S	9 (1)	74 (2)
T	8 (1)	46 (1)
Male	712 (54)	2,319 (53)
Race		
Non-Hispanic Black	489 (37)	1,677 (38)
Non-Hispanic White	521 (40)	1,624 (37)
Hispanic	259 (20)	847 (19)
Other/unknown	47 (4)	221 (5)
GA 24 0/7 – 25 6/7 weeks	565 (43)	1,989 (46)
Antenatal steroids – any	1,266 (96)	3,842 (88)
Antenatal steroids – full course	946 (72)	2,463 (56)

Table 1. Variables Used in Weighting, Pre- and Post- Weighting Counts and Percentages

Outcome	Pre-Weighting Results		Post-Weighting Results	
	CPAP vs. Surfactant %	RR (95% CI)	CPAP vs. Surfactant %	RR (95% CI)
BPD1 or death by 36 weeks PMA	48.7 vs. 54.1	0.91 (0.83, 1.01)	51.9 vs. 58.6	0.89 (0.79, 0.99)
BPD1 among survivors at 36 weeks PMA	40.2 vs. 44.3	0.94 (0.82, 1.06)	43.8 vs. 49.5	0.89 (0.76, 1.03)
BPD2 or death by 36 weeks PMA	47.8 vs. 51.0	0.95 (0.85, 1.05)	51.5 vs. 54.5	0.95 (0.84, 1.07)
BPD2 among survivors at 36 weeks PMA	39.2 vs. 40.6	0.99 (0.87, 1.14)	43.3 vs. 44.4	0.97 (0.83, 1.15)
Death	16.4 vs. 19.6	0.84 (0.67, 1.05)	16.5 vs. 20.2	0.82 (0.64, 1.05)

Table 2a. Analyses of Outcomes in the CPAP vs. Surfactant Treatment Groups, Pre- and Post-Weighting

Outcome	Pre-Weighting Results		Post-Weighting Results	
	Low vs. High Target %	RR (95% CI)	Low vs. High Target %	RR (95% CI)
Severe ROP or death	28.3 vs. 32.1	0.90 (0.76, 1.06)	29.2 vs. 32.0	0.91 (0.75, 1.11)
Severe ROP among survivors	8.6 vs. 17.9	0.52 (0.37, 0.73)	9.1 vs. 18.1	0.50 (0.34, 0.73)
Death	19.9 vs. 16.2	1.27 (1.01, 1.60)	20.6 vs. 16.4	1.26 (0.98, 1.62)

Table 2b. Analyses of Outcomes in the Low vs. High Oxygen Saturation Target Groups, Pre- and Post-Weighting

Enrollment propensity weighting to assess external validity of a randomized clinical trial

Marie Gantz, Darryl Creel, Wade Rich, Rosemary Higgins and Abhik Das for the SUPPORT Trial Subcommittee of the Eunice Kennedy Shriver NICHD Neonatal Research Network (NRN)

Statistics and Epidemiology Unit, RTI International, RTP, NC.

Randomized trials typically enroll a convenience sample of eligible patients without regard to formal probability sampling. However, trial results often substantively change clinical practice for the population at large, without systematic evaluation of external validity.

The Surfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT) used a 2X2 factorial design to test different ventilation and oxygenation strategies for respiratory management of extremely premature babies. This influential and largest of its kind trial demonstrated that a less invasive ventilator strategy may be safe to use and indicated increased mortality at lower oxygen saturation.

Because intervention started upon delivery, antenatal consent was required, and of 4,369 eligible infants, 1,316 were enrolled. Enrolled babies had significantly higher socioeconomic status and greater exposure to antenatal steroids, compared to the non-enrolled. These differences raised questions about the generalizability of the trial results. To address this issue, we conducted a re-analysis of trial outcomes by constructing enrollment propensity weights for enrolled babies, so that the analysis sample better reflected all eligible babies.

We used Classification and Regression Trees to model trial enrollment based on a variety of maternal and infant characteristics available at delivery. We used survey sampling techniques to first construct enrollment propensity weights, and then analyzed the weighted data using models that reduced the variance based on a finite population correction. The results were largely similar to the original unweighted analysis, providing reassurance that the trial results are broadly applicable to the eligible NICU population.

Although weighting to reflect the characteristics of the larger population is common in survey statistics, to our knowledge the approach has not been used to explore external validity for randomized trials conducted on convenience samples of eligible patients. These methods provide a straightforward means to assess validity of trial results when adequate data on the eligible population are available.

From: Vaucher, Yvonne
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT CPAP PAPER
Date: Monday, November 21, 2011 12:40:13 PM

I will also talk with Betty about the best way to proceed.

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]
Sent: Monday, November 21, 2011 9:25 AM
To: Vaucher, Yvonne
Subject: RE: SUPPORT CPAP PAPER

Wait for the comments from others, then we can revise - we should include it!!

Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network
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CDBPM, NIH
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301-496-3790 (FAX)
higginsr@mail.nih.gov

-----Original Message-----
From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]
Sent: Monday, November 21, 2011 12:19 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: SUPPORT CPAP PAPER

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These were my concerns also expressed earlier to the subcommittee.

Yvonne

From: Vohr, Betty [BVohr@WIHRI.org]
Sent: Monday, November 21, 2011 8:39 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; 'Myriam Peralta, M.D.'; Finer, Neil; Wally Carlo, M.D.; Michele Walsh; Gantz, Marie; Laptook, Abbot; 'Bradley Yoder'; 'Roger Faix'; Abhik Das (Adas@rti.org); Rich, Wade; 'kurt.schibler@cchmc.org'; nancy newman; Susan Hintz; 'Kim Yolton'; 'Roy Heyne'; 'drfjcmd@aol.com'; goldb008@mc.duke.edu; 'Michael.Acarregui@providence.org'; 'Evans, Patricia W'; 'Adams-Chapman, Ira'; Pappas, Athina; 'Anna M. Dusick, MD'; 'emcgowan@tuftsmedicalcenter.org'; 'Ehrenkranz, Richard'; 'abodnar@utah.gov'; 'Bauer, Charles R'; 'JaFuller@salud. unm. edu (JaFuller@salud.unm.edu)'; 'Michael O`Shea'; 'gary_myers@URMC.Rochester.edu'
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Betty

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Sent: Saturday, November 19, 2011 7:55 AM
To: 'Myriam Peralta, M.D.'; 'Finer, Neil'; Wally Carlo, M.D.; Michele Walsh; Gantz, Marie; Laptook, Abbot; 'Bradley Yoder'; 'Roger Faix'; Abhik Das (Adas@rti.org); 'Rich, Wade'; 'kurt.schibler@cchmc.org'; nancy newman; Vohr, Betty; Susan Hintz; 'Kim Yolton'; 'Roy Heyne'; (b)(6) @aol.com'; goldb008@mc.duke.edu; 'Michael.Acarregui@providence.org'; 'Evans, Patricia W'; 'Adams-Chapman, Ira'; Pappas, Athina; 'Anna M. Dusick, MD'; 'emegowan@tuftsmedicalcenter.org'; 'Ehrenkranz, Richard'; 'abodnar@utah.gov'; 'Bauer, Charles R'; 'JaFuller@salud. unm. edu (JaFuller@salud.unm.edu)'; 'Michael O`Shea'; 'gary_myers@URMC.Rochester.edu'
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Subject: SUPPORT CPAP PAPER
Importance: High

Hi,
Attached is the SUPPORT CPAP FU Paper for co-author input. Please send your comments to Yvonne Vaucher (yvaucher@ucsd.edu<mailto:yvaucher@ucsd.edu>) by DECEMBER 3. The paper will then go for internal NRN review and clearance. Following this, it will be submitted along with the oximetry FU paper (you will get this in the next few days) to the New England Journal of Medicine.
I have also included the steering committee PI's from the sites involved with the study. If you have any suggestions, feel free to forward them to Yvonne. Thanks to everyone for all the hard work, effort and commitment to this study!!
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Rosemary D. Higgins, MD
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From: Vaucher, Yvonne
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: SUPPORT CPAP PAPER
Date: Monday, November 21, 2011 12:20:15 PM
Attachments: Vaucher SUPPORT FU CPAP PAPER forFUP_PIs_FinalREV111811.docx

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Early CPAP versus Surfactant in Extremely Preterm Infants: Neurodevelopmental Outcomes in Early Childhood

Yvonne E. Vaucher, MD MPH[1]; Myriam Peralta-Carcelen, MD MPH[2]; Neil N. Finer, MD[1]; Waldemar A. Carlo, MD[2]; Michele C. Walsh, MD MS[3]; Marie G. Gantz, PhD[4]; Abbot R. Laptook, MD[5]; Bradley A. Yoder, MD[6]; Roger G. Faix, MD[6]; Abhik Das, PhD[7]; Kurt Schibler, MD[8]; Wade Rich, RRT[2]; Nancy S. Newman, RN[4]; Betty R. Vohr, MD[5]; Kimberly Yolton, PhD[8]; Roy J. Heyne, MD[9]; Deanne E. Wilson-Costello, MD[4]; Patricia W. Evans, MD[10]; Ricki F. Goldstein, MD[11]; Michael J. Acarregui, MD[12]; Ira Adams-Chapman, MD[13]; Athina Pappas, MD[14]; Susan R. Hintz, MD MS Epi[15]; Anna M. Dusick, MD FAAP[16]; Elisabeth C. McGowan, MD[17]; Richard A. Ehrenkranz, MD[18]; Anna Bodnar, MD[6]; Charles R. Bauer, MD[19]; Janell Fuller, MD[20]; T. Michael O'Shea, MD MPH[21]; Gary J. Myers, MD[22]; Rosemary D. Higgins, MD[23] for the SUPPORT Study Group of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network

Corresponding author and reprints:

Yvonne E. Vaucher, M.D., M.P.H. Telephone: 619-543-3759

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[5] Department of Pediatrics, Women & Infants Hospital, Brown University, Providence, RI
[6] Department of Pediatrics, Division of Neonatology, University of Utah School of Medicine, Salt Lake City, UT
[7] Statistics and Epidemiology Unit, RTI International, Rockville, MD
[8] Department of Pediatrics, Cincinnati Children's Hospital Medical Center and University of Cincinnati, Cincinnati, OH
[9] Department of Pediatrics, University of Texas Southwestern Medical Center, Dallas, TX
[10] Department of Pediatrics, University of Texas Medical School at Houston, Houston, TX
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[12] Department of Pediatrics, University of Iowa, Iowa City, IA (current affiliation Children's Hospital at Providence, Anchorage, AK)
[13] Emory University School of Medicine, Department of Pediatrics, and Children's Healthcare of Atlanta, Atlanta, GA
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[15] Department of Pediatrics, Division of Neonatal and Developmental Medicine, Stanford University School of Medicine and Lucile Packard Children's Hospital, Palo Alto, CA
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[17] Department of Pediatrics, Division of Newborn Medicine, Floating Hospital for Children, Tufts Medical Center, Boston, MA
[18] Department of Pediatrics, Yale University School of Medicine, New Haven, CT
[19] University of Miami Miller School of Medicine, Miami, FL
[20] University of New Mexico Health Sciences Center, Albuquerque, NM
[21] Wake Forest University School of Medicine, Winston-Salem, NC
[22] Department of Pediatrics, University of Rochester Medical Center, Rochester, NY
[23] *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD

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ABSTRACT

BACKGROUND: The recent randomized, multicenter SUPPORT trial demonstrated that initial treatment with early, non-invasive CPAP is an alternative to early surfactant administration after intubation and is associated with similar rates of death or BPD in infants born at 24 to 27 weeks gestation. We hypothesized that, compared to treatment with surfactant after intubation, treatment with early CPAP would decrease the composite outcome of mortality or neurodevelopmental impairment at 18-22 months corrected age.

METHODS: We followed surviving infants, 24 0/7 to 27 6/7 weeks gestation, who were randomized in the SUPPORT trial to receive either early CPAP with limited ventilation or intubation with surfactant administration within one hour after birth. A comprehensive, standardized neurodevelopmental assessment was performed at 18-22 months corrected age. The primary composite outcome was death or neurodevelopmental impairment (NDI) which was defined as having any of the following: Bayley Scales of Infant and Toddler Development (3rd ed.) cognitive score < 70, Gross Motor Function Classification System score of ≥ 2, moderate/severe cerebral palsy, bilateral blindness or permanent hearing impairment. Results were adjusted for gestational age stratum, center and familial clustering.

RESULTS: Death or NDI was determined for 1234/1316 (93.8%) of infants enrolled in SUPPORT and 93.5% (990/1058) of survivors to hospital discharge were evaluated at 18-22 months corrected age. Death or NDI occurred in 27.9% (173/621) of the CPAP group and in 29.9% (183/613) of the Surfactant group (p=0.39). Rates of death (CPAP-18.4 vs. Surf-21.9%, p=0.10), and outcomes among survivors including NDI alone (CPAP-10.9 vs. Surf-9.1%, p=0.44), cognitive score < 70 (CPAP-7.2 vs. Surf-7.6%, p=0.84), moderate/severe cerebral palsy (CPAP-4.1 vs. Surf-4.0%, p=0.82), blindness (CPAP-0.8 vs. Surf-1.5%, p=0.31) and hearing impairment (CPAP-3.3 vs. Surf-1.5%, p=0.06) were similar in both treatment arms. In the most immature stratum (24 0/7-25-6/7 weeks gestation) there were fewer deaths [CPAP-26.4% (73/277) vs. Surf-35.5% (97/273), p=0.02].

CONCLUSION: We found no significant differences in the composite outcome of death or NDI at 18-22 months corrected age between extremely premature infants who were randomized to receive either early CPAP with a limited ventilation strategy if needed or early intubation with surfactant administration followed by conventional ventilation.

BACKGROUND

Extremely premature infants are at high risk for death and neurosensory or developmental impairment in early childhood. [1-6]The risk of impairment increases with decreasing gestational age, severity of illness and as consequence of neonatal complications including intraventricular hemorrhage or periventricular leukomalacia, symptomatic patent ductus arteriosus, necrotizing enterocolitis, prolonged ventilation, bronchopulmonary dysplasia and severe retinopathy of prematurity. [7-21] Although surfactant administration decreases both death and BPD, randomized controlled trials of respiratory interventions including high frequency oscillatory ventilation, high frequency jet ventilation, and inhaled nitric oxide have failed to consistently decrease mortality and morbidity or improve developmental outcome. [22-29]

The recent, multicenter, randomized, controlled SUPPORT trial demonstrated that treatment with non-invasive continuous positive airway pressure (CPAP) shortly after birth is an alternative to surfactant administration after intubation and is associated with similar rates of death or BPD in extremely premature infants born at 24 0/7 to 27 6/7 weeks gestation. [30] Compared with surfactant, early CPAP was associated with less frequent need for postnatal steroids and shorter duration of mechanical ventilation. Both treatment groups had similar rates of air leak and severe intraventricular hemorrhage. Mortality was lower in the most immature, 24-25 week gestation, stratum of the CPAP arm..

The Surfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT) in extremely low birth weight (ELBW) infants was designed to have adequate sample size to evaluate early childhood neurodevelopmental outcome of enrolled infants. We hypothesized that compared to treatment with surfactant administration after intubation, treatment with early, non-invasive CPAP and a limited ventilation strategy would result in a pre-specified composite outcome of decreased mortality or neurodevelopmental impairment at 18-22 months corrected age.

METHODS

Study Design

1316 extremely preterm infants (24 weeks 0 days to 27 weeks 6 days) born between February 2005 and February 2009 at 20 centers in the United States participating in the Neonatal Research Network (NRN) of the Eunice Kennedy Shriver National Institute of Child Health and Human Development were enrolled prior to delivery in the prospective, randomized, controlled SUPPORT trial. Permuted block randomization was used, with stratification according to center and gestational age (24 weeks 0 days to 25 weeks 6 days or 26 weeks 0 days to 27 weeks 6 days). The infants were randomly assigned in the delivery room to receive either CPAP immediately following delivery and a limited ventilation strategy if subsequent intubation was required or intubation with surfactant administration within an hour after birth. Using a 2-by-2 factorial design, participants were also randomly assigned to a target oxygen saturation of 85% to 89% (lower oxygen saturation group) or 91 to 95% (higher oxygenation group). Procedures for enrollment, intervention, and data collection have been previously reported.[30] The study was approved by the institutional review board at each participating site and at RTI International, the independent data coordinating center for the Neonatal Research Network. Written informed consent was obtained from the parent or guardian of each child before delivery.

Assessments

A comprehensive neurodevelopmental assessment was performed on survivors at 18-22 months of age, corrected for prematurity (CA), by neurologic examiners and neurodevelopmental testers who were unaware of the treatment assignments and were annually evaluated for testing reliability during a 2-day workshop. Developmental function was assessed using the Bayley Scales of Infant and Toddler Development, 3rd ed. (BSID-III).[31] Cognitive Composite Scores are reported as a standardized score with a mean of 100 and a standard deviation of 15. The modified Gross Motor Function Classification System (GMFCS) describes the gross motor performance and has a range from 0 (normal) to 5 (most impaired).[32] Examiners also recorded the presence of cerebral palsy defined as a nonprogressive disorder of the central nervous system and characterized by abnormal muscle tone in at least one arm or leg associated with abnormal control of movement or posture with delayed attainment of motor milestones. [33] Cerebral palsy was classified depending on severity as mild (GMFCS $\leq$1), moderate (GMFCS 2 or 3) or severe (GMFCS $\geq$ 4). Hearing and visual impairment were determined based on parental report and examination. Definitions of hearing and vision impairment needed

Certified research nurses collected demographic and neonatal outcome data using standard NRN definitions. Demographic and outcome data collected included gestational age, birthweight, gender, multiple gestation, race/ethnicity, history of medical or surgical necrotizing entercolitis (modified Bell's Stage $\geq$ 2), Grades 3-4 intraventricular hemorrhage (IVH) or periventricular leukomalacia (PVL), late onset sepsis, retinopathy of prematurity (ROP), bronchopulmonary dysplasia (BPD), use of postnatal steroids,. Socioeconomic variables included insurance status, maternal marital status, maternal education, household income, language spoken at home, and whether the child was living with biological parents. Outcomes following NICU discharge, including rehospitalizations, interim medical history, surgery and medications were recorded at 18-22 month visit. Socioeconomic data were updated during the 18-22 month visit and were used if data from the neonatal period were not available.

Outcome

The primary neurodevelopmental outcome was the composite of death or neurodevelopmental impairment at 18 to 22 months corrected age. This composite outcome was selected because infants who died before 18 months could not be classified as having neurodevelopmental impairment. Neurodevelopmental impairment was defined as having any of the following: BSID III cognitive composite score less than 70, GMFCS $\geq$ 2, presence of moderate or severe cerebral palsy, permanent hearing loss that does not permit the child to understand directions of the examiner and communicate despite amplification with hearing aids or bilateral visual impairment (vision < 20/200).

Statistical Analysis

The sample size calculations were based on NRN data on infants born in the year 2000 which included the rate of death or neurodevelopmental impairment at 18-22 months corrected age. Details regarding sample size calculations for the SUPPORT trial have been previously reported [30]

Data were entered in standard forms and were transmitted to RTI International which stored, managed and analyzed the data for this study. All analyses were performed according to the intention-to-treat principle. Unadjusted comparisons of demographic and birth characteristics between treatment groups were conducted using chi-square tests for categorical variables and t tests for continuous variables. The primary analyses focused on the percentage of infants in each group for whom the primary outcome of death or NDI at 18-22 months corrected age could be assigned. Analysis of this and all other categorical outcomes was performed with the use of robust Poisson regression in a generalized-estimating-equation model to obtain adjusted relative risks with 95% confidence intervals. The denominator that was used to calculate the rate of each

outcome was the number of infants for whom that outcome was known. Continuous outcomes were analyzed with the use of mixed-effects linear models to obtain adjusted means and standard errors.

In the analysis of all neonatal and 18-22 month outcomes, the results were adjusted, as prespecified, for gestational-age strata, center, and familial clustering. Secondary analyses were adjusted for birth characteristics that differed significantly between the treatment arms and were potentially related to outcomes. Two-sided p values of less than 0.05 were considered to indicate statistical significance, and no adjustments have been made for multiple comparisons. For the 79 secondary outcomes analyzed according to treatment, we would expect no more than 4 tests to have p values of less than 0.05 on the basis of chance alone. Subgroup analyses were conducted within prespecified gestational-age strata for the same outcomes. Although these tests have not been adjusted for multiple comparisons, we would expect no more than 4 tests per stratum to have p values of less than 0.05 on the basis of chance alone.

RESULTS

Two hundred fifty-eight children were known to have died before 18-22 months (Figure). Sixty-eight children of the remaining 1058 (6.4%) were lost to follow-up; the survival status of 35/68 of these children was unknown. A neurodevelopmental assessment at 18-22 months corrected age was performed for 990/1058 (93.6%) children. Of those who were seen for their 18-22 month evaluation exam, NDI was determined for 976 children; 14 children were seen but had an incomplete evaluation that precluded assigning a NDI status. Ultimately, the pre-specified outcome, death or NDI, was determined for 93.8% (1234/1316) of SUPPORT children. There was no difference in the follow-up rate between the CPAP and Surfactant arms (93.7 vs. 93.4%) of the trial.

Compared with mothers of the 990 children who had a neurodevelopmental assessment at 18-22 months, mothers of the 68 children lost to follow-up were less likely to be married (31 vs. 47%, p=0.01), and more likely to have only public insurance (69 vs. 52%, p=0.008). No other demographic variables or neonatal characteristics were significantly different between the groups.

Trial and Follow-up Cohorts: (Table 1) Compared to the Surfactant arm, infants in the CPAP arm of the trial cohort were less likely to be SGA (5.6 vs. 9%, unadjusted p=0.016) and less likely to have been exposed to postnatal steroids (7.2 vs. 13.2 %, adjusted p=0.0005). Almost all mothers (96%) in both arms received antenatal steroids. Thirty-four percent of infants in the CPAP arm were intubated in the delivery room and 67% ultimately received surfactant and ventilation.

In the follow-up cohort there were no significant differences between the CPAP and Surfactant trial arms in the incidence of small for gestational age status, late onset sepsis, or severe retinopathy of prematurity. Birthweight, gestational age, gender, race/ethnicity, multiple birth, mode of delivery, insurance status, maternal education, English as the primary language, household income were also similar in the both groups. Compared to the Surfactant arm, infants in the in the CPAP arm with follow-up at 18-22 months were more likely to have Grade 3-4 IVH or PVL (13.7 vs. 9.6%, adjusted p=0.07) and more likely to have NEC, medical or surgical NEC (11 vs. 6.3%, adjusted p=0.01). Infants in the CPAP arm were less likely to have been exposed to postnatal steroids (6.7 vs. 11.6%, adjusted p=0.01.)

Primary neurodevelopmental outcome: (Table 2) There was not a significant difference in the composite outcome of *death or NDI* at 18-22 months corrected age between the CPAP and surfactant arms (27.9 vs. 29.9%, RR 0.93 (95% CI 0.78, 1.1), adjusted p=0.38). There were fewer *deaths* before 18-22 months corrected

age in the CPAP arm but the difference did not reach statistical significance (18.4 vs. 21.9 %, RR 0.83 (95% CI 0.67,1.04), adjusted p=0.10). The mean corrected age at neurodevelopmental assessment was similar for both treatment arms (CPAP 19.9 ± 2.4 months vs. Surf 20.1 ± 2.7 months, unadjusted p=0.31).

Components of NDI: (Table 2) The incidences of cognitive impairment (BSID-III cognitive composite score < 70 (7.2% vs. 7.6%), gross motor function level ≥ 2 (5.1 vs. 4.8%), moderate/severe cerebral palsy (4.1 vs. 4.0%), and blindness (0.8 vs. 1.5%) among survivors were similar in the CPAP and Surfactant treatment groups. There was a higher incidence of hearing impairment in the early CPAP treatment arm compared to the surfactant treatment arm but the difference was not statistically significant (3.3 vs. 1.5%, adjusted p=.06). Overall 24 infants had permanent hearing impairment, 13 of whom had bilateral hearing aids. I am concerned about the definition of HI in this paper. It seems highly unlikely that 11 children with diagnosed permanent hearing loss would not have hearing aids unless they are all culturally Deaf or unilateral or mild. I think the sites for those 11have to be queried as you will need to explain this unusual finding.There was no association between hearing impairment and Grades 3-4 IVH/PVL or necrotizing enterocolitis which were more frequent in the CPAP arm. There were no significant differences in composite outcomes of death or individual NDI components between the CPAP and Surfactant arms. (Table 3)

Other neurodevelopmental outcomes: Mean BSID-III composite *cognitive scores* were similar in both CPAP and Surfactant arms (adjusted means ± standard error 91.3 ± 0.7 vs. 90.4 ± 0.8). Median BSID-III composite scores were virtually identical to the mean composite scores. Sixty percent of all children seen at 18-22 months corrected age (CPAP 59.7% and Surfactant 59.6%) had normal neuromotor, normal neurosensory and normal developmental (i.e. BSID-III cognitive composite score ≥ 85) evaluations. Were all of the children with I tested ?

Medical outcomes after discharge: Overall readmission rates (CPAP 44.7% vs. Surfactant 46.1%) and readmission rates for respiratory problems (CPAP 23.5% vs. Surfactant 25.3%) were similar in both treatment arms. There were no significant differences in use after discharge of bronchodilators (CPAP 34.7% vs. Surfactant 35.4%), steroids (CPAP 22.7% vs. Surfactant 18.6%), diuretics (CPAP 3% vs. Surfactant 3%) or any respiratory medication (CPAP 37.9% vs. Surfactant 38.3%).There was a similar rate of surgery in both groups (CPAP 47% vs. Surfactant 44.3%).

Comparisons of outcome between gestational age strata: (Tables 2 and 3)

The difference in death before 18-22 months in the CPAP and surfactant arms was statistically significant in the lower 24 0/7 to 25 6/7 weeks gestation stratum (26.4 vs. 35.5%, adjusted p=0.02), but not in the higher gestational age stratum (12.3 vs. 11.8%). There were no significant differences in the composite outcome of *death or NDI* at 18-22 months corrected age between the CPAP and surfactant within either of the two gestational age strata (40.1 vs. 44.5% for 24 0/7-25 6/7 weeks gestation; 18.3 vs. 18.7% for 26 0/7 to 27 6/7 weeks gestation). Neither were there significant differences between the CPAP and Surfactant arms in the incidence of *NDI* alone within either of the two gestational age strata (18.1 vs. 12.5, adjusted p=0.22 for 24 0/7-25 6/7 weeks gestation; 6.3 vs. 7.2%, adjusted p=0.81 for 26 0/7-27 6/7 weeks gestation. Children in the CPAP treatment arm of the lower gestational age stratum (24-25 weeks) had a lower combined risk of death and the individual components of NDI. Within each gestational age stratum the mean BSID-III composite *cognitive scores* were similar in both treatment groups (CPAP 89.2 ± 1.1 vs. Surfactant 88.1 ± 1.2 for 24 0/7-25 6/7 weeks gestation; CPAP 93.4 ± 0.9 vs. Surfactant92.6 ± 0.9 for 26 0/7 to 27 6/7 weeks gestation, adjusted mean ± standard error).

Although neurodevelopmental outcomes were similar between treatment arms within each gestational age stratum, children in the lower gestational age stratum were at higher risk of adverse outcome. Children in the lower gestational age stratum were less likely to be normal (i.e., BSID-III cognitive score ≥85; neurologic and

neurosensory exam normal, GMFCS =0) compared to children in the higher gestational age stratum, (CPAP 47.7% and Surfactant 49.4% for 24 0/7-25 6/7 weeks gestation vs. CPAP 67.5% and Surfactant 65.2% for 26 0/7 to 27 6/7 weeks gestation).

DISCUSSION:

We report the neurodevelopmental outcome in early childhood at 18-22 months corrected age for extremely premature children, 24-27 weeks gestation, enrolled in the SUPPORT trial. There was no significant difference in the primary, pre-specified composite outcome of death or NDI at 18-22 months corrected age between those extremely premature infants randomized to treatment with early CPAP vs. those randomized to treatment with early intubation and surfactant administration. Neither were there significant differences between survivors in the CPAP and Surfactant arms in NDI or its components of severe cognitive impairment (cognitive score < 70), moderate/severe cerebral palsy, moderate/severe motor impairment (GMFSC ≥2), and bilateral blindness, or in mean composite cognitive BSID-III scores. There was a non-significant increase in hearing impairment in the CPAP compared to the Surfactant treated arm. Although the number of affected children was small, this finding needs to be further explored by other large randomized controlled trials. Since this is the only negative finding for CPAP it needs further analysis and discussion.

As reported in previous studies, the most immature infants (24 to 25 weeks gestation) in both CPAP and Surfactant arms were at higher risk for severe cognitive impairment, abnormal gross motor function, moderate/severe cerebral palsy and hearing impairment and less likely to be normal. [10, 11, 34]

Bronchopulmonary dysplasia and longer duration of ventilation are associated with an increased risk of adverse neurodevelopmental outcome. [7, 14-19] Although infants in the CPAP arm had significantly fewer days of ventilation and less often received postnatal steroids compared to the surfactant treated arm, the incidence of physiologic bronchopulmonary dysplasia was similar in both groups before discharge as were the receipt of respiratory medications and readmission for respiratory problems after discharge.

The strengths of this study include the large number of extremely premature, 24-27 weeks gestation, infants enrolled in this national, multicenter trial; sufficient power to detect a clinically significant difference in the pre-specified outcome of death or neurodevelopmental impairment; the very high percentage of participants who were followed and evaluated in early childhood; and the comprehensive and standardized neurodevelopmental evaluation performed on survivors. One third of infants in the CPAP arm were intubated in the delivery room and two thirds ultimately received surfactant treatment and limited ventilation which may have blunted any difference in neurodevelopmental outcomes between the two groups. In addition, an adverse effect on neurodevelopmental outcome associated with the increased incidence of NEC and severe IVH/PVL in the CPAP arm may have counterbalanced adverse outcomes associated with the longer duration of ventilation and the increased need for supplemental oxygen and post-natal steroids in the surfactant treatment arm. The generalizability of this study may be limited by the need for antenatal consent which resulted in a trial cohort with higher socioeconomic status and the higher receipt of antenatal steroids than the entire eligible cohort.[35]

In summary, we found no significant differences in the composite outcome of death or NDI, or in any of the individual components of NDI among survivors to 18-22 months corrected age between extremely preterm infants who were randomized at delivery to either early CPAP with a limited ventilation strategy or early intubation with surfactant administration followed by conventional ventilation. In this study early CPAP, an

alternative respiratory management strategy for the extremely premature infant, was not associated with increased risk of neurodevelopmental impairment in early childhood.

Acknowledgements

The National Institutes of Health, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), and the National Heart, Lung, and Blood Institute (NHLBI) provided grant support for the Neonatal Research Network's SUPPORT Trial.

Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Drs. Abhik Das (DCC Principal Investigator) and Marie Gantz (DCC Statistician) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study. The following investigators, in addition to those listed as authors, participated in this study:

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Figure : Patient Flow diagram

Table 1: Demographic and neonatal characteristics of trial and follow-up cohorts

Table 2: Pre-specified outcomes and components of NDI for entire cohort and by gestational age strata

Table 3: Death and components of NDI for entire cohort and by gestational age strata

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Figure: Patient Flow Diagram

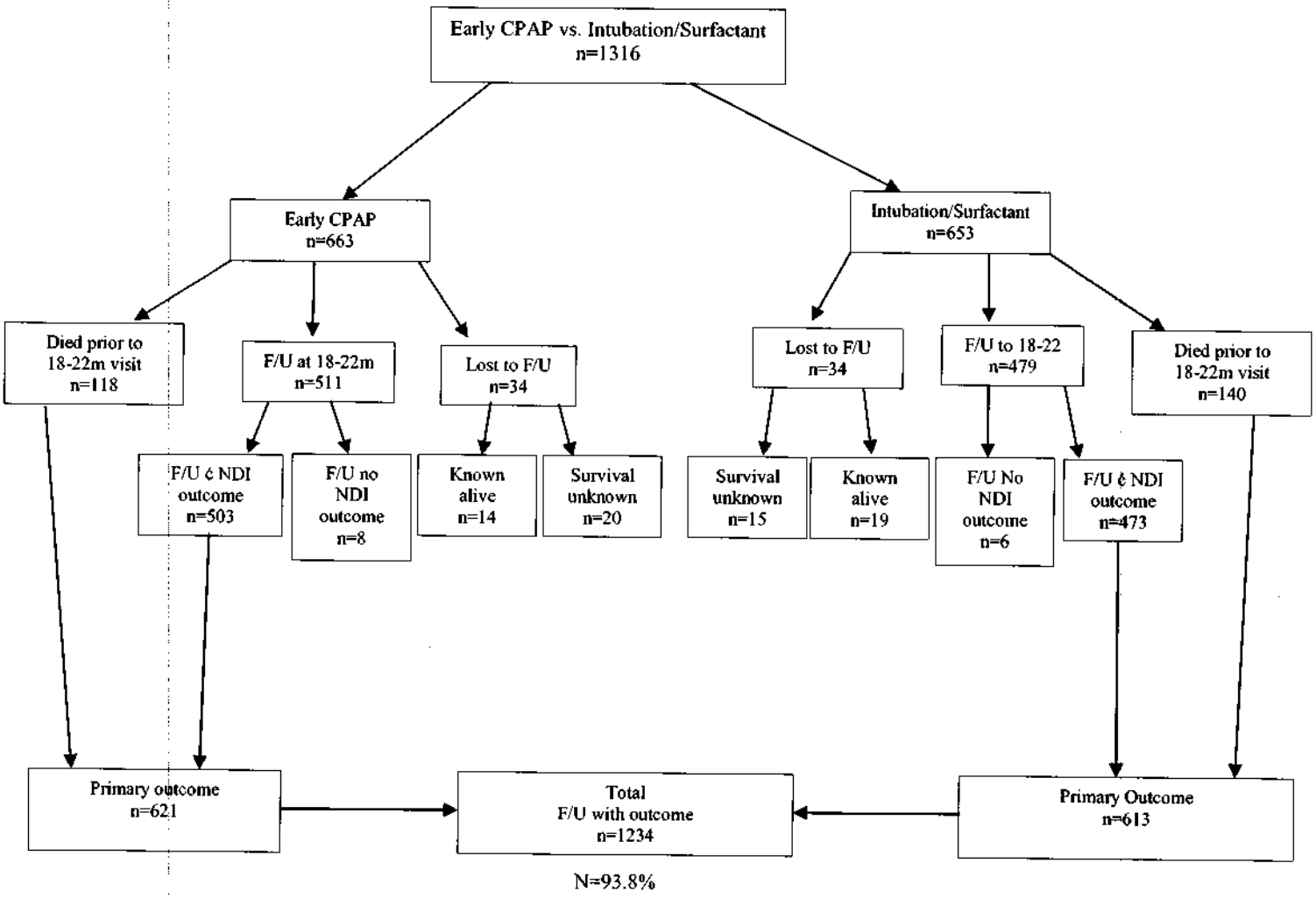

Table 1: Demographics and Characteristics of Trial Cohort and Follow-up Cohorts

	Trial Cohort		Follow-up Cohort	
	CPAP	Surfactant	CPAP	Surfactant
	N=663	N=653	N=511	N=479
Birth weight (grams, Mean ± SD)	835±188	826±198	849±186	852±193
Gestational age (weeks, Mean ± SD)	26.2±1.1	26.2±1.1	26.3±1.1	26.3±1.1
Small for gestational age < 10-no./total no.(%)	37/663(5.6)	59/653(9)**	23/511(4.5)	32/479(6.7)
Male-no./total no.(%)	342/663(51.6)	370/653(56.7)	256/511(50.1)	266/479(55.5)
Race				
Non-Hispanic White-no./total no.(%)	250/663(37.7)	271/653(41.5)	196/511(38.4)	200/479(41.8)
Non-Hispanic Black-no./total no.(%)	254/663(38.3)	235/653(36)	200/511(39.1)	177/479(37)
Hispanic-no./total no.(%)	138/663(20.8)	121/653(18.5)	98/511(19.2)	85/479(17.7)
Other or unknown-no./total no.(%)	21/663(3.2)	26/653(4)	17/511(3.3)	17/479(3.5)
Multiples-no./total no.(%)	178/663(26.8)	159/653(24.3)	138/511(27)	114/479(23.8)
Antenatal steroids(any)-no./total no.(%)	642/663(96.8)	623/652(95.6)	493/511(96.5)	456/479(95.2)
Cesarean section-no./total no.(%)	449/663(67.7)	434/653(66.5)	352/511(68.9)	315/479(65.8)
Public health insurance only-no./total no.(%)	351/661(53.1)	353/649(54.4)	262/511(51.3)	257/479(53.7)
Mother married-no./total no.(%)	305/662(46.1)	287/651(44.1)	244/511(47.7)	221/479(46.1)

With both biological parents-no./total no.(%)	365/539(67.7)	353/516(68.4)	348/510(68.2)	329/479(68.7)
Maternal education < 12-no./total no.(%)	161/616(26.1)	152/590(25.8)	128/506(25.3)	116/469(24.7)
Income < $30,000/year†-no./total no.(%)	270/514(52.5)	268/488(54.9)	260/493(52.7)	251/461(54.4)
English as primary language at FUP -no./total no.(%)	427/511(83.6)	404/479(84.3)	426/510(83.5)	403/478(84.3)
Severe ROP in survivors to discharge-no./total no.(%)	67/511(13.1)	65/473(13.7)	62/479(12.9)	58/434(13.4)
Bronchopulmonary dysplasia in survivors up to 36 weeks gestational age-no./total no.(%)	223/569(39.2)	219/539(40.6)	193/511(37.8)	187/479(39)
IVH grade 3-4/PVL-no./total no.(%)	111/642(17.3)	87/628(13.9)	70/510(13.7)	46/478(9.6)
NEC-stage ≥2 -no./total no.(%)	83/654(12.7)	63/636(9.9)	56/511(11)	30/479(6.3)**
Late onset sepsis/meningitis-no./total no.(%)	224/634(35.3)	230/624(36.9)	167/511(32.7)	154/479(32.2)
Postnatal steroids-no./total no.(%)	47/649(7.2)	83/631(13.2)***	34/508(6.7)	55/476(11.6)**
Died before discharge-no./total no.(%)	109/663(16.4)	128/653(19.6)		

†Not available for infants who did not survive to discharge

p<0.02,*p<0.001

Tests comparing neonatal outcomes (i.e., Severe ROP through Died before discharge) adjusted for stratification factors (study center and gestational age group) and familial clustering

Table 2: Death and NDI for entire cohort and gestational age strata*

CPAP vs. Surfactant (All)	CPAP	Surfactant	RR	p
Death before 18-22 mo CA-no./total no.(%)	118/643(18.4)	140/638(21.9)	0.83(0.67,1.04)	0.10
Death/NDI determined-no./total no.(%)	621/663(93.7)	613/653(93.9)	1(0.97,1.03)	0.83
Death or NDI-no./total no.(%)	173/621(27.9)	183/613(29.9)	0.93(0.78,1.1)	0.38
NDI-no./total no.(%)	55/503(10.9)	43/473(9.1)	1.16(0.79,1.71)	0.44
BSID-III cognitive score < 70-no./total no.(%)	36/502(7.2)	36/472(7.6)	0.95(0.61,1.5)	0.84
Gross motor function level ≥ 2-no./total no.(%)	26/511(5.1)	23/479(4.8)	0.98(0.57,1.69)	0.95
Moderate/severe cerebral palsy-no./total no.(%)	21/511(4.1)	19/479(4)	0.93(0.51,1.72)	0.82
Blindness, bilateral-no./total no.(%)	4/511(0.8)	7/479(1.5)	0.53(0.16,1.78)	0.31
Hearing impairment-no./total no.(%)	17/511(3.3)	7/479(1.5)	2.27(0.96-5.37	0.06

b. 24 0/7-25 6/7 weeks Gestational Age	CPAP	Surfactant	RR	p
Death before 18-22 mo CA-no./total no.(%)	73/277(26.4)	97/273(35.5)	0.74(0.57,0.96)	0.02
Death/NDI determined-no./total no.(%)	272/285(95.4)	265/280(94.6)	1.01(0.97,1.05)	0.68
NDI or death-no./total no.(%)	109/272(40.1)	118/265(44.5)	0.9 (0.74,1.09)	0.27
NDI-no./total no.(%)	36/199(18.1)	21/168(12.5)	1.37(0.83,2.27)	0.22
BSID-III cognitive score < 70-no./total no.(%)	23/198(11.6)	16/167(9.6)	1.16(0.64,2.12)	0.62
Gross motor function level ≥ 2-no./total no.(%)	17/201(8.5)	9/172(5.2)	1.52(0.7,3.29)	0.29
Moderate/severe cerebral palsy-no./total no.(%)	14/201(7.0)	8/172(4.7)	1.32(0.57,3.04)	0.51
Blindness, bilateral -no./total no.(%)	2/201(1.0)	2/172(1.2)	0.86(0.12,6.02)	0.88
Hearing impairment-no./total no.(%)	11/201(5.5)	3/172(1.7)	3.24(0.9,11.71)	0.07

c. **26 0/7-27 6/7 weeks Gestational Age**	CPAP	Surfactant	RR	p
Death before 18-22 mo CA-no./total no.(%)	45/366(12.3)	43/365(11.8)	1.05(0.71,1.55)	0.82
Death/NDI determined-no./total no.(%)	349/378(92.3)	348/373(93.3)	0.99(0.95,1.03)	0.57
NDI or death-no./total no.(%)	64/349(18.3)	65/348(18.7)	0.99(0.72,1.35)	0.93
NDI-no./total no.(%)	19/304(6.3)	22/305(7.2)	0.93(0.5,1.72)	0.81
BSID-III cognitive score < 70-no./total no.(%)	13/304(4.3)	20/305(6.6)	0.74(0.36,1.51)	0.41
Gross motor function level ≥ 2-no./total no.(%)	9/310(2.9)	14/307(4.6)	0.61(0.27,1.4)	0.24
Moderate/severe cerebral palsy-no./total no.(%)	7/310(2.3)	11/307(3.6)	0.62(0.24,1.58)	0.31
Blindness, bilateral-no./total no.(%)	2/310(0.6)	5/307(1.6)	0.39(0.08,1.99)	0.26
Hearing impairment-no./total no.(%)	6/310(1.9)	4/307(1.3)	1.53(0.44,5.26)	0.50

*Relative risk and p values adjusted for stratification factors (study center and gestational age group) and familial clustering (except blindness was not adjusted for study center due to small N)

Table 3: Death and Components of NDI for entire cohort and gestational age strata*

a. CPAP vs. Surfactant (All)	CPAP	Surfactant	RR	p
Death or cognitive composite<70-no./total no.(%)	154/620(24.8)	176/612(28.8)	0.86(0.72,1.03)	0.11
Death or GMF level ≥2-no./total no.(%)	144/629(22.9)	163/619(26.3)	0.87(0.72,1.05)	0.16
Death or moderate/severe CP-no./total no.(%)	139/629(22.1)	159/619(25.7)	0.86(0.71,1.05)	0.14
Death or blind in both eyes-no./total no.(%)	122/629(19.4)	147/619(23.7)	0.82(0.67,1.02)	0.07
Death or hearing impairment-no./total no.(%)	135/629(21.5)	147/619(23.7)	0.9(0.74,1.11)	0.33
b. 24 0/7-25 6/7 weeks Gestational Age				
Death or cognitive composite<70-no./total no.(%)	96/271(35.4)	113/264(42.8)	0.83(0.67,1.02)	0.08
Death or GMF level ≥2-no./total no.(%)	90/274(32.8)	106/269(39.4)	0.84(0.67,1.04)	0.12
Death or moderate/severe CP-no./total no.(%)	87/274(31.8)	105/269(39)	0.82(0.65,1.02)	0.08
Death or blind in both eyes-no./total no.(%)	75/274(27.4)	99/269(36.8)	0.75(0.58,0.96)	0.03
Death or hearing impairment-no./total no.(%)	84/274(30.7)	100/269(37.2)	0.83(0.65,1.05)	0.12

c. **26 0/7-27 6/7 weeks Gestational Age**	CPAP	Surfactant	RR	p
Death or cognitive composite<70-no./total no.(%)	58/349(16.6)	63/348(18.1)	0.93(0.67,1.29)	0.67
Death or GMF level ≥2-no./total no.(%)	54/355(15.2)	57/350(16.3)	0.94(0.67,1.33)	0.74
Death or moderate/severe CP-no./total no.(%)	52/355(14.6)	54/350(15.4)	0.96(0.68,1.36)	0.82
Death or blind in both eyes-no./total no.(%)	47/355(13.2)	48/350(13.7)	0.97(0.67,1.42)	0.89
Death or hearing impairment-no./total no.(%)	51/355(14.4)	47/350(13.4)	1.07(0.74,1.55)	0.71

*Relative risk and p values adjusted for stratification factors (study center and gestational age group) and familial clustering

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Gantz, Marie"; "Rich, Wade"; "Finer, Neil"; "Wally Carlo, M.D."
Cc: "Creel, Darryl"; "Das, Abhik"
Subject: RE: SUPPORT weighted analysis
Date: Monday, November 21, 2011 11:58:00 AM

I am fine with sending to the entire subcommittee for approval. Let me know if ok to send. I do not need to be an author

Rose

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Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Monday, November 21, 2011 11:54 AM
To: Rich, Wade; Finer, Neil; Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Creel, Darryl; Das, Abhik
Subject: SUPPORT weighted analysis
Importance: High

Attached are two items: (1) results of the weighted analysis of SUPPORT data (in which the enrolled infants are weighted to reflect the characteristics of the eligible population), and (2) an abstract for the Society for Clinical Trials meeting in May on the statistical methods used for this analysis. Wade is listed as a coauthor on the abstract, which we would like to submit for SUPPORT subcommittee and Steering Committee approval this week (the abstract deadline is December 1). Please let us know if you have any comments on the abstract. We would like to send it to the subcommittee today so that we can request SC approval on the call tomorrow afternoon.

If you have any questions about the weighted analysis, please let Darryl and I know. Darryl does survey analysis at RTI, and he performed the weighting and weighted analyses presented in the attached.

Thanks,
Marie

Marie Gantz, Ph.D.
Senior Research Statistician
RTI International

mgantz@rti.org
828-254-6255

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Michael O`Shea"
Cc: "yvaucher@ucsd.edu"
Subject: RE: SUPPORT CPAP PAPER
Date: Monday, November 21, 2011 10:08:00 AM

Mike
Thanks for reviewing so quick!!
Rose

Rosemary D. Higgins, MD
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-----Original Message-----
From: Michael O`Shea [mailto:moshea@wakehealth.edu]
Sent: Sunday, November 20, 2011 7:17 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: yvaucher@ucsd.edu
Subject: RE: SUPPORT CPAP PAPER

Rose and Yvonne,

This is very well done. Thank you for including me.

I have offered a very few suggestions in the attached.

Yellow highlighting indicates suggested additions; magenta indicates suggested deletions.

Thanks very much,

Mike

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]
Sent: Saturday, November 19, 2011 7:55 AM

To: 'Myriam Peralta, M.D.'; 'Finer, Neil'; Wally Carlo, M.D.; Michele Walsh; Gantz, Marie; 'Laptook, Abbot'; 'Bradley Yoder'; 'Roger Faix'; Abhik Das (Adas@rti.org); 'Rich, Wade'; 'kurt.schibler@cchmc.org'; nancy newman; Vohr, Betty; Susan Hintz; 'Kim Yolton'; 'Roy Heyne'; (b)(6) @aol.com'; goldb008@mc.duke.edu; 'Michael.Acarregui@providence.org'; 'Evans, Patricia W'; 'Adams-Chapman, Ira'; Pappas, Athina; 'Anna M. Dusick, MD'; 'emcgowan@tuftsmedicalcenter.org'; 'Ehrenkranz, Richard'; 'abodnar@utah.gov'; 'Bauer, Charles R'; 'JaFuller@salud. unm. edu (JaFuller@salud.unm.edu)'; Michael O`Shea; 'gary_myers@URMC.Rochester.edu'
Cc: yvaucher@ucsd.edu; Pablo Sanchez; 'Shankaran, Seetha'; 'Duara, Shahnaz'; Barbara Stoll; 'Poindexter, Brenda B'; 'Krisa Van Meurs'; 'Kennedy, Kathleen A'; goldb008@mc.duke.edu; 'Phelps, Dale'; 'Bell, Edward (Pediatrics)'; 'Frantz, Ivan'; 'Kristi Watterberg'; Archer, Stephanie (NIH/NICHD) [E]
Subject: SUPPORT CPAP PAPER

Hi,
Attached is the SUPPORT CPAP FU Paper for co-author input. Please send your comments to Yvonne Vaucher (yvaucher@ucsd.edu<mailto:yvaucher@ucsd.edu>) by DECEMBER 3. The paper will then go for internal NRN review and clearance. Following this, it will be submitted along with the oximetry FU paper (you will get this in the next few days) to the New England Journal of Medicine.
I have also included the steering committee PI's from the sites involved with the study. If you have any suggestions, feel free to forward them to Yvonne. Thanks to everyone for all the hard work, effort and commitment to this study!!
Rose

Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network Pregnancy and Perinatology Branch CDBPM, NIH 6100 Executive Blvd., Room 4B03 MSC 7510 Bethesda, MD 20892 For overnight delivery use Rockville, MD 20852
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higginsr@mail.nih.gov<mailto:higginsr@mail.nih.gov>

From: D"Angio, Carl
To: Phelps, Dale; Higgins, Rosemary (NIH/NICHD) [E]; yvaucher@ucsd.edu
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: SUPPORT CPAP PAPER
Date: Saturday, November 19, 2011 2:19:32 PM

Thanks, Dale.

Carl

Carl T. D'Angio, MD
Associate Professor of Pediatrics and Medical Humanities
Director, Neonatal Clinical Research
Director, Pediatric Clinical Research Office
Division of Neonatology
Golisano Children's Hospital
University of Rochester Medical Center
601 Elmwood Avenue, Box 651
Rochester, NY 14642
Phone (585) 273-4911, Fax (585) 461-3614
carl_dangio@urmc.rochester.edu

From: Phelps, Dale
Sent: Saturday, November 19, 2011 10:37 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; yvaucher@ucsd.edu
Cc: Archer, Stephanie (NIH/NICHD) [E]; D'Angio, Carl
Subject: RE: SUPPORT CPAP PAPER

These authors still need to be corrected for the University of Rochester.
Please correct, and also Stephanie, please be sure the oximetry follow up paper is corrected too.

University of Rochester Medical Center, Golisano Children's Hospital (U10 HD40521, M01 RR44) – Nirupama Laroia, MD; Dale L. Phelps, MD; Gary David Markowitz, MD; Linda J. Reubens, RN CCRC; Diane Hust, MS RN CS; Lisa Augostino; Julie Babish Johnson, MSW; Erica Burnell, RN; ~~Harris Gelbard, MD PhD;~~ Rosemary L. Jensen; Emily Kushner, MA; Joan Merzbach, LMSW; ~~Jonathan Mink, MD PhD; Carlos Torres, MD; David Wang, MD;~~ Kelley Yost, PhD.

Dale Phelps, MD

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Saturday, November 19, 2011 4:55 AM
To: 'Myriam Peralta, M.D.'; 'Finer, Neil'; Wally Carlo, M.D.; Michele Walsh; Gantz, Marie; 'Laptook, Abbot'; 'Bradley Yoder'; 'Roger Faix'; Abhik Das (Adas@rti.org); 'Rich, Wade'; 'kurt.schibler@cchmc.org'; nancy newman; Vohr, Betty; Susan Hintz; 'Kim Yolton'; 'Roy Heyne'; (b)(6) @aol.com'; goldb008@mc.duke.edu; 'Michael.Acarregui@providence.org'; 'Evans, Patricia W'; 'Adams-Chapman, Ira'; Pappas, Athina; 'Anna M. Dusick, MD'; 'emcgowan@tuftsmedicalcenter.org'; 'Ehrenkranz, Richard'; 'abodnar@utah.gov'; 'Bauer, Charles R'; 'JaFuller@salud. unm. edu (JaFuller@salud.unm.edu)'; 'Michael O`Shea'; Myers, Gary
Cc: yvaucher@ucsd.edu; Pablo Sanchez; 'Shankaran, Seetha'; 'Duara, Shahnaz'; Barbara Stoll; 'Poindexter, Brenda B'; 'Krisa Van Meurs'; 'Kennedy, Kathleen A'; goldb008@mc.duke.edu; Phelps, Dale; 'Bell, Edward (Pediatrics)'; 'Frantz, Ivan'; 'Kristi Watterberg'; Archer, Stephanie (NIH/NICHD) [E]
Subject: SUPPORT CPAP PAPER
Importance: High

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I have also included the steering committee PI's from the sites involved with the study. If you have any suggestions, feel free to forward them to Yvonne. Thanks to everyone for all the hard work, effort and commitment to this study!!

Rose

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Myriam Peralta, M.D."; "Finer, Neil"; "Wally Carlo, M.D."; "Michele Walsh"; "Gantz, Marie"; "Laptook, Abbot"; "Bradley Yoder"; "Roger Faix"; "Abhik Das (Adas@rti.org)"; "Rich, Wade"; "kurt.schibler@cchmc.org"; "nancy newman"; "Vohr, Betty"; "Susan Hintz"; "Kim Yolton"; "Roy Heyne"; (b)(6) @aol.com"; "goldb008@mc.duke.edu"; "Michael.Acarregui@providence.org"; "Evans, Patricia W."; "Adams-Chapman, Ira"; "Pappas, Athina"; "Anna M. Dusick, MD"; "emcgowan@tuftsmedicalcenter.org"; "Ehrenkranz, Richard"; "abodnar@utah.gov"; "Bauer, Charles R"; "JaFuller@salud.unm.edu (JaFuller@salud.unm.edu)"; "Michael O`Shea"; "gary_myers@URMC.Rochester.edu"
Cc: "yvaucher@ucsd.edu"; "Pablo Sanchez"; "Shankaran, Seetha"; "Duara, Shahnaz"; "Barbara Stoll"; "Poindexter, Brenda B"; "Krisa Van Meurs"; "Kennedy, Kathleen A"; "goldb008@mc.duke.edu"; "Phelps, Dale"; "Bell, Edward (Pediatrics)"; "Frantz, Ivan"; "Kristi Watterberg"; Archer, Stephanie (NIH/NICHD) [E]
Subject: SUPPORT CPAP PAPER
Date: Saturday, November 19, 2011 7:55:00 AM
Attachments: Vaucher SUPPORT FU CPAP PAPER forFUP_PIs_FinalREV111811.docx
Importance: High

Hi,

Attached is the SUPPORT CPAP FU Paper for co-author input. Please send your comments to Yvonne Vaucher (yvaucher@ucsd.edu) by **DECEMBER 3**. The paper will then go for internal NRN review and clearance. Following this, it will be submitted along with the oximetry FU paper (you will get this in the next few days) to the New England Journal of Medicine.

I have also included the steering committee PI's from the sites involved with the study. If you have any suggestions, feel free to forward them to Yvonne. Thanks to everyone for all the hard work, effort and commitment to this study!!

Rose

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Early CPAP versus Surfactant in Extremely Preterm Infants: Neurodevelopmental Outcomes in Early Childhood

Yvonne E. Vaucher, MD MPH[1]; Myriam Peralta-Carcelen, MD MPH[2]; Neil N. Finer, MD[1]; Waldemar A. Carlo, MD[2]; Michele C. Walsh, MD MS[3]; Marie G. Gantz, PhD[4]; Abbot R. Laptook, MD[5]; Bradley A. Yoder, MD[6]; Roger G. Faix, MD[6]; Abhik Das, PhD[7]; Kurt Schibler, MD[8]; Wade Rich, RRT[2]; Nancy S. Newman, RN[4]; Betty R. Vohr, MD[5]; Kimberly Yolton, PhD[8]; Roy J. Heyne, MD[9]; Deanne E. Wilson-Costello, MD[4]; Patricia W. Evans, MD[10]; Ricki F. Goldstein, MD[11]; Michael J. Acarregui, MD[12]; Ira Adams-Chapman, MD[13]; Athina Pappas, MD[14]; Susan R. Hintz, MD MS Epi[15]; Anna M. Dusick, MD FAAP[16]; Elisabeth C. McGowan, MD[17]; Richard A. Ehrenkranz, MD[18]; Anna Bodnar, MD[6]; Charles R. Bauer, MD[19]; Janell Fuller, MD[20]; T. Michael O'Shea, MD MPH[21]; Gary J. Myers, MD[22]; Rosemary D. Higgins, MD[23] for the SUPPORT Study Group of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network

Corresponding author and reprints:

Yvonne E. Vaucher, M.D., M.P.H. Telephone: 619-543-3759

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[21] Wake Forest University School of Medicine, Winston-Salem, NC
[22] Department of Pediatrics, University of Rochester Medical Center, Rochester, NY
[23] *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD

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ABSTRACT

BACKGROUND: The recent randomized, multicenter SUPPORT trial demonstrated that initial treatment with early, non-invasive CPAP is an alternative to early surfactant administration after intubation and is associated with similar rates of death or BPD in infants born at 24 to 27 weeks gestation. We hypothesized that, compared to treatment with surfactant after intubation, treatment with early CPAP would decrease the composite outcome of mortality or neurodevelopmental impairment at 18-22 months corrected age.

METHODS: We followed surviving infants, 24 0/7 to 27 6/7 weeks gestation, who were randomized in the SUPPORT trial to receive either early CPAP with limited ventilation or intubation with surfactant administration within one hour after birth. A comprehensive, standardized neurodevelopmental assessment was performed at 18-22 months corrected age. The primary composite outcome was death or neurodevelopmental impairment (NDI) which was defined as having any of the following: Bayley Scales of Infant and Toddler Development (3rd ed.) cognitive score < 70, Gross Motor Function Classification System score of ≥ 2, moderate/severe cerebral palsy, bilateral blindness or permanent hearing impairment. Results were adjusted for gestational age stratum, center and familial clustering.

RESULTS: Death or NDI was determined for 1234/1316 (93.8%) of infants enrolled in SUPPORT and 93.5% (990/1058) of survivors to hospital discharge were evaluated at 18-22 months corrected age. Death or NDI occurred in 27.9% (173/621) of the CPAP group and in 29.9% (183/613) of the Surfactant group (p=0.39). Rates of death (CPAP-18.4 vs. Surf-21.9%, p=0.10), and outcomes among survivors including NDI alone (CPAP-10.9 vs. Surf-9.1%, p=0.44), cognitive score < 70 (CPAP-7.2 vs. Surf-7.6%, p=0.84), moderate/severe cerebral palsy (CPAP-4.1 vs. Surf-4.0%, p=0.82), blindness (CPAP-0.8 vs. Surf-1.5%, p=0.31) and hearing impairment (CPAP-3.3 vs. Surf-1.5%, p=0.06) were similar in both treatment arms. In the most immature stratum (24 0/7-25-6/7 weeks gestation) there were fewer deaths [CPAP-26.4% (73/277) vs. Surf-35.5% (97/273), p=0.02].

CONCLUSION: We found no significant differences in the composite outcome of death or NDI at 18-22 months corrected age between extremely premature infants who were randomized to receive either early CPAP with a limited ventilation strategy if needed or early intubation with surfactant administration followed by conventional ventilation.

BACKGROUND

Extremely premature infants are at high risk for death and neurosensory or developmental impairment in early childhood. [1-6]The risk of impairment increases with decreasing gestational age, severity of illness and as consequence of neonatal complications including intraventricular hemorrhage or periventricular leukomalacia, symptomatic patent ductus arteriosus, necrotizing enterocolitis, prolonged ventilation, bronchopulmonary dysplasia and severe retinopathy of prematurity. [7-21] Although surfactant administration decreases both death and BPD, randomized controlled trials of respiratory interventions including high frequency oscillatory ventilation, high frequency jet ventilation, and inhaled nitric oxide have failed to consistently decrease mortality and morbidity or improve developmental outcome. [22-29]

The recent, multicenter, randomized, controlled SUPPORT trial demonstrated that treatment with non-invasive continuous positive airway pressure (CPAP) shortly after birth is an alternative to surfactant administration after intubation and is associated with similar rates of death or BPD in extremely premature infants born at 24 0/7 to 27 6/7 weeks gestation. [30] Compared with surfactant, early CPAP was associated with less frequent need for postnatal steroids and shorter duration of mechanical ventilation. Both treatment groups had similar rates of air leak and severe intraventricular hemorrhage. Mortality was lower in the most immature, 24-25 week gestation, stratum of the CPAP arm..

The Surfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT) in extremely low birth weight (ELBW) infants was designed to have adequate sample size to evaluate early childhood neurodevelopmental outcome of enrolled infants. We hypothesized that compared to treatment with surfactant administration after intubation, treatment with early, non-invasive CPAP and a limited ventilation strategy would result in a pre-specified composite outcome of decreased mortality or neurodevelopmental impairment at 18-22 months corrected age.

METHODS

Study Design

1316 extremely preterm infants (24 weeks 0 days to 27 weeks 6 days) born between February 2005 and February 2009 at 20 centers in the United States participating in the Neonatal Research Network (NRN) of the Eunice Kennedy Shriver National Institute of Child Health and Human Development were enrolled prior to delivery in the prospective, randomized, controlled SUPPORT trial. Permuted block randomization was used, with stratification according to center and gestational age (24 weeks 0 days to 25 weeks 6 days or 26 weeks 0 days to 27 weeks 6 days). The infants were randomly assigned in the delivery room to receive either CPAP immediately following delivery and a limited ventilation strategy if subsequent intubation was required or intubation with surfactant administration within an hour after birth. Using a 2-by-2 factorial design, participants were also randomly assigned to a target oxygen saturation of 85% to 89% (lower oxygen saturation group) or 91 to 95% (higher oxygenation group). Procedures for enrollment, intervention, and data collection have been previously reported.[30] The study was approved by the institutional review board at each participating site and at RTI International, the independent data coordinating center for the Neonatal Research Network. Written informed consent was obtained from the parent or guardian of each child before delivery.

Assessments

A comprehensive neurodevelopmental assessment was performed on survivors at 18-22 months of age, corrected for prematurity (CA), by neurologic examiners and neurodevelopmental testers who were unaware of the treatment assignments and were annually evaluated for testing reliability during a 2-day workshop. Developmental function was assessed using the Bayley Scales of Infant and Toddler Development, 3rd ed. (BSID-III).[31] Cognitive Composite Scores are reported as a standardized score with a mean of 100 and a standard deviation of 15. The modified Gross Motor Function Classification System (GMFCS) describes the gross motor performance and has a range from 0 (normal) to 5 (most impaired).[32] Examiners also recorded the presence of cerebral palsy defined as a nonprogressive disorder of the central nervous system and characterized by abnormal muscle tone in at least one arm or leg associated with abnormal control of movement or posture with delayed attainment of motor milestones. [33] Cerebral palsy was classified depending on severity as mild (GMFCS $\leq$1), moderate (GMFCS 2 or 3) or severe (GMFCS $\geq$ 4). Hearing and visual impairment were determined based on parental report and examination.

Certified research nurses collected demographic and neonatal outcome data using standard NRN definitions. Demographic and outcome data collected included gestational age, birthweight, gender, multiple gestation, race/ethnicity, history of medical or surgical necrotizing entercolitis (modified Bell's Stage $\geq$ 2), Grades 3-4 intraventricular hemorrhage (IVH) or periventricular leukomalacia (PVL), late onset sepsis, retinopathy of prematurity (ROP), bronchopulmonary dysplasia (BPD), use of postnatal steroids,. Socioeconomic variables included insurance status, maternal marital status, maternal education, household income, language spoken at home, and whether the child was living with biological parents. Outcomes following NICU discharge, including rehospitalizations, interim medical history, surgery and medications were recorded at 18-22 month visit. Socioeconomic data were updated during the 18-22 month visit and were used if data from the neonatal period were not available.

Outcome

The primary neurodevelopmental outcome was the composite of death or neurodevelopmental impairment at 18 to 22 months corrected age. This composite outcome was selected because infants who died before 18 months could not be classified as having neurodevelopmental impairment. Neurodevelopmental impairment was defined as having any of the following: BSID III cognitive composite score less than 70, GMFCS $\geq$ 2, presence of moderate or severe cerebral palsy, permanent hearing loss that does not permit the child to understand directions of the examiner and communicate despite amplification with hearing aids or bilateral visual impairment (vision < 20/200).

Statistical Analysis

The sample size calculations were based on NRN data on infants born in the year 2000 which included the rate of death or neurodevelopmental impairment at 18-22 months corrected age. Details regarding sample size calculations for the SUPPORT trial have been previously reported [30]

Data were entered in standard forms and were transmitted to RTI International which stored, managed and analyzed the data for this study. All analyses were performed according to the intention-to-treat principle. Unadjusted comparisons of demographic and birth characteristics between treatment groups were conducted using chi-square tests for categorical variables and t tests for continuous variables. The primary analyses focused on the percentage of infants in each group for whom the primary outcome of death or NDI at 18-22 months corrected age could be assigned. Analysis of this and all other categorical outcomes was performed with the use of robust Poisson regression in a generalized-estimating-equation model to obtain adjusted relative risks with 95% confidence intervals. The denominator that was used to calculate the rate of each

outcome was the number of infants for whom that outcome was known. Continuous outcomes were analyzed with the use of mixed-effects linear models to obtain adjusted means and standard errors.

In the analysis of all neonatal and 18-22 month outcomes, the results were adjusted, as prespecified, for gestational-age strata, center, and familial clustering. Secondary analyses were adjusted for birth characteristics that differed significantly between the treatment arms and were potentially related to outcomes. Two-sided p values of less than 0.05 were considered to indicate statistical significance, and no adjustments have been made for multiple comparisons. For the 79 secondary outcomes analyzed according to treatment, we would expect no more than 4 tests to have p values of less than 0.05 on the basis of chance alone. Subgroup analyses were conducted within prespecified gestational-age strata for the same outcomes. Although these tests have not been adjusted for multiple comparisons, we would expect no more than 4 tests per stratum to have p values of less than 0.05 on the basis of chance alone.

RESULTS

Two hundred fifty-eight children were known to have died before 18-22 months (Figure). Sixty-eight children of the remaining 1058 (6.4%) were lost to follow-up; the survival status of 35/68 of these children was unknown. A neurodevelopmental assessment at 18-22 months corrected age was performed for 990/1058 (93.6%) children. Of those who were seen for their 18-22 month evaluation exam, NDI was determined for 976 children; 14 children were seen but had an incomplete evaluation that precluded assigning a NDI status. Ultimately, the pre-specified outcome, death or NDI, was determined for 93.8% (1234/1316) of SUPPORT children. There was no difference in the follow-up rate between the CPAP and Surfactant arms (93.7 vs. 93.4%) of the trial.

Compared with mothers of the 990 children who had a neurodevelopmental assessment at 18-22 months, mothers of the 68 children lost to follow-up were less likely to be married (31 vs. 47%, p=0.01), and more likely to have only public insurance (69 vs. 52%, p=0.008). No other demographic variables or neonatal characteristics were significantly different between the groups.

Trial and Follow-up Cohorts: (Table 1) Compared to the Surfactant arm, infants in the CPAP arm of the trial cohort were less likely to be SGA (5.6 vs. 9%, unadjusted p=0.016) and less likely to have been exposed to postnatal steroids (7.2 vs. 13.2 %, adjusted p=0.0005). Almost all mothers (96%) in both arms received antenatal steroids. Thirty-four percent of infants in the CPAP arm were intubated in the delivery room and 67% ultimately received surfactant and ventilation.

In the follow-up cohort there were no significant differences between the CPAP and Surfactant trial arms in the incidence of small for gestational age status, late onset sepsis, or severe retinopathy of prematurity. Birthweight, gestational age, gender, race/ethnicity, multiple birth, mode of delivery, insurance status, maternal education, English as the primary language, household income were also similar in the both groups. Compared to the Surfactant arm, infants in the in the CPAP arm with follow-up at 18-22 months were more likely to have Grade 3-4 IVH or PVL (13.7 vs. 9.6%, adjusted p=0.07) and more likely to have NEC, medical or surgical NEC (11 vs. 6.3%, adjusted p=0.01). Infants in the CPAP arm were less likely to have been exposed to postnatal steroids (6.7 vs. 11.6%, adjusted p=0.01.)

Primary neurodevelopmental outcome: (Table 2) There was not a significant difference in the composite outcome of *death or NDI* at 18-22 months corrected age between the CPAP and surfactant arms (27.9 vs. 29.9%, RR 0.93 (95% CI 0.78, 1.1), adjusted p=0.38). There were fewer *deaths* before 18-22 months corrected

age in the CPAP arm but the difference did not reach statistical significance (18.4 vs. 21.9 %, RR 0.83 (95% CI 0.67,1.04), adjusted p=0.10). The mean corrected age at neurodevelopmental assessment was similar for both treatment arms (CPAP 19.9 ± 2.4 months vs. Surf 20.1 ± 2.7 months, unadjusted p=0.31).

Components of NDI: (Table 2) The incidences of cognitive impairment (BSID-III cognitive composite score < 70 (7.2% vs. 7.6%), gross motor function level ≥ 2 (5.1 vs. 4.8%), moderate/severe cerebral palsy (4.1 vs. 4.0%), and blindness (0.8 vs. 1.5%) among survivors were similar in the CPAP and Surfactant treatment groups. There was a higher incidence of hearing impairment in the early CPAP treatment arm compared to the surfactant treatment arm but the difference was not statistically significant (3.3 vs. 1.5%, adjusted p=.06). Overall 24 infants had permanent hearing impairment, 13 of whom had bilateral hearing aids. There was no association between hearing impairment and Grades 3-4 IVH/PVL or necrotizing enterocolitis which were more frequent in the CPAP arm. There were no significant differences in composite outcomes of death or individual NDI components between the CPAP and Surfactant arms. (Table 3)

Other neurodevelopmental outcomes: Mean BSID-III composite *cognitive scores* were similar in both CPAP and Surfactant arms (adjusted means ± standard error 91.3 ± 0.7 vs. 90.4 ± 0.8). Median BSID-III composite scores were virtually identical to the mean composite scores. Sixty percent of all children seen at 18-22 months corrected age (CPAP 59.7% and Surfactant 59.6%) had normal neuromotor, normal neurosensory and normal developmental (i.e. BSID-III cognitive composite score ≥ 85) evaluations.

Medical outcomes after discharge: Overall readmission rates (CPAP 44.7% vs. Surfactant 46.1%) and readmission rates for respiratory problems (CPAP 23.5% vs. Surfactant 25.3%) were similar in both treatment arms. There were no significant differences in use after discharge of bronchodilators (CPAP 34.7% vs. Surfactant 35.4%), steroids (CPAP 22.7% vs. Surfactant 18.6%), diuretics (CPAP 3% vs. Surfactant 3%) or any respiratory medication (CPAP 37.9% vs. Surfactant 38.3%).There was a similar rate of surgery in both groups (CPAP 47% vs. Surfactant 44.3%).

Comparisons of outcome between gestational age strata: (Tables 2 and 3)
The difference in death before 18-22 months in the CPAP and surfactant arms was statistically significant in the lower 24 0/7 to 25 6/7 weeks gestation stratum (26.4 vs. 35.5%, adjusted p=0.02), but not in the higher gestational age stratum (12.3 vs. 11.8%). There were no significant differences in the composite outcome of *death or NDI* at 18-22 months corrected age between the CPAP and surfactant within either of the two gestational age strata (40.1 vs. 44.5% for 24 0/7-25 6/7 weeks gestation; 18.3 vs. 18.7% for 26 0/7 to 27 6/7 weeks gestation). Neither were there significant differences between the CPAP and Surfactant arms in the incidence of *NDI* alone within either of the two gestational age strata (18.1 vs. 12.5, adjusted p=0.22 for 24 0/7-25 6/7 weeks gestation; 6.3 vs. 7.2%, adjusted p=0.81 for 26 0/7-27 6/7 weeks gestation. Children in the CPAP treatment arm of the lower gestational age stratum (24-25 weeks) had a lower combined risk of death and the individual components of NDI. Within each gestational age stratum the mean BSID-III composite *cognitive scores* were similar in both treatment groups (CPAP 89.2 ± 1.1 vs. Surfactant 88.1 ± 1.2 for 24 0/7-25 6/7 weeks gestation; CPAP 93.4 ± 0.9 vs. Surfactant92.6 ± 0.9 for 26 0/7 to 27 6/7 weeks gestation, adjusted mean ± standard error).

Although neurodevelopmental outcomes were similar between treatment arms within each gestational age stratum, children in the lower gestational age stratum were at higher risk of adverse outcome. Children in the lower gestational age stratum were less likely to be normal (i.e., BSID-III cognitive score ≥85; neurologic and neurosensory exam normal, GMFCS =0) compared to children in the higher gestational age stratum, (CPAP 47.7% and Surfactant 49.4% for 24 0/7-25 6/7 weeks gestation vs. CPAP 67.5% and Surfactant 65.2% for 26 0/7 to 27 6/7 weeks gestation).

DISCUSSION:

We report the neurodevelopmental outcome in early childhood at 18-22 months corrected age for extremely premature children, 24-27 weeks gestation, enrolled in the SUPPORT trial. There was no significant difference in the primary, pre-specified composite outcome of death or NDI at 18-22 months corrected age between those extremely premature infants randomized to treatment with early CPAP vs. those randomized to treatment with early intubation and surfactant administration. Neither were there significant differences between survivors in the CPAP and Surfactant arms in NDI or its components of severe cognitive impairment (cognitive score < 70), moderate/severe cerebral palsy, moderate/severe motor impairment (GMFSC ≥2), and bilateral blindness, or in mean composite cognitive BSID-III scores. There was a non-significant increase in hearing impairment in the CPAP compared to the Surfactant treated arm. Although the number of affected children was small, this finding needs to be further explored by other large randomized controlled trials.

As reported in previous studies, the most immature infants (24 to 25 weeks gestation) in both CPAP and Surfactant arms were at higher risk for severe cognitive impairment, abnormal gross motor function, moderate/severe cerebral palsy and hearing impairment and less likely to be normal. [10, 11, 34]

Bronchopulmonary dysplasia and longer duration of ventilation are associated with an increased risk of adverse neurodevelopmental outcome. [7, 14-19] Although infants in the CPAP arm had significantly fewer days of ventilation and less often received postnatal steroids compared to the surfactant treated arm, the incidence of physiologic bronchopulmonary dysplasia was similar in both groups before discharge as were the receipt of respiratory medications and readmission for respiratory problems after discharge.

The strengths of this study include the large number of extremely premature, 24-27 weeks gestation, infants enrolled in this national, multicenter trial; sufficient power to detect a clinically significant difference in the pre-specified outcome of death or neurodevelopmental impairment; the very high percentage of participants who were followed and evaluated in early childhood; and the comprehensive and standardized neurodevelopmental evaluation performed on survivors. One third of infants in the CPAP arm were intubated in the delivery room and two thirds ultimately received surfactant treatment and limited ventilation which may have blunted any difference in neurodevelopmental outcomes between the two groups. In addition, an adverse effect on neurodevelopmental outcome associated with the increased incidence of NEC and severe IVH/PVL in the CPAP arm may have counterbalanced adverse outcomes associated with the longer duration of ventilation and the increased need for supplemental oxygen and post-natal steroids in the surfactant treatment arm. The generalizability of this study may be limited by the need for antenatal consent which resulted in a trial cohort with higher socioeconomic status and the higher receipt of antenatal steroids than the entire eligible cohort.[35]

In summary, we found no significant differences in the composite outcome of death or NDI, or in any of the individual components of NDI among survivors to 18-22 months corrected age between extremely preterm infants who were randomized at delivery to either early CPAP with a limited ventilation strategy or early intubation with surfactant administration followed by conventional ventilation. In this study early CPAP, an alternative respiratory management strategy for the extremely premature infant, was not associated with increased risk of neurodevelopmental impairment in early childhood.

Acknowledgements

The National Institutes of Health, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), and the National Heart, Lung, and Blood Institute (NHLBI) provided grant support for the Neonatal Research Network's SUPPORT Trial.

Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Drs. Abhik Das (DCC Principal Investigator) and Marie Gantz (DCC Statistician) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study. The following investigators, in addition to those listed as authors, participated in this study:

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Figure : Patient Flow diagram

Table 1: Demographic and neonatal characteristics of trial and follow-up cohorts

Table 2: Pre-specified outcomes and components of NDI for entire cohort and by gestational age strata

Table 3: Death and components of NDI for entire cohort and by gestational age strata

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Figure: Patient Flow Diagram

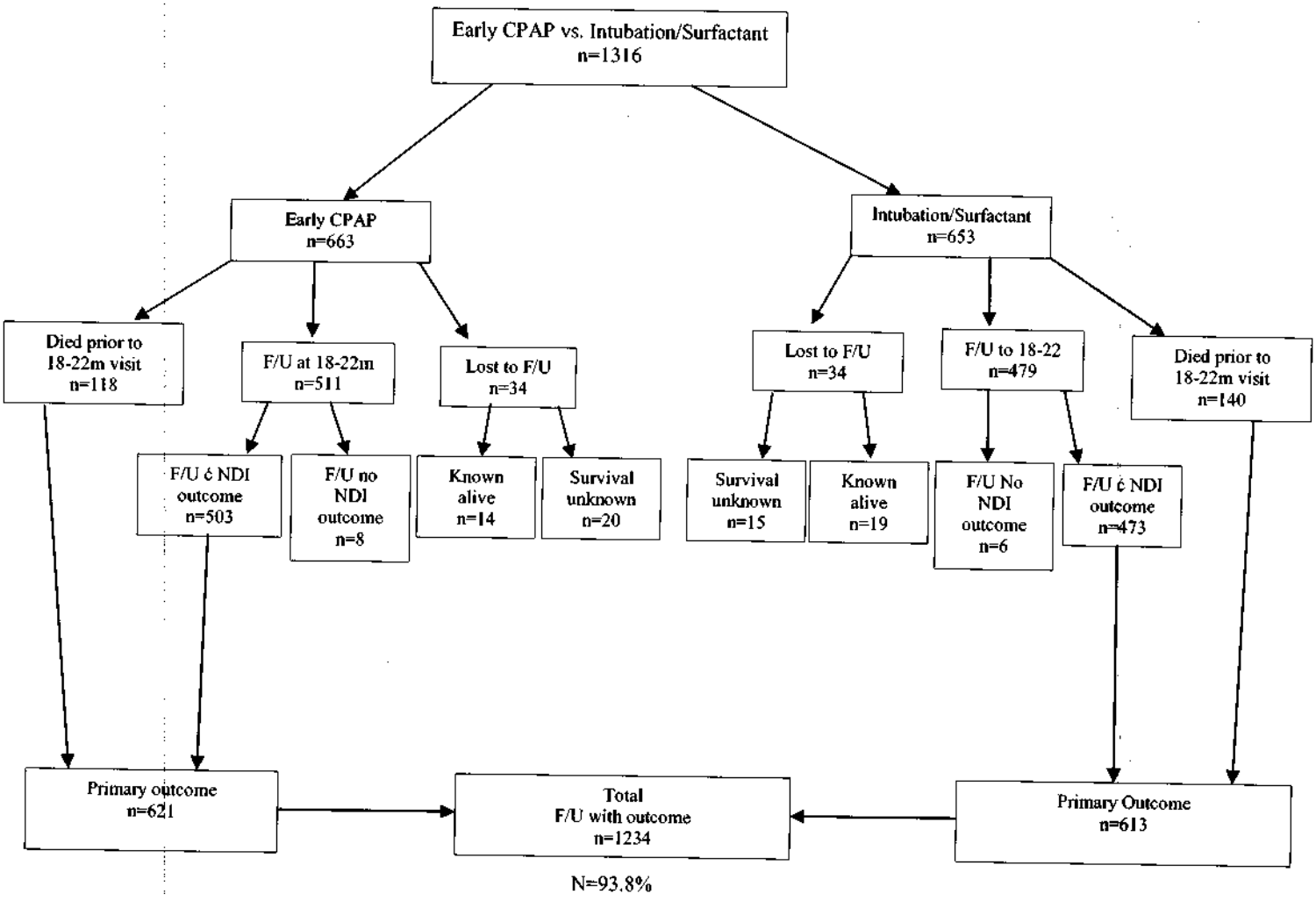

Table 1: Demographics and Characteristics of Trial Cohort and Follow-up Cohorts

	Trial Cohort		Follow-up Cohort	
	CPAP	Surfactant	CPAP	Surfactant
	N=663	N=653	N=511	N=479
Birth weight (grams, Mean ± SD)	835±188	826±198	849±186	852±193
Gestational age (weeks, Mean ± SD)	26.2±1.1	26.2±1.1	26.3±1.1	26.3±1.1
Small for gestational age < 10-no./total no.(%)	37/663(5.6)	59/653(9)**	23/511(4.5)	32/479(6.7)
Male-no./total no.(%)	342/663(51.6)	370/653(56.7)	256/511(50.1)	266/479(55.5)
Race				
Non-Hispanic White-no./total no.(%)	250/663(37.7)	271/653(41.5)	196/511(38.4)	200/479(41.8)
Non-Hispanic Black-no./total no.(%)	254/663(38.3)	235/653(36)	200/511(39.1)	177/479(37)
Hispanic-no./total no.(%)	138/663(20.8)	121/653(18.5)	98/511(19.2)	85/479(17.7)
Other or unknown-no./total no.(%)	21/663(3.2)	26/653(4)	17/511(3.3)	17/479(3.5)
Multiples-no./total no.(%)	178/663(26.8)	159/653(24.3)	138/511(27)	114/479(23.8)
Antenatal steroids(any)-no./total no.(%)	642/663(96.8)	623/652(95.6)	493/511(96.5)	456/479(95.2)
Cesarean section-no./total no.(%)	449/663(67.7)	434/653(66.5)	352/511(68.9)	315/479(65.8)
Public health insurance only-no./total no.(%)	351/661(53.1)	353/649(54.4)	262/511(51.3)	257/479(53.7)
Mother married-no./total no.(%)	305/662(46.1)	287/651(44.1)	244/511(47.7)	221/479(46.1)

With both biological parents-no./total no.(%)	365/539(67.7)	353/516(68.4)	348/510(68.2)	329/479(68.7)
Maternal education < 12-no./total no.(%)	161/616(26.1)	152/590(25.8)	128/506(25.3)	116/469(24.7)
Income < $30,000/year†-no./total no.(%)	270/514(52.5)	268/488(54.9)	260/493(52.7)	251/461(54.4)
English as primary language at FUP -no./total no.(%)	427/511(83.6)	404/479(84.3)	426/510(83.5)	403/478(84.3)
Severe ROP in survivors to discharge-no./total no.(%)	67/511(13.1)	65/473(13.7)	62/479(12.9)	58/434(13.4)
Bronchopulmonary dysplasia in survivors up to 36 weeks gestational age-no./total no.(%)	223/569(39.2)	219/539(40.6)	193/511(37.8)	187/479(39)
IVH grade 3-4/PVL-no./total no.(%)	111/642(17.3)	87/628(13.9)	70/510(13.7)	46/478(9.6)
NEC-stage ≥2 -no./total no.(%)	83/654(12.7)	63/636(9.9)	56/511(11)	30/479(6.3)**
Late onset sepsis/meningitis-no./total no.(%)	224/634(35.3)	230/624(36.9)	167/511(32.7)	154/479(32.2)
Postnatal steroids-no./total no.(%)	47/649(7.2)	83/631(13.2)***	34/508(6.7)	55/476(11.6)**
Died before discharge-no./total no.(%)	109/663(16.4)	128/653(19.6)		

†Not available for infants who did not survive to discharge

p<0.02,*p<0.001

Tests comparing neonatal outcomes (i.e., Severe ROP through Died before discharge) adjusted for stratification factors (study center and gestational age group) and familial clustering

Table 2: Death and NDI for entire cohort and gestational age strata*

CPAP vs. Surfactant (All)	CPAP	Surfactant	RR	p
Death before 18-22 mo CA-no./total no.(%)	118/643(18.4)	140/638(21.9)	0.83(0.67,1.04)	0.10
Death/NDI determined-no./total no.(%)	621/663(93.7)	613/653(93.9)	1(0.97,1.03)	0.83
Death or NDI-no./total no.(%)	173/621(27.9)	183/613(29.9)	0.93(0.78,1.1)	0.38
NDI-no./total no.(%)	55/503(10.9)	43/473(9.1)	1.16(0.79,1.71)	0.44
BSID-III cognitive score < 70-no./total no.(%)	36/502(7.2)	36/472(7.6)	0.95(0.61,1.5)	0.84
Gross motor function level ≥ 2-no./total no.(%)	26/511(5.1)	23/479(4.8)	0.98(0.57,1.69)	0.95
Moderate/severe cerebral palsy-no./total no.(%)	21/511(4.1)	19/479(4)	0.93(0.51,1.72)	0.82
Blindness, bilateral-no./total no.(%)	4/511(0.8)	7/479(1.5)	0.53(0.16,1.78)	0.31
Hearing impairment-no./total no.(%)	17/511(3.3)	7/479(1.5)	2.27(0.96-5.37	0.06

b. 24 0/7-25 6/7 weeks Gestational Age	CPAP	Surfactant	RR	p
Death before 18-22 mo CA-no./total no.(%)	73/277(26.4)	97/273(35.5)	0.74(0.57,0.96)	0.02
Death/NDI determined-no./total no.(%)	272/285(95.4)	265/280(94.6)	1.01(0.97,1.05)	0.68
NDI or death-no./total no.(%)	109/272(40.1)	118/265(44.5)	0.9 (0.74,1.09)	0.27
NDI-no./total no.(%)	36/199(18.1)	21/168(12.5)	1.37(0.83,2.27)	0.22
BSID-III cognitive score < 70-no./total no.(%)	23/198(11.6)	16/167(9.6)	1.16(0.64,2.12)	0.62
Gross motor function level ≥ 2-no./total no.(%)	17/201(8.5)	9/172(5.2)	1.52(0.7,3.29)	0.29
Moderate/severe cerebral palsy-no./total no.(%)	14/201(7.0)	8/172(4.7)	1.32(0.57,3.04)	0.51
Blindness, bilateral -no./total no.(%)	2/201(1.0)	2/172(1.2)	0.86(0.12,6.02)	0.88
Hearing impairment-no./total no.(%)	11/201(5.5)	3/172(1.7)	3.24(0.9,11.71)	0.07

c. 26 0/7-27 6/7 weeks Gestational Age	CPAP	Surfactant	RR	p
Death before 18-22 mo CA-no./total no.(%)	45/366(12.3)	43/365(11.8)	1.05(0.71,1.55)	0.82
Death/NDI determined-no./total no.(%)	349/378(92.3)	348/373(93.3)	0.99(0.95,1.03)	0.57
NDI or death-no./total no.(%)	64/349(18.3)	65/348(18.7)	0.99(0.72,1.35)	0.93
NDI-no./total no.(%)	19/304(6.3)	22/305(7.2)	0.93(0.5,1.72)	0.81
BSID-III cognitive score < 70-no./total no.(%)	13/304(4.3)	20/305(6.6)	0.74(0.36,1.51)	0.41
Gross motor function level ≥ 2-no./total no.(%)	9/310(2.9)	14/307(4.6)	0.61(0.27,1.4)	0.24
Moderate/severe cerebral palsy-no./total no.(%)	7/310(2.3)	11/307(3.6)	0.62(0.24,1.58)	0.31
Blindness, bilateral-no./total no.(%)	2/310(0.6)	5/307(1.6)	0.39(0.08,1.99)	0.26
Hearing impairment-no./total no.(%)	6/310(1.9)	4/307(1.3)	1.53(0.44,5.26)	0.50

*Relative risk and p values adjusted for stratification factors (study center and gestational age group) and familial clustering (except blindness was not adjusted for study center due to small N)

Table 3: Death and Components of NDI for entire cohort and gestational age strata*

a. CPAP vs. Surfactant (All)	CPAP	Surfactant	RR	p
Death or cognitive composite<70-no./total no.(%)	154/620(24.8)	176/612(28.8)	0.86(0.72,1.03)	0.11
Death or GMF level ≥2-no./total no.(%)	144/629(22.9)	163/619(26.3)	0.87(0.72,1.05)	0.16
Death or moderate/severe CP-no./total no.(%)	139/629(22.1)	159/619(25.7)	0.86(0.71,1.05)	0.14
Death or blind in both eyes-no./total no.(%)	122/629(19.4)	147/619(23.7)	0.82(0.67,1.02)	0.07
Death or hearing impairment-no./total no.(%)	135/629(21.5)	147/619(23.7)	0.9(0.74,1.11)	0.33
b. 24 0/7-25 6/7 weeks Gestational Age				
Death or cognitive composite<70-no./total no.(%)	96/271(35.4)	113/264(42.8)	0.83(0.67,1.02)	0.08
Death or GMF level ≥2-no./total no.(%)	90/274(32.8)	106/269(39.4)	0.84(0.67,1.04)	0.12
Death or moderate/severe CP-no./total no.(%)	87/274(31.8)	105/269(39)	0.82(0.65,1.02)	0.08
Death or blind in both eyes-no./total no.(%)	75/274(27.4)	99/269(36.8)	0.75(0.58,0.96)	0.03
Death or hearing impairment-no./total no.(%)	84/274(30.7)	100/269(37.2)	0.83(0.65,1.05)	0.12

c. **26 0/7-27 6/7 weeks Gestational Age**	CPAP	Surfactant	RR	p
Death or cognitive composite<70-no./total no.(%)	58/349(16.6)	63/348(18.1)	0.93(0.67,1.29)	0.67
Death or GMF level ≥2-no./total no.(%)	54/355(15.2)	57/350(16.3)	0.94(0.67,1.33)	0.74
Death or moderate/severe CP-no./total no.(%)	52/355(14.6)	54/350(15.4)	0.96(0.68,1.36)	0.82
Death or blind in both eyes-no./total no.(%)	47/355(13.2)	48/350(13.7)	0.97(0.67,1.42)	0.89
Death or hearing impairment-no./total no.(%)	51/355(14.4)	47/350(13.4)	1.07(0.74,1.55)	0.71

*Relative risk and p values adjusted for stratification factors (study center and gestational age group) and familial clustering

From: Vaucher, Yvonne
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: CPAP SUPPORT Follow-Up paper
Date: Friday, November 18, 2011 5:27:04 PM
Attachments: Vaucher SUPPORT FU CPAP PAPER forFUP PIs FinalREV111811.docx

Rose,

Here is the CPAP SUPPORT FUP paper with all the subcommittee comments added; ready to distribute to FUP PIs for their input.

Yvonne

Yvonne E. Vaucher, M.D., M.P.H.
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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "yvaucher@ucsd.edu"; "Myriam Peralta, M.D."
Cc: "Finer, Neil"; "Wally Carlo, M.D."
Subject: SUPPORT FU Papers
Date: Friday, November 18, 2011 8:48:00 AM

Hi,

Please send me the latest version of he SUPPORT FU papers so we can get final author approval, move to internal review and get them submitted!!

Thanks

Rose

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From: Juliann Di Fiore
To: jmd3@case.edu
Cc: Richard Martin; Michele Walsh; Wally Carlo; Wade Rich; Neil Finer; Higgins, Rosemary (NIH/NICHD) [E]; Wrage, Lisa Ann
Subject: Re: Final Draft_ effect of low target range on the incidence of IH NRN reviewer response
Date: Friday, November 18, 2011 1:01:53 PM
Attachments: Final Draft_ effect of low target range on the incidence of IH NRN reviewer response.docx
fig4.jpg
fig3.jpg
fig2.jpg
fig1.jpg
Table.docx
DiFioreReview.docx

Sorry, I forgot to attach the reviewer comments. Here are the documents again.

Julie

On 11/18/2011 12:41 PM, Juliann Di Fiore wrote:
> Attached is the NRN reviewer comments and the next version of the IH
> and O2 target range manuscript. I am hoping to get this manuscript
> sent out by the end of the month if I can get everyone's comments back
> by then.
>
> thanks.
>
> Julie
>
>
>

--
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Low oxygen saturation target range is associated with increased incidence of intermittent hypoxemia

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Financial Assistance:

Supported by the National Institute of Child Health and Human Development Cooperative Multicenter Neonatal Research Network (Grant HD021364-23)

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Keywords: preterm infants, hypoxia

The authors state no conflicts of interest

Abstract:

Objective:

To test the hypothesis that preterm infants randomized to a low versus high O_2 saturation target range have a higher incidence of intermittent hypoxemia (IH).

Study Design:

A subcohort of 115 preterm infants with high resolution pulse oximetry enrolled in the SUPPORT trial, were randomized to low (85-89%) or high (90-95%) oxygen saturation target ranges. Oxygen saturation was monitored until 36wks postmenstrual age or until the infant was breathing room air without respiratory support for ≥72hrs.

Results:

The low target oxygen saturation group had a higher rate of IH events (≤80% for ≥10 sec and ≤3 min) prior to 12 days and beyond 57 days of life ($p<0.05$). The duration shortened ($p<0.01$) and the severity increased ($p<0.01$) with increasing postnatal age with no differences between target saturation groups. The higher rate of IH events in the low target group was associated with a time interval between events of <1min.

Conclusion:

A low oxygen saturation target was associated with an increased rate of IH events that was dependent on postnatal age. The duration and severity of events was comparable between target groups. Further investigation is needed to assess the role of IH events and their timing on neonatal morbidity.

Background:

Intermittent hypoxemia (IH) may be associated with morbidity in preterm infants. In newborn animal models, administered IH paradigms have been shown to impair dopamine signaling[1], contribute to neurological handicap[1-3], and exacerbate retinal neovascularization[4]. Although, IH events are common in preterm infants, data relating to the prevalence of these events have been limited. Pulse oximetry technology has enabled non-invasive recording of spontaneous intermittent hypoxemic events in preterm infants over prolonged periods of time. This has allowed for accurate documentation of the temporal changes in the incidence of IH events over the first few months of life. Recent data in a previous cohort of preterm infants of 24-28 weeks gestation have shown relatively few IH events over the first week of life, a progressive increase in events until approximately 5 weeks post natal age followed by a decline thereafter[5].

The multi-center SUPPORT trial examined the role of high versus low O_2 saturation target ranges on retinopathy of prematurity. Following randomization to lower (85-89%) or higher (91-95%) oxygen saturation target ranges, infants in the lower target group were found to have a lower incidence of severe ROP. This was associated with an unexpected higher mortality in infants targeted to low baseline oxygen saturation in two separate clinical trials[6,7]. The effect of these oxygenation target ranges on the occurrence of intermittent hypoxemia (IH) is unknown. As a lower baseline oxygen saturation target may increase hypoxic vulnerability and the likelihood of IH, we prospectively designed this study to test the hypothesis that infants randomized to a low compared to high O_2 saturation target range would have an increase in the incidence of intermittent hypoxemia.

Methods:

The study population included a new subcohort of 115 preterm infants enrolled in the multi-center SUPPORT study from two sites: Rainbow Babies & Children's Hospital, Cleveland, and University of California San Diego. Due to the massive file sizes, storage and analysis costs only 2 centers from the main trial collected data with the highest resolution of 2 sec averaging and 2 sec sample rate needed for this data analysis (main SUPPORT study settings: 16 sec averaging and 10 sec sample rate). These files included up to 3.6 million oxygen saturation values per subject.

The study was approved by the Institutional Review Board at each site and by RTI International, which is the independent data coordinating center for the Neonatal Research Network. Written informed consent was obtained from the parent or guardian of each child before delivery. Additional approval and informed consent included permission to perform secondary analysis of de-identified data.

Enrollment criteria included infants who were born between 24 weeks 0 days and 27 weeks 6 days of gestation for whom a decision had been made to provide full resuscitation. Infants born in other hospitals and those known to have major anomalies were excluded. Using a permuted-block randomization design, with stratification according to study center and gestational age (24 weeks 0 days to 25 weeks 6 days or 26 weeks 0 days to 27 weeks 6 days), infants were randomized to a low (85-89%) or high (91-95%) oxygen saturation target group within two hours of birth. Infants who were part of multiple births were randomly assigned to the same group.

Electronically altered pulse oximeters (Radical SET, Masimo, Irvine, CA) were used to blind the staff to the randomization group. The clinical staff was instructed to maintain infants in an oxygen saturation range of 88-92%, with altered monitors showing target levels of 88-92% with a maximum offset of 3%. For example a displayed value of 90% corresponded to an actual oxygen saturation value of 87% in the low target group and 93% in the high target group[6]. Actual values were displayed when the oxygen saturation values were <85% or ≥95% in both treatment groups.

Targeting of oxygen saturation and high resolution (2 sec sample rate and 2 sec time averaging) data collection began within 2 hours after birth and continued until 36 wks postmenstrual age or until the infant was breathing air without respiratory support, defined as high frequency ventilation, conventional mechanical ventilation, Nasal SIMV, CPAP, nasal cannula, or hood, for ≥ 72 hours, whichever came first. Infants weaned to room air but re-administered supplemental oxygen were returned to the original randomization group.

We defined an IH event as a fall in oxygen saturation to ≤80% for ≥10sec and ≤3min. We then characterized these events by their duration and the time interval between each event (Figure 1). The time interval between each event was calculated as the time between the end of the IH event (designated by the return of oxygen saturation above 80%) and the beginning the next IH event (designated by a fall below 80%). The severity, or nadir, of each event was also documented. For each postnatal day for each subject a calculation was made of the mean number, duration and time interval between IH events. These values were then used in the model.

Demographic and clinical variables were compared between high and low SaO_2 target groups using Generalized Estimating Equation (GEE) regression models, adjusting for SUPPORT study stratification variables site and gestational age group, where appropriate. Due to sparse data a Fisher's exact test was used to evaluate death prior to 36 weeks. To model counts of intermittent hypoxemia events a GEE regression model assuming a negative binomial distribution was used. The GEE model provided robust standard error estimates which take into account the correlations within multiple-birth clusters, including correlations between repeated measurements. Variables included in the final model for IH events were treatment group, linear and quadratic terms for postnatal age, interactions between treatment group and postnatal age variables, gestational age group, and respiratory support (yes or no, per day). An additional quadratic term which allowed the quadratic relationship of postnatal age and IH events to vary before and after 28 days was also included; this spline regression approach provided a better fit than simpler models[8]. Also considered were interactions between GA group and postnatal age, between GA group and treatment group, and between the additional quadratic term and treatment group, as well as variables for gender, race, center, CPAP versus surfactant treatment group (an additional randomization of the main SUPPORT trial protocol), and caffeine use. Each of these additional terms considered were not significant and thus were not included in the final model. Similar models for the <1 minute and 1 to 20 minute time interval between event subsets of IH events were run with the same final set of variables as the overall model. Additional models were run to model duration and severity of IH events. These models included variables for treatment group, linear and quadratic terms for age, gestational age group, and center.

Results:

The population of 115 infants had a mean birth weight of 830±181gm and gestational age of 25.8 ±1.0wks. There were 50 infants in the gestational age range of 24 to 25 weeks 6 days and 65 infants in the gestational age range of 26 to 27 weeks 6 days range. Fifty one percent of the infants were male and 35% were non-Hispanic white. Characteristics of infants randomized to the high (n=62) and low (n=53) target group are presented in Table 1. There were no differences between groups in birth weight, gestational age, incidence of bronchopulmonary dysplasia or severe retinopathy of prematurity (ROP). In this small cohort, there was a trend towards a higher mortality in the low target group (p=.09), mirroring the finding in the main trial, but this did not reach statistical significance. Caffeine use occurred on approximately 80% of days during the monitoring period in both infant groups. Infants in the low target group received respiratory support for 86% of the monitoring period compared with 92% in the high target group (adjusted RR low versus high target, .93, 95% CI 0.86-0.99, p=.029).

The model based estimates showed an increase in IH events over the first 3 weeks of life in both infant groups followed by a decrease in IH events in the high target group compared to a plateau in the low target group (Figure 2a). The adjusted relative rate of IH events (RR), (the ratio of the adjusted mean number of IH events in the low target group/ the adjusted mean number of IH events in the high target group, per day), revealed a significantly higher rate of IH events prior to 12 days, and beyond 57 days of age in the low target group ($p<0.05$, Figure 2b). Higher rates of IH events were associated with lower gestational age, (adjusted RR 1.24,

95% CI 1.01-1.5, p=.032), and respiratory support, adjusted (RR 1.85, 95% CI 1.52-2.49, p<.0001).

The mean duration of IH events shortened (p<.01) and the severity worsened (p<.01) with increasing day of life (Figure 3). However, there were no differences in duration or severity between infant groups.

There was a wide range in the time interval between sequential IH events both within and between infants. To address the association between the timing of IH events and the oxygen saturation target group, the number of IH events was documented for three time interval ranges 1) <1 minute, 2) 1-20 minutes and, 3) >20 minutes between IH events. The highest incidence of events occurred with a time interval between events of <1 min, followed by a time interval of 1-20 minutes between events. There were relatively few IH events that occurred with a time interval of >20 minutes between events (Figure 4). IH events occurring with a time interval between events of <1 minute were associated with a significantly higher relative rate of IH events in the low target group at <15 and >54 days of life (p<0.05). After 65 days of life, there were a significantly higher number of IH events with a time interval of 1-20 minutes between events in the low target group (p<.05) with no differences between groups for IH events with a time interval of >20 minutes between events.

The above analysis examined the characteristics of IH events with increasing postnatal age. In addition, the effect of post menstrual age on the occurrence of IH events was also assessed.The number of IH events was not significantly different by treatment group, at any postmenstrual

age, indicating that postnatal rather than postmenstrual age is the major determinant of the incidence of IH.

Discussion:

This study showed an association between a low oxygen saturation target range and an escalation in the incidence of IH events that changed with increasing day of life. Infants in the low target range had a higher number of IH events during the first two weeks and after 57 days of life but followed a similar trajectory as the high saturation target group between these time periods. IH events became shorter and more severe with increasing post natal age, however, there were no differences in duration or severity between infant groups. Lastly, the higher incidence of IH events in the low target group was predominantly associated with a time interval between IH events of <1minute in duration.

Intermittent hypoxemic events are ubiquitous in preterm infants, both ventilated[9,10] and spontaneously breathing[11]. Nonetheless, the precise incidence of these events has not been well documented. This is important in order to address their potential pathophysiological consequences. This study showed a higher incidence of IH in the low target group which is consistent with McEvoy et al[12] showing a relationship between oxygen levels and IH in former preterm infants with chronic lung disease. Although these events are thought to be a consequence of immature respiratory control, this study and previous data in a similar infant cohort[5] suggest that other developmentally regulated pathological mechanisms may be contributing. There were relatively few IH events during the 1st week of life regardless of the level of oxygen exposure. This early phase was followed by a linear increase in IH events

through weeks two to three of life that was not affected by the oxygen saturation target range. The third phase of IH events began after four weeks of age with a plateau in IH events. After this time group differences emerge with a decline in events in the high target group while remaining relatively constant in the low target group. This may be due to a low baseline alveolar PO2 in the low target group which, in a model based analysis, has been shown to cause early onset of desaturation[13]. It remains unclear why this low reserve did not consistently result in a higher number of IH events at earlier post natal ages.

Caffeine use and respiratory support are the main clinical therapies for apnea and accompanying desaturation. Although caffeine has been shown to decrease apnea[14], interestingly, it has been shown to have little if any effect on desaturation episodes[15] although this is based on a single small series. Both infant groups spent a high percentage of the monitoring period on caffeine therapy with no significant difference in caffeine usage between infant groups, therefore, it is unlikely that caffeine use affected the results of this study. Respiratory support was associated with a higher incidence of IH events within each treatment group. However, with the high target group having a higher percentage of time receiving respiratory support, this cannot explain the increased incidence of IH in the low target infants.

Both groups showed a comparable decrease in duration and increase in severity of IH events during the first four weeks of life with no further changes throughout the study monitoring period. Previous data have suggested that convalescing preterm infants, of 30 wks gestation, with increased spontaneous apnea have an augmented ventilatory response to acute hypoxia[16]. Thus, although infants in the low target group may have been more susceptible to initiation of a

hypoxic event, they may have been able to rally a compensatory ventilatory response and recover as well as infants in the high target group.

The lower incidence of severe ROP in the main trial is in contrast to our previous findings of an association between IH and severe ROP[5]. This discrepancy may relate to the fact that the initial hyperoxia induced inhibition of angiogenesis is enhanced in the high oxygen target group at a time when IH episodes are not prominent. Time interval between IH events may also play a role. Previous data in animal models have suggested that the timing of patterns of IH events is important and may affect morbidity. In response to hypoxic exposure, measurements of reactive oxygen species have shown an increase in superoxide anion concentration during the recovery phase, with a delayed response of several minutes[17]. Current preterm infant data from our group suggest that ROP is associated with a time interval between events of 1-20 min potentially consistent with the ability to initiate an increase in reactive oxygen species (ROS). In contrast, the higher number of IH events in the low target group predominantly occurred with a time interval between events of less than 1 minute which may have limited the ROS response. The effect of the duration of recovery time between IH events on the resultant oxidative stress response has yet to be determined and merits further investigation.

There are limited data on the long term consequences of IH events in preterm infants[18]. A history of apnea of prematurity during hospitalization[19] and cardiorespiratory events in the home[20] have been associated with neurodevelopmental impairment. These studies have focused on apnea rather than the accompanying hypoxemic events. The only study to address the latter issue is the observation that mean oxygen saturation during apnea has been shown

to predict motor scores[21]. Further analysis is ongoing to assess the relationship between IH events and neurodevelopmental outcome in this infant cohort.

This study was limited by the known challenge of keeping infants in a designated oxygen saturation target range[22,23]. The main SUPPORT trial revealed overlap in the median level of oxygen saturation between target groups with actual median oxygen saturation levels slightly higher than targeted levels in both treatment groups[6]. This may have affected the number of IH events as lowering the median baseline saturation and increasing the time in the actual low target level may have resulted in an even higher incidence of IH events. In addition, the data used in this analysis were collected via pulse oximeters which remained in use from birth up to 36 weeks postmenstrual age (PMA), but only during times when the infants were receiving respiratory support and during the three days after respiratory support was discontinued. Thus, data do not exist for time points four or more days after discontinuation of respiratory support, transfer to a non-study hospital, discharge, or 36 weeks PMA (whichever came first). The GEE models used in this analysis assume that any missing data are missing completely at random. This assumption may be violated by these data, because infants who dropped out of the data due to a poor outcome such as death, or a favorable outcome such as discharge or being able to breathe room air without support, are likely to differ from those who remained on respiratory support through 36 weeks PMA. Thus, this should be considered a conditional analysis; that is, it is conditioned upon being alive and on respiratory support, and the results provided by the GEE model for any given point in time should be interpreted as applying only to the subset of infants who were alive and on respiratory support at that time. Lastly, enrollment for this study was limited by the low pulse oximeter settings (16 sec averaging and 10 sec

sample rate) per the main SUPPORT trial protocol. Due to memory storage and analysis costs only 2 sites acquired data at a high enough resolution to adequately detect IH events.

In conclusion, a low oxygen saturation target range is associated with an increased incidence of intermittent hypoxemic events that is dependent on postnatal age. These events tend to occur less than one minute apart but are of comparable duration and severity regardless of level of oxygen exposure. Two clinical trials have now demonstrated an association between low oxygen targets and increased mortality. While the etiology of such a mortality increase is unknown at this time, we speculate that the association between a low oxygen saturation target and increasing incidence of IH might provide insight to unraveling underlying pathophysiology. Further studies are needed to assess the contribution of timing of IH events on neonatal morbidity. We speculate that, to minimize episodes of IH, the optimal O_2 saturation target may need to be adjusted by postnatal age.

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Figure Legends:

Figure 1

A raw SaO2 waveform with the duration of the event and the time interval between events denoted by the arrows.

Figure 2

A) The model based estimates showed an increase in IH events over the first 3 weeks of life in both infant groups followed by a decrease in IH events in the high target group (- - -)compared to a plateau in the low target group (—) . B) The relative rate of IH events (RR), (the ratio of the adjusted mean number of IH events in the low target group/ the adjusted mean number of IH events in the high target group, per day), revealed a higher rate of IH events from <12 days, and >57 days of age in the low target group (* $p<0.05$).

Figure 3

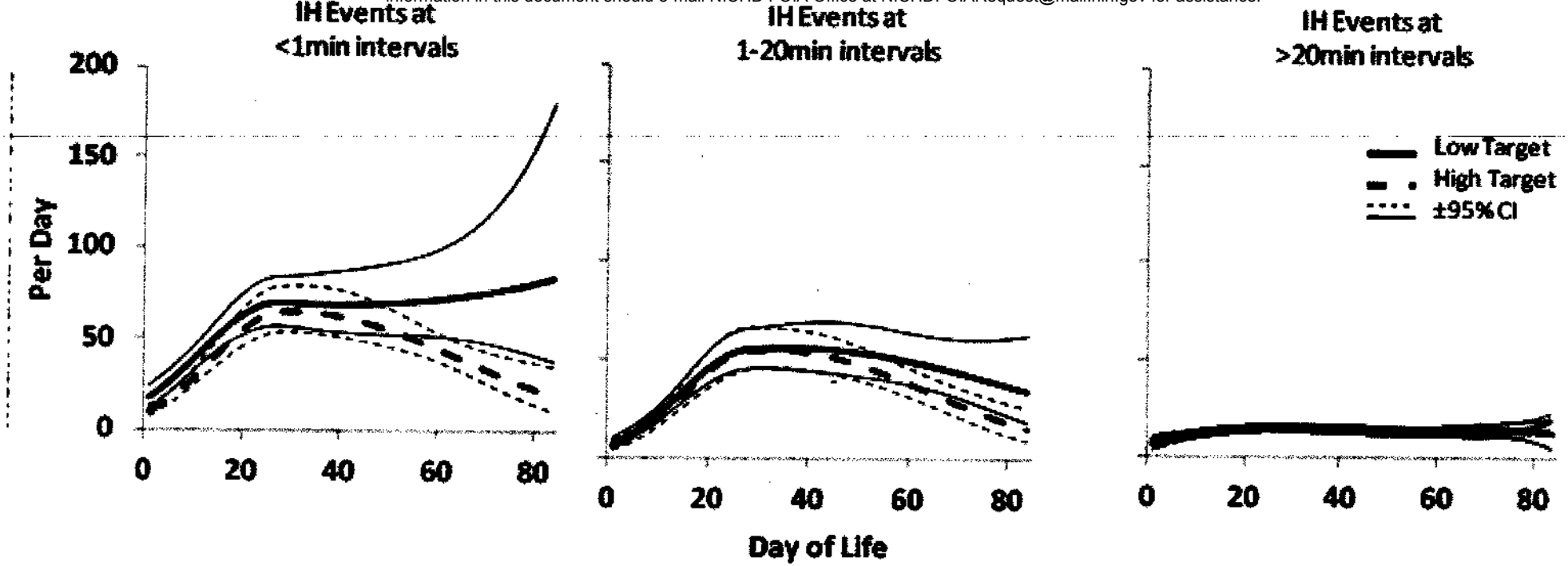
IH event duration decreased and severity worsened with increasing postnatal age in both the low and high target groups with no differences between groups.

Figure 4

A) The number of IH events was documented for three time interval ranges; <1 minute, 1-20 minutes and, >20 minutes between IH events. The highest incidence of events occurred with a time interval between events of <1 min, followed by a time interval of 1-20 minutes. There were relatively few IH events that occurred with a time interval of >20 minutes between

events. B) IH events occurring with a time interval between events of <1 minute were associated with a significantly higher relative rate of IH events in the low target group at <15 and >54 days of life ($p<0.05$). IH events occurring with a time interval of 1-20 minutes between event had a higher relative rate of IH events >65 days of life ($p<0.05$). IH events occurring >20 min apart were comparable between target groups with a relative rate of approximately one throughout the monitoring period.

A



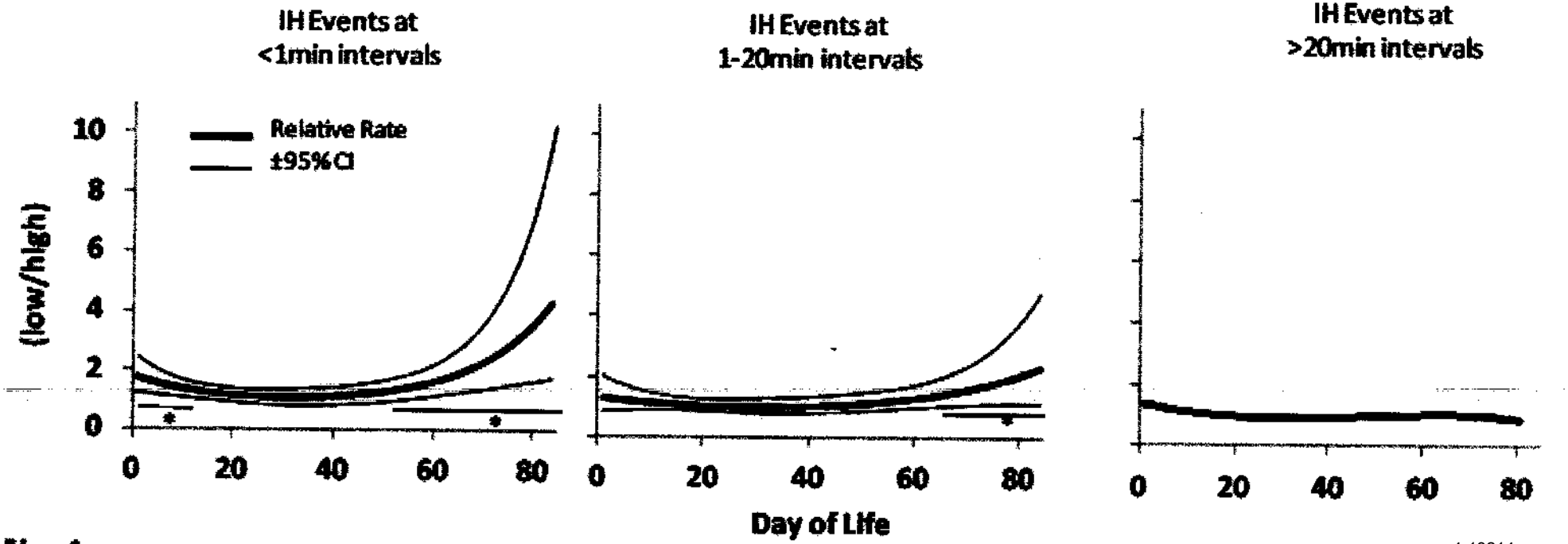
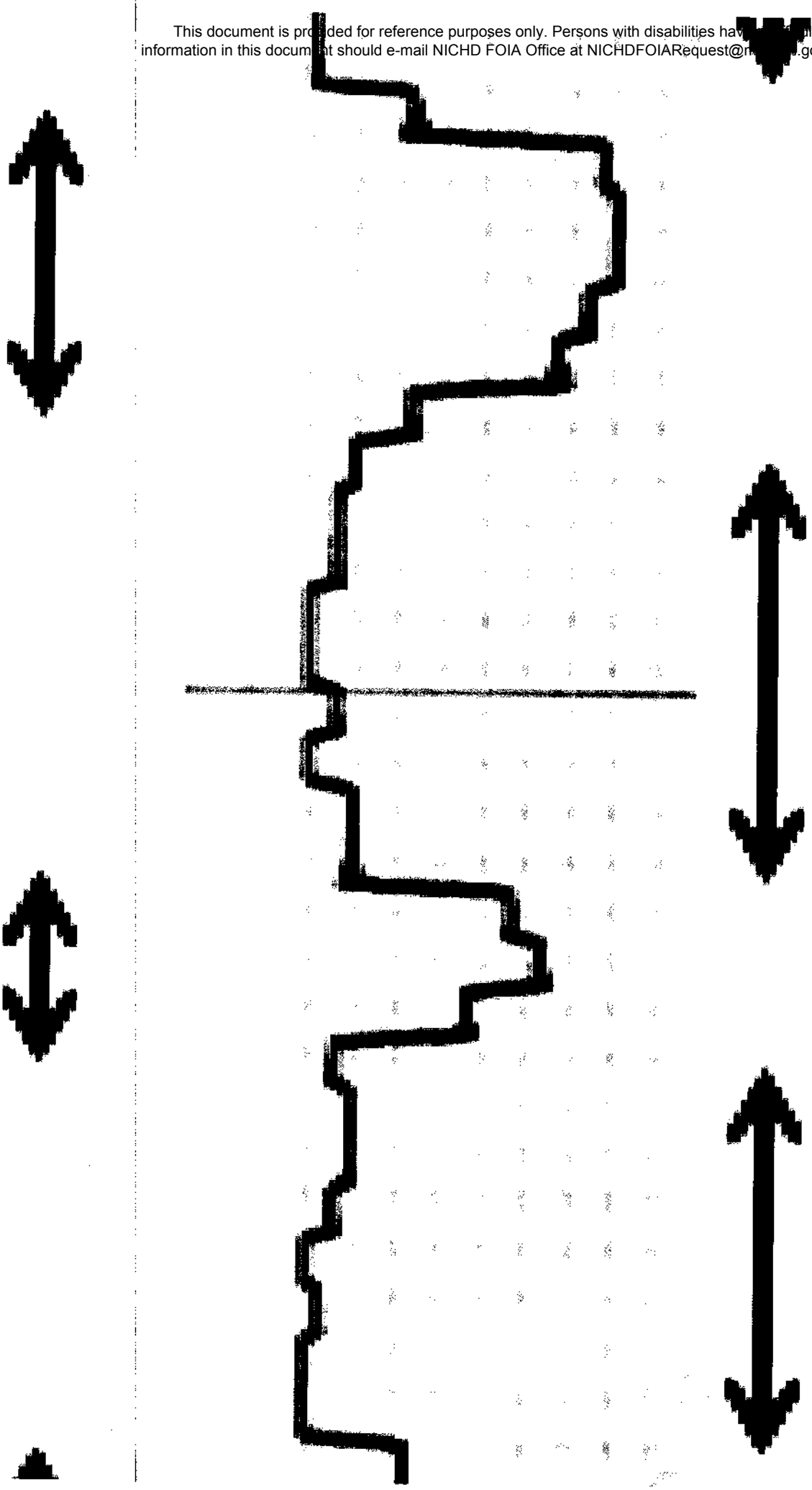


Fig 4

4-13214

B



	Low Target (53)	High Target (62)	p value*
Birth Weight (gm), mean(SD)	855(191)	808(171)	0.47
Gestational Age (wk), mean(SD)	25.8(1.1)	25.8(1.0)	0.76
BPD (O_2 @ 36 wk), n/N(%)	14/50(28%)	24/62(39%)	0.45
Death before 36 wk PMA, n(%)	3 (6%)	0 (0%)	0.09
Severe ROP, n/N(%)	8/49(16%)	13/58(22%)	0.41
Caffeine, n/N(%) of monitored days	2245/2838 (79%)	2757/3417 (81%)	0.87
Respiratory Support[t], n/N(%) of monitored days	2451/2849 (86%)	3085/3369 (92%)	0.03

*results adjusted for stratification factors (study center and gestational age group) and familial clustering except for gestational age (adjusted for study center and familial clustering) and death (Fisher's exact test).

[t]High frequency jet ventilation, CPAP, conventional ventilation, nasal cannula, Nasal SIMV, or hood

Reviewer 1

Review : "Low oxygen target range is associated with increased incidence of intermittent hypoxemia" Juliann M. Di Fiore, Michele Walsh, Lisa Wrage, et. al.

Overall this paper addresses an important issue of incidence oxygen desaturation/hypoxemia in ELBW infants who were in the NICHD Neonatal Network SUPPORT study. The initial results of the SUPPORT trial were published in NEJM in 2010 and of interest the first author and co-investigators published on the relationship between a higher incidence of intermittent hypoxic episodes associated with severe retinopathy of prematurity (data from individual site n=79). **-ADDRESSED IN NEW VERSION (REMOVED FROM INTRO)** In the background the authors summarize pertinent findings from the first report of

(b)(4)

(b)(4)

Reviewer 2

This is an interesting manuscript that reports an important problem. Below, I have divided my comments into general comments, and comments that refer to each section of the manuscript. I hope that these comments are helpful.

General comments:

(b)(4)

Withheld pursuant to exemption

(b)(4)

of the Freedom of Information and Privacy Act

Withheld pursuant to exemption

(b)(4)

of the Freedom of Information and Privacy Act

Withheld pursuant to exemption

(b)(4)

of the Freedom of Information and Privacy Act

From: Vaucher, Yvonne
To: Earl, Pam
Cc: Myriam Peralta, M.D.; Vaucher, Yvonne; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: NICHD Support Trial Follow-Up Outcomes
Date: Wednesday, November 16, 2011 9:20:10 PM

Dear Ms. Earl,

We very much appreciate your interest in the NICHD SUPPORT Trial Outcome data, however we must respectfully decline your invitation to participate in the filming, live broadcast, and sharing of Powerpoint slides as the SUPPORT trial Outcome manuscripts have not yet been submitted and we do not want to jeopardize their publication.

Sincerely,

Yvonne E. Vaucher, M.D., M.P.H.
Division of Neonatal/Perinatal Medicine
Clinical Professor of Pediatrics
UCSD School of Medicine

tele: 619-543-3759
FAX: 619-543-3812

From: Earl, Pam [mailto:PEarl@nemours.org]
Sent: Wednesday, November 16, 2011 12:32 PM
To: mperalta@peds.uab.edu; lcallier@peds.uab.edu; yvaucher@ucsd.edu
Subject: FW: NICHD Support Trial Follow-Up Outcomes

We haven't heard back from you and wondered if you have had a chance to consider this, particularly the live broadcast? Could we possibly get a response today?

From: Earl, Pam
Sent: Monday, November 14, 2011 2:58 PM
To: 'mperalta@peds.uab.edu'; 'lcallier@peds.uab.edu'; 'yvaucher@ucsd.edu'
Cc: 'Robert Bieber'
Subject: NICHD Support Trial Follow-Up Outcomes

Dr. Pamela Arn, Dr. Carl Gartner, and Dr. Jay Greenspan, Editors-in-Chief of PedsUniversity.org and NICUniversity.org, Nemours' Continuing Medical Education (CME) websites, have **selected your presentation (NICHD Support Trial Follow-Up Outcomes)** to be broadcast live (on the NICUniversity.org website) during the December 4-6, 2011 Hot Topics in Neonatology meeting to be held at the Omni Shoreham Hotel in Washington, D.C., and to be recorded and converted into an online presentation for the website. We provide these lectures *free of charge* to all attendees. This is a wonderful opportunity to share your knowledge and expertise with an even larger audience, who will receive free CME credit at

www.NICUniversity.org. It is also of value to you in that, should we publish your presentation on the site, you can include the posting on your CV.

We would like to film your presentation for video/audio of you speaking at the conference and obtain a copy of the PowerPoint presentation (at the conference) to publish online. We will combine your video/audio and slides into a multimedia presentation in which users will see you and hear your voice, see your slides, and see a synchronized (and edited) transcript of the talk. We may also create a downloadable PDF version for those who prefer to read your talk. Before posting, we will ask that you review this PDF to ensure that your intent and content has remained sound.

With that information, **we request your permission to live broadcast your presentation within the NICUniversity.org website and to capture this presentation. I have attached an authorization form. Please sign it and return it to me.**

Because we intend to make this presentation available on the Internet, we have to be cautiously aware of copyright and privacy concerns just as if we were submitting an article for publication to a journal. You can assist us in getting your presentation online as soon as possible by trying to avoid using copyright images (when possible) or, when copyright images are needed, taking careful note of the source. If copyrights are a problem, depending on how much you actually refer to the images, sometimes we can remove the image and edit the audio without detracting from the lecture.

If you have any questions, please do not hesitate to contact me.

Pam Earl
PedsEducation.org
Nemours Children's Clinic Home Office
10140 Centurion Parkway North
Jacksonville, FL 32256
Phone: 904-697-5664
Fax: 904-697-4004

From: Vaucher, Yvonne <yvaucher@ucsd.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wed Nov 16 18:16:07 2011
Subject: Request for broadcast at Hot Topics

Rose,

How do you want us to respond or do you want to respond representing the SUPPORT Subcommittee? We should send one response.

Thanks

Yvonne

From: Myriam Peralta, M.D. [mailto:MPeralta@peds.uab.edu]
Sent: Wednesday, November 16, 2011 12:36 PM
To: Vaucher, Yvonne
Subject: FW: NICHD Support Trial Follow-Up Outcomes

Yvonne do you want to have a joined response on this so we are consistent, thanks

---

From: Earl, Pam [mailto:PEarl@nemours.org]
Sent: Wednesday, November 16, 2011 2:32 PM
To: Myriam Peralta, M.D.; LaTanya Callier; yvaucher@ucsd.edu
Subject: FW: NICHD Support Trial Follow-Up Outcomes

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conference and obtain a copy of the PowerPoint presentation (at the conference) to publish online. We will combine your video/audio and slides into a multimedia presentation in which users will see you and hear your voice, see your slides, and see a synchronized (and edited) transcript of the talk. We may also create a downloadable PDF version for those who prefer to read your talk. Before posting, we will ask that you review this PDF to ensure that your intent and content has remained sound.

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If you have any questions, please do not hesitate to contact me.

Pam Earl
PedsEducation.org
Nemours Children's Clinic Home Office
10140 Centurion Parkway North
Jacksonville, FL 32256
Phone: 904-697-5664
Fax: 904-697-4004

From: Vaucher, Yvonne
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Request for broadcast at Hot Topics
Date: Wednesday, November 16, 2011 6:25:24 PM

So Myriam and I will reply personally.

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, November 16, 2011 3:23 PM
To: Vaucher, Yvonne
Cc: Finer, Neil; 'wcarlo@peds.uab.edu'
Subject: Re: Request for broadcast at Hot Topics

We should respectfully decline - the manuscripts are not submitted/accepted and we do not want to jeopardize publication

From: Vaucher, Yvonne <yvaucher@ucsd.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wed Nov 16 18:16:07 2011
Subject: Request for broadcast at Hot Topics

Rose,

How do you want us to respond or do you want to respond representing the SUPPORT Subcommittee? We should send one response.

Thanks

Yvonne

From: Myriam Peralta, M.D. [mailto:MPeralta@peds.uab.edu]
Sent: Wednesday, November 16, 2011 12:36 PM
To: Vaucher, Yvonne
Subject: FW: NICHD Support Trial Follow-Up Outcomes

Yvonne do you want to have a joined response on this so we are consistent, thanks

From: Earl, Pam [mailto:PEarl@nemours.org]
Sent: Wednesday, November 16, 2011 2:32 PM
To: Myriam Peralta, M.D.; LaTanya Callier; yvaucher@ucsd.edu
Subject: FW: NICHD Support Trial Follow-Up Outcomes

We haven't heard back from you and wondered if you have had a chance to consider this, particularly the live broadcast? Could we possibly get a response today?

From: Earl, Pam
Sent: Monday, November 14, 2011 2:58 PM
To: 'mperalta@peds.uab.edu'; 'lcallier@peds.uab.edu'; 'yvaucher@ucsd.edu'
Cc: 'Robert Bieber'

Subject: NICHD Support Trial Follow-Up Outcomes

Dr. Pamela Arn, Dr. Carl Gartner, and Dr. Jay Greenspan, Editors-in-Chief of PedsUniversity.org and NICUniversity.org, Nemours' Continuing Medical Education (CME) websites, have **selected your presentation (NICHD Support Trial Follow-Up Outcomes)** to be broadcast live (on the NICUniversity.org website) during the December 4-6, 2011 Hot Topics in Neonatology meeting to be held at the Omni Shoreham Hotel in Washington, D.C., and to be recorded and converted into an online presentation for the website. We provide these lectures *free of charge* to all attendees. This is a wonderful opportunity to share your knowledge and expertise with an even larger audience, who will receive free CME credit at www.NICUniversity.org. It is also of value to you in that, should we publish your presentation on the site, you can include the posting on your CV.

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From: Vaucher, Yvonne
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Request for broadcast at Hot Topics
Date: Wednesday, November 16, 2011 6:16:49 PM
Attachments: vaucher_authform.doc
carceleen_authform.doc

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AUTHORIZATION

(To Record Presentation and Use Materials)

Speaker: **Yvonne E. Vaucher, MD, MPH**

Presentation: **NICHD Support Trial Follow-Up Outcomes**

Nemours and its operating entities are dedicated to enhancing pediatric health care through education and research. Nemours often chooses outstanding presentations for use in various teaching forums, including our website. We would appreciate your granting Nemours permission to utilize your Presentation. If you agree please answer the following questions and sign the permission statement below.

I am the original author of the Presentation. Yes _____ No_____

The Presentation contains materials produced by a third party (such as graphs or images). Yes _____ No_____

I have secured appropriate signed authorization to use any such third party materials contained in the Presentation. Yes _____ No_____

If your answer is no, would you be willing to allow Nemours to do so?
Yes _____ No_____

The Presentation contains photographs (or other images) of patients.
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I have secured appropriate signed HIPAA authorization to use any patient images.
Yes _____ No_____

Please read and sign the following release.

I (the "Speaker") hereby authorize Nemours to record my voice, likeness and/or appearance and the above referenced Presentation in all media and grant Nemours permission to use all such recordings and photographs and the Presentation materials ("Materials") for any educational, research and informational purposes in any media and by all means in perpetuity. Speaker represents and warrants to Nemours, except as set forth above, that the Speaker is the original author of the Presentation and the Materials, including all text, graphics and images used or included therein, or that the Speaker has sufficient rights to grant the rights granted to Nemours hereunder, and that the exercise by Nemours of any right granted hereunder shall not violate or infringe any third party's rights. The foregoing Authorization shall be binding on the Speaker and his/her heirs and successors. I hereby represent that I am of legal age and that I have every right to contract in my own name without violating any other commitment. I state further that I have read, or have had read to me, and understand this authorization and release, prior to its execution, and that I duly understand the contents herein.

By: _____ Date: _____
Speaker's Signature

Last revised 11/14/11

AUTHORIZATION

(To Record Presentation and Use Materials)

Speaker: **Myriam Peralta Carceleen, MD, MPH**

Presentation: **NICHD Support Trial Follow-Up Outcomes**

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By: _____ Date: _____
Speaker's Signature

Last revised 11/14/11

From: Vaucher, Yvonne
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: PAS Abstract Submission: Important Information
Date: Wednesday, November 16, 2011 4:43:59 PM
Attachments: CPAPSUPPORTAbstractPAS2012Submitted.docx

Rose,

PAS 2012 CPAP SUPPORT Abstract attached

Yvonne

First Author: Yvonne E Vaucher, MD, MPH **Filename:** 750265
Responsible Author: Yvonne E Vaucher, MD, MPH
Presenting Author: Yvonne E Vaucher, MD, MPH
Contact Person: Yvonne E Vaucher, MD. MPH

2012 PAS Annual Meeting

Subspecialty: Neonatal Epidemiology & Follow-Up
Theme: Neonatal Medicine: Clinical Trials

Contact Author: Yvonne E Vaucher, MD. MPH
Department/Institution/Address: Pediatrics,Division of Neonatology, Univ California, San Diego, 200 West Arbor Drive MC 8774, San Diego, CA, 92103, United States
Phone: 1-619-543-3759 **Fax:** 1-619-543-3812 **E-mail:** yvaucher@ucsd.edu

Reponsible Author: Yvonne E Vaucher, MD, MPH
Department/Institution/Address: Pediatrics, Div. of neonatology, Univ of California, San Diego, 200 West Arbor Drive MC 8774, San Diego, CA, 92037-8774, United States
Phone: 1-619-543-3759 **Fax:** 1-619-543-3759
Responsible Author E-mail: yvaucher@ucsd.edu
Responsible Author Declaration: As the responsible author, I confirm that the individual listed as the sponsor has been contacted and given the opportunity to review the abstract and has subsequently agreed to sponsor this abstract.

Presenting Author: Yvonne E Vaucher, MD, MPH
Department/Institution/Address: Pediatrics, Div of Neonatology, 200 West Arbor Drive MC 8774, San Diego, CA, 92103-8774, United States
Phone: 1-619-543-3759 **Fax:** 1-619-543-3812
Presenting Author E-mail: yvaucher@ucsd.edu
The presenting author is member of these Alliance Societies:
Is Presenting Author a Trainee? No, Not a Trainee
Presenter Copyright Declaration:
I certify that any material I will use, display, distribute, reproduce or have reproduced or distributed in connection with my above noted presentation for which I do not have permission to use, is my original work and/or is public information or another type of material which does not require securing permission from another party to use, display, distribute, reproduce or have reproduced or distributed.

QUESTIONNAIRE INFORMATION

Eastern Society for Pediatric Research: No, Do not consider this abstract for the Eastern SPR
Pediatric Hospital Medicine: No, Do not consider this abstract for presentation at the Pediatric Hospital Medicine, July 19-22, 2012
Research Type: Clinical
Presentation Sabbath Conflict on: N/A
APA Special Interest Groups, Committees or Regions: None

AWARDS APPLIED FOR:

No awards selected

SPONSOR INFORMATION

Sponsoring Member for PAS/ASPR abstract:
Sponsor Name: Yvonne Vaucher

Email: yvaucher@ucsd.edu
Is the Sponsor an Author? Yes
Sponsoring Societies:
Academic Pediatric Association
American Academy of Pediatrics
Global Pediatric Research Program

Title: Neurodevelopmental Outcome of Extremely Premature Infants Enrolled in the SUPPORT trial: Early CPAP versus Intubation with Surfactant Administration

Yvonne E Vaucher, MD, MPH[1], Marie G Gantz, PhD[2], Neil N Finer, MD[1] and Rosemary D Higgins, MD[3]. [1]Division of Neonatology, Department of Pediatrics, University of California,, San Diego, CA, United States; [2]Statistics and Epidemiology, RTI International, Research Triangle Park, NC, United States and [3]SUPPORT Subcommittee of the NICHD Neonatal Research Network, NICHD, Rockville, MD, United States.

Background: The multicenter SUPPORT randomized, controlled trial demonstrated that initial treatment with non-invasive CPAP is an alternative to early surfactant administration after intubation and is associated with similar rates of death or BPD in infants born at 24 to 27 weeks gestation.

Objective: We hypothesized that, compared to treatment with surfactant administration after intubation, treatment with early CPAP would decrease the composite outcome of death or neurodevelopmental impairment (NDI).

Design/Methods: The SUPPORT Trial enrolled 1316 extremely premature infants, 24 to 27 weeks gestation, randomized to receive either CPAP in the delivery room with a limited ventilation strategy for two weeks (CPAP) or intubation with surfactant administration within one hour after birth (SURF). Infants were randomized within each center by gestational age strata (24 0/7-25 6/7 and 26 0/7-27 6/7 weeks). A standardized neurodevelopmental assessment was performed at 18-22 months corrected age. The primary, pre-specified composite outcome was death or NDI including at least one of the following: BSID-III cognitive score < 70, Gross Motor Function Classification System (GMFCS) score 2, moderate/severe cerebral palsy, bilateral blindness or permanent hearing impairment. Results were adjusted for gestational age, center and familial clustering.

Results: Death or NDI was determined for 1234/1316 (93.8%) enrolled infants. Death or NDI occurred in 27.9% (173/621) of CPAP and 29.9% (183/613) of SURF infants (p=0.38). Rates of death (CPAP-18.4 vs. SURF-21.9%, p=0.10), NDI alone (CPAP-10.9 vs. SURF 9.1%, p=0.44), cognitive score < 70 (CPAP-7.2 vs. SURF-7.6%, p=0.84), moderate/severe cerebral palsy (CPAP-4.1 vs. SURF-4.0%, p=0.82), GMFCS 2 (CPAP-5.1 vs. SURF 4.8%, p=0.95); blindness (CPAP-0.8 vs. SURF 1.5%, p=0.31), and permanent hearing impairment (CPAP-3.3 vs. SURF-1.5%, p=0.06) were similar in both treatment arms. There were no significant differences in neurodevelopmental outcomes between CPAP and SURF groups within each GA stratum.

Conclusions: We found no significant difference in the composite outcome of death or neurodevelopmental impairment at 18-22 months corrected age between extremely premature infants randomized to treatment with either early CPAP or intubation and surfactant administration.

Other Previews:
Abstract Disclosure Info:

From: Vaucher, Yvonne
To: Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]; "Wally Carlo, M.D."; Myriam Peralta, M.D.
Cc: wacarlo@uab.edu; Das, Abhik
Subject: RE: NICHD Support Trial Follow-Up Outcomes
Date: Wednesday, November 16, 2011 10:31:02 AM

Since what may constitute publication is unclear, and might differ from one journal to another, this seems to be the best course.

Yvonne

From: Finer, Neil
Sent: Wednesday, November 16, 2011 7:18 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; 'Wally Carlo, M.D.'; Myriam Peralta, M.D.; Vaucher, Yvonne
Cc: wacarlo@uab.edu; Das, Abhik
Subject: RE: NICHD Support Trial Follow-Up Outcomes

If this is seen as equivalent to publication, I would demur with thanks
Agree with Rose
Neil

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, November 16, 2011 6:36 AM
To: 'Wally Carlo, M.D.'; Myriam Peralta, M.D.; Vaucher, Yvonne
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I think we should thank them for considering the SUPPORT FU presentation for broad dissemination. However, given that the manuscript has not been published, we do not want to jeopardize its publication potential by having it available in an on line manner and thus cannot agree to making it available on line.

Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]

Sent: Tuesday, November 15, 2011 4:03 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Myriam Peralta, M.D.; yvaucher@ucsd.edu
Cc: wacarlo@uab.edu
Subject: RE: NICHD Support Trial Follow-Up Outcomes

This is risky. I agree with Rose that it should only be done if approved by NEJM. Other journals such a Lancet and JAMA may disqualify us.

I do not see the upside of this for us. I only see many downsides. They should do it after it is peer reviewed and published.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
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Director, Newborn Nurseries
1700 6th Avenue South
176F Suite 9380R
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: (b)(6)

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, November 15, 2011 2:57 PM
To: Myriam Peralta, M.D.; 'yvaucher@ucsd.edu'
Cc: 'wacarlo@uab.edu'
Subject: Re: NICHD Support Trial Follow-Up Outcomes

If this would preclude publication in NEJM, we would not want to allow it.

Do you have the updated version of the manuscript for review by all authors and the steering committee? Do you want me to check with NEJM?

Thanks
Rose

From: Myriam Peralta, M.D. <MPeralta@peds.uab.edu>
To: yvaucher@ucsd.edu <yvaucher@ucsd.edu>; Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tue Nov 15 15:39:36 2011
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To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: NICHD Support Trial Follow-Up Outcomes
Date: Wednesday, November 16, 2011 10:24:36 AM

This sounds like a good approach

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
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University of Alabama at Birmingham

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Director, Newborn Nurseries
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Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 (b)(6)

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publish online. We will combine your video/audio and slides into a multimedia presentation in which users will see you and hear your voice, see your slides, and see a synchronized (and edited) transcript of the talk. We may also create a downloadable PDF version for those who prefer to read your talk. Before posting, we will ask that you review this PDF to ensure that your intent and content has remained sound.

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If you have any questions, please do not hesitate to contact me.

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From: Vaucher, Yvonne
To: Wally Carlo, M.D.
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Myriam Peralta, M.D.; wacarlo@uab.edu
Subject: Re: NICHD Support Trial Follow-Up Outcomes
Date: Tuesday, November 15, 2011 5:08:58 PM

I agree with Wally since the implications are uncertain.

Sent from my iPhone

On Nov 15, 2011, at 4:03 PM, "Wally Carlo, M.D." <WCarlo@peds.uab.edu<mailto:WCarlo@peds.uab.edu>> wrote:

This is risky. I agree with Rose that it should only be done if approved by NEJM. Other journals such a Lancet and JAMA may disqualify us.

I do not see the upside of this for us. I only see many downsides. They should do it after it is peer reviewed and published.

Wally

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From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, November 15, 2011 2:57 PM
To: Myriam Peralta, M.D.; 'yvaucher@ucsd.edu<mailto:yvaucher@ucsd.edu>'
Cc: 'wacarlo@uab.edu<mailto:wacarlo@uab.edu>'
Subject: Re: NICHD Support Trial Follow-Up Outcomes

If this would preclude publication in NEJM, we would not want to allow it.

Do you have the updated version of the manuscript for review by all authors and the steering committee?
Do you want me to check with NEJM?

Thanks
Rose

From: Myriam Peralta, M.D. <MPeralta@peds.uab.edu<mailto:MPeralta@peds.uab.edu>>
To: yvaucher@ucsd.edu<mailto:yvaucher@ucsd.edu> <yvaucher@ucsd.edu<mailto:yvaucher@ucsd.edu>>; Higgins, Rosemary (NIH/NICHD) [E]

Sent: Tue Nov 15 15:39:36 2011
Subject: RE: NICHD Support Trial Follow-Up Outcomes
Rose: I had received this email. please let me know how should I respond, given that this is the entire group and that we had not submitted for publication yet. Thanks.

From: Earl, Pam [mailto:PEarl@nemours.org]
Sent: Mon 11/14/2011 1:58 PM
To: Myriam Peralta, M.D.; LaTanya Callier; <mailto:yvaucher@ucsd.edu>
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Cc: Robert Bieber
Subject: NICHD Support Trial Follow-Up Outcomes
Dr. Pamela Arn, Dr. Carl Gartner, and Dr. Jay Greenspan, Editors-in-Chief of PedsUniversity.org<http://PedsUniversity.org> and NICUniversity.org<http://NICUniversity.org>, Nemours' Continuing Medical Education (CME) websites, have selected your presentation (NICHD Support Trial Follow-Up Outcomes) to be broadcast live (on the NICUniversity.org<http://NICUniversity.org> website) during the December 4-6, 2011 Hot Topics in Neonatology meeting to be held at the Omni Shoreham Hotel in Washington, D.C., and to be recorded and converted into an online presentation for the website. We provide these lectures free of charge to all attendees. This is a wonderful opportunity to share your knowledge and expertise with an even larger audience, who will receive free CME credit at www.NICUniversity.org<http://www.NICUniversity.org>. It is also of value to you in that, should we publish your presentation on the site, you can include the posting on your CV.

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If you have any questions, please do not hesitate to contact me.

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Vaucher, Yvonne"
Subject: RE: CPAP SUPPORT ND Outcome Abstract
Date: Monday, November 14, 2011 11:13:00 AM

Please send me the final submitted version
Thanks
Rose

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From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]
Sent: Friday, November 11, 2011 5:17 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie; Finer, Neil
Cc: Vaucher, Yvonne
Subject: CPAP SUPPORT ND Outcome Abstract

Submitted to PAS 11/11/11.

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From: Vaucher, Yvonne
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Rich, Wade; Susan Hintz; Finer, Neil; Vaucher, Yvonne
Subject: SUPPORT ND Outcome: Enrolled vs. Eligible/Non-enrolled
Date: Friday, November 11, 2011 8:09:30 PM
Attachments: Comparison ND outcome enrolled vs eligible nonenrolled SUPPORT trial children at 18_22moRevYV110711.docx

Rose,

I have attached a proposal to compare the neurodevelopmental outcome of children enrolled vs. those eligible but not enrolled in the SUPPORT trial. This is a topical subject with important implications for clinical trial design and interpretation. In addition the enrolled SUPPORT group is the largest cohort of 24-27 week gestation children with ND outcome reported in any US RCT. Pediatrics would probably be interested as they have published the preceding papers comparing antenatal characteristics and neonatal outcomes of enrolled and eligible/non-enrolled infants. We will first need to identify the optimal eligible/non-enrolled GA group to use for comparison, (i.e., those who were assessed with the BSID-III and had the highest FUP rate.) To do this we will need to determine the FUP rate for all eligible/not enrolled by week gestation. I suspect that will be the <27 week gestation children, most of whom would have qualified for the GDB either by BW (<1000g) or GA. If approved, I would like to begin working on this as soon as the primary SUPPORT papers are submitted.

Yvonne

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Proposal to compare early childhood neurodevelopmental outcome of 24-25 week gestation ELBW children enrolled vs. those not-enrolled in SUPPORT Trial

Proposed authors: Yvonne Vaucher, Susan Hintz, Wade Rich

Background: Neurodevelopmental outcome results from the SUPPORT trial demonstrate that children born at 24-25 week gestation are at substantially higher risk for adverse neurorodevelopmental outcome including NDI, MDI < 70, cerebral palsy and deafness compared to those born at 26-27 week gestation. These results support the findings of prior studies of ELBW or ELGAN children [1-4].

An important question for any multicenter trial including neurodevelopmental follow-up is whether the sample studied is representative of the larger population and therefore generalizable to the larger population. Selection bias may from biases arising during study enrollment or through lack of data for those who were lost to follow-up. Concerning the latter, the SUPPORT trial follow-up rate of 94% was outstanding, and as such, the bias resulting from loss to follow-up is likely quite small. However, the need for antenatal consent in the SUPPORT trial resulted in higher rates of adverse demographic, clinical and neonatal outcome factors in the eligible, non-enrolled group compared with the enrolled group. [5, 6] For example the rate of resuscitation at delivery, BPD, severe IVH (Grades 3-4) and death were all significantly higher in the eligible, non-enrolled group.

It is important, therefore, to determine whether enrollment selection bias inherent in the need to obtain antenatal consent is associated with more adverse neurodevelopmental outcome in children who were eligible but not enrolled in trial, thereby reducing the generalizability of the study results. Alternatively it is possible that the effect of extremely low gestational age alone might predominate such that the incremental y increased risk associated with the higher rate of adverse demographic and neonatal outcome factors in the non-enrolled group would not be evident.

The SUPPORT trial included a very large group (N=565) of extremely premature children born in the US at 24-25 weeks gestation with over 350 survivors. This group provides a unique opportunity to examine the effect of enrollment selection bias on early childhood neurodevelopmental outcome in children who are at the highest neurodevelopmental risk. The initial step of determining the maternal and neonatal outcome biases has already been accomplished. [5, 6]The next logical step is to determine whether there is an associated neurodevelopmental outcome bias evident at 18-22 months corrected age. This short-term outcome information will also inform results from the longer term outcome study planned for SUPPORT children at 7 years.

We therefore propose to compare the neurodevelopmental outcome of surviving 24-25 weeks gestation children at 18-22 months corrected age born between Jan 2006 and February 2009 who were enrolled in the SUPPORT trial to the outcome of those surviving 24-25 week gestation children who born during the same time period and who were eligible but not enrolled in the SUPPORT trial.

We will focus on a subgroup of the most immature children not only because they are at highest risk, but also because almost all of the 24-25 week gestation eligible but non-enrolled children would also

have been enrolled during the SUPPORT trial in the NRN GDB using the gestational age and birthweight criteria.*

We hypothesize;

1) That the incidence of death and therefore the composite outcome of death or NDI will be higher in the non-enrolled group
2) Among survivors to 18-22 month follow up, the neurodevelopmental outcome of the enrolled vs. eligible/non-enrolled groups will not be significantly different

Methods: This study would be a post-hoc, subgroup analysis of neurodevelopmental outcome for the most immature and highest risk cohort of extremely premature children born at 24-25 weeks gestation and enrolled in the SUPPORT trial. The outcome data for these children would be compared with that of the 24-25 week cohort who were eligible for, but not enrolled in, the SUPPORT trial. All neurodevelopmental outcome data for both groups was prospectively collected, sent to RTI and recorded in the GDB database maintained by RTI.

Rationale for date limiters (DOB 1/2006-2/20090): We would include children born at 24-25 weeks children between January 2006-February 2009, all of whom would have been assessed using Bayley Scales of Infant and Toddler Development-III anticipating that almost all the eligible/nonenrolled children born between 1/12006 and 12/31/2007 also had birthweights < 1000 g and are therefore included in the GDB follow-up database.

Sample size: The first step is to determine 1) how many of the enrolled 24-25 weeks gestation SUPPORT children were born between 1/2006 to 2/2009 and had a developmental assessment at 18-22 month corrected age; 2) how many of 24-25 week gestation eligible/non-enrolled children born in the same time period (1/2006 to 2/2009) were enrolled in the GDB follow-up and had a developmental assessment at 18-22 month corrected age. From this information we can then determine the sample size and the magnitude of difference in neurodevelopmental outcomes which could be detected.

Analyses: Neurodevelopmental outcome variables analyzed would be the same as those analyzed in the CPAP and Oximeter arms of the SUPPORT trial (i.e., NDI and the components thereof, Bayley cognitive and language scores and proportion <70,<80,<85, neuromotor outcome). Among survivors, regression models will be developed to examine the independent association of enrollment, as well as demographic, early neonatal and late neonatal factors, with neurodevelopmental outcome.

Results:

Figure:

Consort/Patient flow diagram: Enrolled vs. eligible/nonenrolled for death, follow up, lost-to-follow up, neurodevelopmental assessment determined

Tables: Comparisons of enrolled and eligible/non-enrolled groups

1. Comparison of demographic and neonatal clinical outcome data between enrolled, eligible/non-enrolled and lost to FUP groups
2. Comparison of Death and NDI, NDI, components of severe NDI (cognitive < 70, cognitive < 80, GMFCS ≥2, moderate-severe CP, bilateral blindness, permanent hearing impairment)
3. Comparison developmental and neuromotor outcomes (i.e., Bayley cognitive and language scores and proportion < 70, <80, >85; abnormal neurologic exam, normal, mild, moderate-severe CP
4. Regression model predicting factors (antenatal, neonatal, postnatal) independently associated with differences in neurodevelopmental outcome.

References:

1. Raz, S., et al., *Extreme prematurity and neuropsychological outcome in the preschool years.* J Int Neuropsychol Soc, 2010. **16**(1): p. 169-79.
2. Leversen, K.T., et al., *Prediction of neurodevelopmental and sensory outcome at 5 years in Norwegian children born extremely preterm.* Pediatrics, 2011. **127**(3): p. e630-8.
3. Tyson, J.E., et al., *Intensive care for extreme prematurity--moving beyond gestational age.* N Engl J Med, 2008. **358**(16): p. 1672-81.
4. Wood, N.S., et al., *Neurologic and developmental disability after extremely preterm birth. EPICure Study Group.* N Engl J Med, 2000. **343**(6): p. 378-84.
5. Rich, W.D., et al., *Antenatal consent in the SUPPORT trial: challenges, costs, and representative enrollment.* Pediatrics, 2010. **126**(1): p. e215-21.
6. Rich, W., *Enrollment of ELBW Infants in a clinical research study may not be representative.* Pediatrics. **in press**.

*1. Prior to January 2008 the criteria for GDB enrollment was birthweight <1000g; subsequently it has been a gestational age < 27 weeks. 2. The transition from administration of the Bayley II to the Bayley III at 18-22 months occurred in 2/2007 for all children born in 2006.]

From: Vaucher, Yvonne
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Need Disclosures from you in order to submit abstract
Date: Thursday, November 10, 2011 9:09:00 AM

Thanks!

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, November 10, 2011 5:32 AM
To: Vaucher, Yvonne; Gantz, Marie
Subject: RE: Need Disclosures from you in order to submit abstract

I just did mine – let me know if you need anything else

Rose

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From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]
Sent: Wednesday, November 09, 2011 6:10 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie
Subject: Need Disclosures from you in order to submit abstract

Rose and Marie,

Cannot submit abstract until your disclosures are on file. Have attached abstract and present Disclosure form. Let me know when you have filled the disclosure form out or if you want me to fill it out for you.
Thanks.

Yvonne

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From: Vaucher, Yvonne
To: Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie
Subject: Need Disclosures from you in order to submit abstract
Date: Wednesday, November 09, 2011 6:13:48 PM
Attachments: CPAPSUPPORTAbstractPAS2012Final110911.docx
PAS 2012 - Abstract Disclosure form.mht

Rose and Marie,

Cannot submit abstract until your disclosures are on file. Have attached abstract and present Disclosure form. Let me know when you have filled the disclosure form out or if you want me to fill it out for you.
Thanks.

Yvonne

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Filename: 750265

2012 Eastern SPR Annual Meeting

Subspecialty: Neonatal Epidemiology & Follow-Up
Theme: Neonatal Medicine: Clinical Trials

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Responsible Author Declaration: As the responsible author, I confirm that the individual listed as the sponsor has been contacted and given the opportunity to review the abstract and has subsequently agreed to sponsor this abstract.

Presenting Author: Yvonne E Vaucher, MD, MPH
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Eastern Society for Pediatric Research: Yes, Consider for Eastern SPR ONLY (not PAS/ASPR)
Pediatric Hospital Medicine: No, Do not consider this abstract for presentation at the Pediatric Hospital Medicine, July 19-22, 2012
Research Type: Clinical
Presentation Sabbath Conflict on: N/A
APA Special Interest Groups, Committees or Regions: None

AWARDS APPLIED FOR:

No awards selected

SPONSOR INFORMATION

Sponsoring Member for Eastern SPR abstract:
Sponsor Name: Yvonne Vaucher
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Is the Sponsor an Author? Yes

Title: Neurodevelopmental Outcome of Extremely Premature Infants Enrolled in the SUPPORT trial: Early CPAP versus Intubation with Surfactant Administration

Yvonne E Vaucher, MD, MPH[1], Marie G Gantz, PhD[2], Neil N Finer, MD[1] and Rosemary D Higgins, MD[3]. [1]Division of Neonatology, Department of Pediatrics, University of California,, San Diego, CA, United States; [2]Statistics and Epidemiology, RTI International, Research Triangle Park, NC, United States and [3]SUPPORT Subcommittee of the NICHD Neonatal Research Network, NICHD, Rockville, MD, United States.

Background: The multicenter SUPPORT randomized, controlled trial demonstrated that initial treatment with non-invasive CPAP is an alternative to early surfactant administration after intubation and is associated with similar rates of death or BPD in infants born at 24 to 27 weeks gestation.

Objective: We hypothesized that, compared to treatment with surfactant administration after intubation, treatment with early CPAP would decrease the composite outcome of death or neurodevelopmental impairment (NDI).

Design/Methods: The SUPPORT Trial enrolled 1316 extremely premature infants, 24 to 27 weeks gestation, randomized to receive either CPAP in the delivery room with a limited ventilation strategy for two weeks (CPAP) or intubation with surfactant administration within one hour after birth (SURF). Infants were randomized within each center by gestational age strata (24 0/7-25 6/7 and 26 0/7-27 6/7 weeks). A standardized neurodevelopmental assessment was performed at 18-22 months corrected age. The primary, pre-specified composite outcome was death or NDI including at least one of the following: BSID-III cognitive score < 70, Gross Motor Function Classification System (GMFCS) score ≥2, moderate/severe cerebral palsy, bilateral blindness or permanent hearing impairment. Results were adjusted for gestational age, center and familial clustering.

Results: Death or NDI was determined for 1234/1316 (93.8%) enrolled infants. Death or NDI occurred in 27.9% (173/621) of CPAP and 29.9% (183/613) of SURF infants (p=0.38). Rates of death (CPAP-18.4 vs. SURF-21.9%, p=0.10), NDI alone (CPAP-10.9 vs. SURF 9.1%, p=0.44), cognitive score < 70 (CPAP-7.2 vs. SURF-7.6%, p=0.84), moderate/severe cerebral palsy (CPAP-4.1 vs. SURF-4.0%, p=0.82), GMFCS ≥2 (CPAP-5.1 vs. SURF 4.8%, p=0.95); blindness (CPAP-0.8 vs. SURF 1.5%, p=0.31), and permanent hearing impairment (CPAP-3.3 vs. SURF-1.5%, p=0.06) were similar in both treatment arms. There were no significant differences in neurodevelopmental outcomes between CPAP and SURF groups within each GA stratum.

Conclusions: We found no significant difference in the composite outcome of death or neurodevelopmental impairment at 18-22 months corrected age between extremely premature infants randomized to treatment with either early CPAP or intubation and surfactant administration.

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2012 Pediatric Academic Societies' Annual Meeting

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Abstract Number: 750265

Responsible Author: Yvonne E Vaucher, MD, MPH

Presenting Author: Yvonne E Vaucher, MD, MPH

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Disclosure for Author: Yvonne E Vaucher, MD, MPH

2012 Pediatric Academic Societies' Annual Meeting

DISCLOSURE NUMBER: 202355

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I have read and will comply with Tulane's Disclosure & Conflict of Interest Policies

Participant Role

Abstract Author/Co-Author
SIG Chair/Presenter

Disclosure

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Disclosure for Author: Marie G Gantz, PhD

No Confirmed Disclosure

Disclosure for Author: Neil N Finer, MD

2012 Pediatric Academic Societies' Annual Meeting

DISCLOSURE NUMBER: 200525

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Participant Role

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Discussant
Introducer
Moderator/Chair

Disclosure

A. Do you (and/or an immediate family member including spouse partner) have a financial relationship, arrangement, or affiliation with a commercial interest (currently or within the past 12 months) that may have a direct or indirect impact on your participation in this CME activity? No

B. Is the focus of your presentation a commercially funded study? No
C. The presentation or participation will involve comments or discussion concerning unapproved or off-label uses of a medical device or pharmaceuticals. If any unapproved or off-label uses of products will be discussed, **disclosure must be made to the participants regarding the unapproved or off-label use.** If the presenter will be discussing any such uses, please indicate the products to be discussed and the unapproved and/or off-label uses. **If any other comments concerning unapproved or off-label uses of products take place during the discussion, you are advised that the presenter must disclose this information to the attendees.** No

D. Agreement to Participate in a CME Activity - All representations require an answer

1. **I will be responsible** for disclosing information from A and B to the audience on a slide **(Procedure #5)**, verbally from the podium, , and noted on a presentation slide or poster presentation; for reading and complying with the Tulane CME Conflict of Interest Policy.
   I agree
2. I will comply with the requirements to protect health information under the Health Insurance Portability & Accountability Act of 1998 (HIPAA).
   I agree
3. To the best of my knowledge, I **have not engaged** in any activities that do not comply with the American Medical Association's Ethical Opinion on Continuing Medical Education and Gifts to Physicians from Industry (http://www.ama-assn.org/), the Food and Drug Administration's regulations regarding industry-supported scientific and educational activities (http://www.fda.gov/), the Office of Inspector General's Compliance Program Guidance for Pharmaceutical Manufacturers (http://www.oig.hhs.gov/), PhRMA's Code on Interactions with Healthcare Professionals (http://www.phrma.org/), and the AdvaMed Code (http://www.advamed.org/). I further represent that I have not violated or received notice of violation of any laws or ACCME policy or other relevant accreditation body or standards in the last two (2) years.
   I agree
4. I acknowledge that I am not included in either the OIG Exclusion List (http://exclusions.oig.hhs.gov/) or the GSA Department List (http://epls.gov/).
   I agree
5. I further represent that information contained in my presentation or participation will be based on research that, to the best of my knowledge, does not involve fabrication, falsification, plagiarism, or other practices that seriously deviate from those that are commonly accepted within the academic research community for proposing, conducting or reporting research.
   I agree
6. I acknowledge that any vertebrate animal studies must have been conducted according to a protocol approved by an institutional animal care and use committee and any research with human subjects must have been conducted according to a protocol approved by the institutional review board (IRB) or equivalent committee for the ethics of human investigation conforming to the principles of the Declaration of Helsinki of the World Medical Association (2008).
   I agree
7. If disclosure information and/or the nature of my presentation/participation changes prior to the CME educational activity, I affirm that it is my responsibility to notify COI_info@pas-meeting.org. (After April 15th, notify COI_Info@aps-spr.org of your requested change.)
   I agree
8. I will not or have not received payment directly from a commercial interest as defined by the ACCME, e.g. pharmaceutical or medical device company, for honoraria, travel, lodging, or personal expenses for a CME certified activity. (ACCME SCS 3.7-3.10)
   I agree

Disclosure for Author: Rosemary D Higgins, MD

No Confirmed Disclosure

Print

From: Bradley Yoder
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Abstract again
Date: Wednesday, November 09, 2011 1:33:46 PM

Sorry, was in plane most of day yesterday.
I would vote to submit the abstract; I think there is potentially valuable info to convey.

Brad Yoder
Division of Neonatology
University of Utah SOM

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, November 07, 2011 12:42 PM
To: Finer, Neil; 'Wally Carlo, M.D.'; Das, Abhik; 'Gantz, Marie'; 'kurt.schibler@cchmc.org'; 'mcw3@cwru.edu'; Rogers, Jill (NIH/NICHD) [E]; alaptook@WIHRI.org; Bradley Yoder; nxs5@cwru.edu; 'Rich, Wade'
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: Abstract again
Importance: High

Hi,
Please let me know by tomorrow November 8 if you want this to be submitted – I had only heard from one individual thus far.

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, October 19, 2011 9:10 AM
To: Finer, Neil; wcarlo@peds.uab.edu; 'Das, Abhik'; 'Gantz, Marie'; kurt.schibler@cchmc.org; mcw3@cwru.edu; Roger Faix; 'Laptook, Abbot'; Bradley Yoder; nxs5@cwru.edu; 'Rich, Wade'
Cc: vvaucher@ucsd.edu; MPeralta@PEDS.UAB.EDU; Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: Abstract again

HI,
See the note below from Neil – please send suggestions regarding submission or not.

Thanks
Rose

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From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Monday, October 17, 2011 7:19 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; 'WCarlo@peds.uab.edu'
Subject: Abstract again

Hi Rose and Wally
After reviewing this abstract and after our phone call I realized that the data in this abstract is the strongest data upon which to actually show that for all infants irrespective of CPAP vs SURF, while CPAP lowers mortality in the most immature, a high SpO2 range lowers death for each treatment arm in each strata
I reworked to emphasize this
I think this abstract provides useful information on this issue and for the specific gestational ages and the usual treatments used
Please relook and let me know
Be well
Neil

First Author: Neil N Finer, MD

Filename: 750127

Responsible Author: Neil N Finer, MD
Presenting Author: Neil N Finer, MD
Contact Person: Neil N Finer, MD

2012 PAS Annual Meeting

Subspecialty: Neonatology - General
Theme: Neonatal - Patient-Oriented Research

Contact Author: Neil N Finer, MD
Department/Institution/Address: Neonatology, Dept Pediatrics, UCSD, 200 W Arbor Dr, San Diego, Ca, 92103, United States
Phone: 1 619 543 3285 **Fax:** 1 619 543 3812 **E-mail:** nfiner@ucsd.edu

Reponsible Author: Neil N Finer, MD
Department/Institution/Address: 200 W Arbor Dr, San Diego, United States
Phone: 1 619 543 3285 **Fax:** 1 619 543 3812
Responsible Author E-mail: nfiner@ucsd.edu
Responsible Author Declaration: As the responsible author, I confirm that the individual listed as the sponsor has been contacted and given the opportunity to review the abstract and has subsequently agreed to sponsor this abstract.

Presenting Author: Neil N Finer, MD
Department/Institution/Address: Neonatology Pediarics, UCSD, 200 W Arbor Dr, San Diego, United States
Phone: 1 619 543 3285 **Fax:** 1 619 543 3812
Presenting Author E-mail: nfiner@ucsd.edu
The presenting author is member of these Alliance Societies:
Is Presenting Author a Trainee? No, Not a Trainee

QUESTIONNAIRE INFORMATION
Eastern Society for Pediatric Research: No, Do not consider this abstract for the Eastern SPR
Pediatric Hospital Medicine: No, Do not consider this abstract for presentation at the Pediatric Hospital Medicine, July 19-22, 2012
Research Type: Clinical
Presentation Sabbath Conflict on: N/A
APA Special Interest Groups, Committees or Regions: None

AWARDS APPLIED FOR:
No awards selected

SPONSOR INFORMATION
Sponsoring Member for PAS/ASPR abstract:
Sponsor Name: Neil Norman Finer
Email: nfiner@ucsd.edu
Is the Sponsor an Author? Yes
Sponsoring Societies:
Society for Pediatric Research

Title: Early CPAP Versus Surfactant: The Effect Of A Lower SpO2 Range: Secondary Outcomes Of The SUPPORT Trial.

Neil N Finer, MD[UCSD], Waldemar Carlo, MD[University of A] and Support Group[NICHD]. [1]Neonatology, Pediatrics, University California San Diego, San Diego, Ca, 92103, United States.

Background: The SUPPORT Trial prospectively compared early CPAP and a limited ventilator strategy to early surfactant and randomized all infants to a lower (85-89%) versus a higher (91-95%) SpO2 range .(NEJM 2010). A prespecified secondary outcome was that infants randomized to CPAP and a low SpO2 strategy would have a lower rate of death/ROP.

Objective: This study evaluated the effect of the SpO2 range on the outcomes for infants in the 2 gestational age strata, 24-25 wks, and 26-27 weeks

Design/Methods: The surviving infants were assessed at 18 to 22 months for full neurodevelopmental evaluation, which included hearing, vision, and mental and motor outcomes using the Bayley 3. Tests for interaction were adjusted for GA center and family clustering.

Results: There were 1316 infants randomized and deaths prior to discharge, (16.4% vs 19.6%), and prior to follow-up (18.4% vs 21.9%) and the overall ROP rates among survivors (13.1% vs 13.7%) were not different between CPAP and Surf infants. ROP was less frequent in the 24-25wk strata, (22.2% vs 31.6%, p=0.04) whereas ROP was greater in CPAP infants in the 26-27 wk strata (7.3% vs 3.6% p=0.04). Death at follow-up for the 24-25 wk infants remained significantly lower for the CPAP infants (26.4% vs 35.5%, p=0.019). For the overall study and for the 26-27 wk strata there were no significant intercations between SpO2 group and the intervention groups for death/ROP or death/NDI for both strata. For the outcome of death or ROP, while no interaction was seen in the overall study, the 24-25wk infants in the Low SpO2 strata had a lower rate of ROP/death (p=.001),

Death/ROP for 24-25 wk Strata and 26-27 wk Strata - Low vs High SpO2

SpO2 Range	CPAP/Surf	Death - (24-25)	ROP	Death/ROP	Death - (26-27)	ROP	Death/ROP
Low	CPAP	37/142(26%)	11/95(12%)**	48/132(36%)*	25/194(13%)	8/153(5%)	33/178(19%)
	Surf	48/134(36%)	21/76(28%)**	69/124(56%)*	20/184(11%)	1/151(1%)	21/171(12%)
High	CPAP	31/143(22%)	33/103(32%)	64/134(48%)	15/185(9%)	15/160(9%)	31/176(18%)
	Surf	42/146(29%)	33/95(35%)	75/137(55%)	18/189(10%)	10/141(7%)	28/169(17%)

* p = 0.001, ** p=0.01

Conclusions: The lowest death rate was seen in both the CPAP and Surf infants in each strata treated with a high SpO2 approach whereas ROP was higher in the Low SpO2 arm. These results provide further evidence that the use of the higher SpO2 range is associated with decreased mortality in all infants and that these differences are magnified in the most immature infants

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: PAS SUPPORT FU abstract
Date: Wednesday, November 09, 2011 8:38:00 AM

NO

Rosemary D. Higgins, MD
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301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Archer, Stephanie (NIH/NICHD) [E]
Sent: Wednesday, November 09, 2011 8:38 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: PAS SUPPORT FU abstract

Should this go back through clearance?

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tuesday, November 08, 2011 4:40 PM
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: PAS SUPPORT FU abstract

Rosemary D. Higgins, MD
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301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]
Sent: Tuesday, November 08, 2011 4:37 PM
To: Higgins, Rosemary (NIH/NICHD) [E]

Cc: Vaucher, Yvonne
Subject: RE: PAS SUPPORT FU abstract

Rose,

Thanks. The abstract does need a small change due to the new SGA analysis which showed that after adjusting for SGA differences in the trial cohort the result is no longer significant. I have therefore deleted reference to increased deaths in the lower GA stratum in the last sentence of results. Revision attached.

Do you want me to send the whole thing to you again. Nothing else changed.

Yvonne

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, November 08, 2011 11:37 AM
To: Vaucher, Yvonne
Cc: Finer, Neil; Archer, Stephanie (NIH/NICHD) [E]
Subject: PAS SUPPORT FU abstract

Hi
Your PAS abstract has gone through NICHD clearance. Once you have a final submitted copy, please forward it to us.

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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higginsr@mail.nih.gov

From: Vaucher, Yvonne
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: PAS SUPPORT FU abstract
Date: Tuesday, November 08, 2011 4:48:13 PM

Will submit.

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, November 08, 2011 1:39 PM
To: Vaucher, Yvonne
Subject: RE: PAS SUPPORT FU abstract

NO this is fine

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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higginsr@mail.nih.gov

From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]
Sent: Tuesday, November 08, 2011 4:37 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Vaucher, Yvonne
Subject: RE: PAS SUPPORT FU abstract

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Yvonne

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, November 08, 2011 11:37 AM
To: Vaucher, Yvonne
Cc: Finer, Neil; Archer, Stephanie (NIH/NICHD) [E]

Subject: PAS SUPPORT FU abstract

Hi

Your PAS abstract has gone through NICHD clearance. Once you have a final submitted copy, please forward it to us.

Thanks

Rose

Rosemary D. Higgins, MD
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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: PAS SUPPORT FU abstract
Date: Tuesday, November 08, 2011 4:39:00 PM
Attachments: CPAPSUPPORTAbstractPAS2012_RevYEV11082011.docx

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301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]
Sent: Tuesday, November 08, 2011 4:37 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Vaucher, Yvonne
Subject: RE: PAS SUPPORT FU abstract

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Do you want me to send the whole thing to you again. Nothing else changed.

Yvonne

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, November 08, 2011 11:37 AM
To: Vaucher, Yvonne
Cc: Finer, Neil; Archer, Stephanie (NIH/NICHD) [E]
Subject: PAS SUPPORT FU abstract

Hi
Your PAS abstract has gone through NICHD clearance. Once you have a final submitted copy, please forward it to us.

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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higginsr@mail.nih.gov

Title: Neurodevelopmental Outcome of Extremely Premature Infants Enrolled in the SUPPORT trial: Early CPAP versus Intubation with Surfactant Administration

Yvonne E Vaucher, MD,MPH[1], Marie Gantz, PhD[2], Neil N Finer, MD[1] and SUPPORT Study Group[3]. [1]Division of Neonatology, Department of Pediatrics, University of California,, San Diego, CA, United States; [2]Statistics and Epidemiology, RTI International, Research Triangle Park, NC, United States and [3]Neonatal research Network, Eunice Kennedy Shriver National Insitute of Child Health and Human Development, Bethesda, MD, United States.

Background: The multicenter SUPPORT randomized, controlled trial demonstrated that initial treatment with non-invasive CPAP is an alternative to early surfactant administration after intubation and is associated with similar rates of death or BPD in infants born at 24 to 27 weeks gestation.

Objective: We hypothesized that, compared to treatment with surfactant administration after intubation, treatment with early CPAP would decrease the composite outcome of death or neurodevelopmental impairment (NDI).

Design/Methods: The SUPPORT Trial enrolled 1316 extremely premature infants, 24 to 27 weeks gestation, randomized to receive either CPAP in the delivery room with a limited ventilation for strategy for two weeks (CPAP) or intubation with surfactant administration within one hour after birth (SURF). Infants were randomized within each center by gestational age strata (24 0/7-25 6/7 and 26 0/7-27 6/7 weeks). A standardized neurodevelopmental assessment was performed at 18-22 months corrected age. The primary, pre-specified composite outcome was death or NDI including at least one of the following: BSID-III cognitive score < 70, Gross Motor Function Classification Score (GMFCS) ≥2, moderate/severe cerebral palsy, bilateral blindness or permanent hearing impairment. Results were adjusted for gestational age, center and familial clustering.

Results: Death or NDI was determined for 1234/1316 (93.8%) enrolled infants. Death or NDI occurred in 27.9% (173/621) of CPAP and 29.9% (183/613) of SURF infants (p=0.39). Rates of death (CPAP-18.4 vs. SURF-21.9%, p=0.10), NDI alone (CPAP-0.9 vs. SURF 9.1%, p=0.44), cognitive score < 70 (CPAP-7.2 vs. SURF-7.6%, p=0.84), moderate/severe cerebral palsy (CPAP-4.1 vs. SURF-4.0%, p=0.82), GMFCS ≥2 (CPAP-5.1 vs. SURF 4.8%, p=0.95); blindness (CPAP-0.8 vs. SURF 1.5%, p=0.31), and permanent hearing impairment (CPAP-3.3 vs. SURF-1.5%, p=0.06) were similar in both treatment arms. There were no significant differences in neurodevelopmental outcomes between CPAP and SURF groups within each GA stratum.

Conclusions: We found no significant difference in the composite outcome of death or neurodevelopmental impairment at 18-22 months corrected age between extremely premature infants randomized to treatment with either early CPAP or intubation and surfactant administration.

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Blaisdell, Carol (NIH/NHLBI) [E]
Subject: RE: NICHD NRN DSMC Meeting -- Agenda and SUPPORT Analysis Reports
Date: Tuesday, November 08, 2011 1:42:00 PM

Carol

The FU portions of the SUPPORT Trial (both arms) are slated to be presented at Hot Topics in Neonatology on December 6 at the Omni Shoreham in DC. Both papers are written and making their way through the NRN review process. The investigators are also submitting the FU abstracts (one for CPAP/surf and one for oximetry) to PAS 2012 for consideration for presentation. The plan is to submit both Follow Up papers concurrently to NEJM.

There are multiple other ongoing analyses including the Neuroimaging cohort, breathing outcomes and growth secondary studies.

We are also planning to follow a subset of these children to school age – they include the infants that had an early head US 94-14 days) along with a 36 week head US and cranial MRI.

I will send the abstracts and papers to you as they come through.

Thanks for all the help with this study

Rose

Rosemary D. Higgins, MD
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From: Blaisdell, Carol (NIH/NHLBI) [E]
Sent: Tuesday, November 08, 2011 8:05 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: NICHD NRN DSMC Meeting -- Agenda and SUPPORT Analysis Reports

Hi Rose,

Congrats on finishing SUPPORT.

When do the PIs plan to publish these f/u results?

This was the final DSMB meeting, so is the study closing out, or are there further analyses and NCE?

Thanks for working so well to keep me informed.

Appreciate the chance to work with you,

Carol

Carol J. Blaisdell M.D.
Medical Officer
Lung Development and Pediatrics
Lung Biology and Diseases Branch
Division of Lung Diseases
NHLBI, NIH
301-435-0222

From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Monday, November 07, 2011 2:37 PM
To: Blaisdell, Carol (NIH/NHLBI) [E]
Subject: FW: NICHD NRN DSMC Meeting -- Agenda and SUPPORT Analysis Reports

Hi Dr. Blaisdell,

Below are the minutes from the very brief Support Trial Follow Up data discussion during this past NICHD NRN DSMC mtg; please let me know if you have any comments or concerns, The final Support Trial minutes will be sent once approved.

The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants. Short Title; SUPPORT Trial (Final Analysis of the 18 To 22 Month Follow Up Data)

Presentation of the Final Data

Dr. Das presented the final follow-up data. Please refer to the report for further details.

Discussion and Final Recommendations

Despite the higher rates of severe ROP and eye surgery in the high SpO2 group, there was not a significant difference in blindness among survivors to 18-22 months corrected age between the groups. Though this was a concern at first, it no longer is.

The DMSC agreed that this provided important results that should be shared with the community.

Thanks,
Kris

Kris Zaterka-Baxter, RN, BSN, CCRP
RTI International
Res Clinical Study Specialist

3340 Cornwallis Rd
Research Triangle Park, NC 27709
Phone: 919-485-7750
Fax: 919-485-7762

From: Zaterka-Baxter, Kristin
Sent: Tuesday, October 18, 2011 3:45 PM
To: 'Thomson, Merran'; 'blaisdellcj@nhlbi.nih.gov'
Subject: NICHD NRN DSMC Meeting -- Agenda and SUPPORT Analysis Reports

Dear NICHD NRN SUPPORT Trial DSMC Members,

Please find attached the agenda for the upcoming NRN DSMC meeting scheduled next Tuesday October 25th. Please note the times and call in information for the SUPPORT Trial session is included in this agenda. Additionally, please also find the final analysis reports for the SUPPORT trial 18 month follow up.

If you experience any difficulty dialing in, please call 919-414-1911 or email (kzaterka@rti.org)a$ a back up and I will contact the operator for assistance.

Thanks and please let me know if you have any questions,
Kris

Kris Zaterka-Baxter, RN, BSN, CCRP
RTI International
Res Clinical Study Specialist

3340 Cornwallis Rd
Research Triangle Park, NC 27709
Phone: 919-485-7750
Fax: 919-485-7762

From: Cunningham, Meg
Sent: Monday, October 10, 2011 11:14 AM
To: Gabrio, Jenna; Das, Abhik; Wallace, Dennis; Christine A. Gleason (cgleason@u.washington.edu); [SCRN] Willinger, Marian; 'Marilee C. Allen, MD'; 'Menachem Miodovnik'; 'Michael O'Shea'; Robert Boyle (RJB6J@hscmail.mcc.virginia.edu); Steven Weiner (Weiner@Biostat.bsc.gwu.edu); Traci Clemons (tclemons@emmes.com)
Cc: 'ekforbes@u.washington.edu'; 'Susan.L.Cunningham@Medstar.net'; 'Brenda Barron'; Zaterka-Baxter, Kristin; Huitema, Carolyn Petrie
Subject: RE: NICHD NRN DSMC Meeting -- New Protocol Materials

Dear DSMC Members,

Attached you will find the materials for the new studies to be reviewed at the upcoming DSMC meeting. Please note that the final analysis reports for the Vitamin E and SUPPORT trials will be sent to all by Monday, October 17th.

For the three new studies, attached you will find the protocol and sample consent for each study.

Please note; the Prediction of Outcome in Hypoxic Ischemic Encephalopathy using Amplitude Integrated Electroencephalography (Secondary Protocol To The Optimizing Cooling For HIE Trial) is a combination of two protocols (both included in the pdf attached) that were combined for functional purposes using the same study manual, forms and opt in/opt out consent addendum to the original Optimizing Cooling trial consent. The reason the protocol documents remain separate is for analysis purposes.

Please let me know if you have any questions.
Meg

From: Gabrio, Jenna
Sent: Thursday, September 15, 2011 10:34 AM
To: Gantz, Marie; Hansen, Nellie I.; Das, Abhik; Wallace, Dennis; Christine A. Gleason (cgleason@u.washington.edu); Marian Willinger (willingm@mail.nih.gov); 'Marilee C. Allen, MD'; 'Menachem Miodovnik'; 'Michael O'Shea'; Robert Boyle (RJB6J@hscmail.mcc.virginia.edu); Steven Weiner (Weiner@Biostat.bsc.gwu.edu); Traci Clemons (tclemons@emmes.com); Carol J. Blaisdell (blaisdellcj@nhlbi.nih.gov); Merran A. Thomson (merran.thomson@ic.ac.uk)
Cc: 'ekforbes@u.washington.edu'; 'Susan.L.Cunningham@Medstar.net'; 'Brenda Barron'; Zaterka-Baxter, Kristin; Cunningham, Meg; 'Monica Bocaner'; Huitema, Carolyn Petrie
Subject: NICHD NRN DSMC Meeting -- SAVE THE DATE: Tuesday, October 25, 2011

Dear NICHD NRN DSMC Members,

This is the official Save-The-Date notice for the face-to-face NICHD NRN DSMC meeting to review the studies listed below. The meeting has been scheduled for:

Tuesday, October 25, 2011
12:00pm – 4:00pm US ET (for those attending in person)
Lunch will be served from 12:00pm-12:30pm US ET for those attending in person.

Location: **Rockville, MD RTI Office**
6110 Executive Boulevard, Suites 902 & 415
Rockville, Maryland 20852-3907

For those planning to call into the meeting:
Main DSMC Members: Discussion will start at 12:30 PM US ET
SUPPORT DSMC Members: Discussion of the SUPPORT trial will start at 3:00 PM US ET
Note: We will send out call in information with the official agenda.

Please contact Monica Bocaner(monica@bocaner.net) if you need assistance with making hotel reservations in the Rockville area.

The official agenda and meeting materials are forthcoming. Please let me know if you have any questions or concerns.

Thanks,
Jenna

Studies to be reviewed:

Final Reviews:

SINGLE-DOSE VITAMIN E FOR PREVENTION OF MORTALITY AND MORBIDITY IN EXTREMELY PRETERM INFANTS: PILOT STUDY. SHORT TITLE: VITAMIN E PILOT STUDY (IND 105988)

THE SURFACTANT POSITIVE AIRWAY PRESSURE AND PULSE OXIMETRY TRIAL IN EXTREMELY LOW BIRTH WEIGHT INFANTS; THE SUPPORT TRIAL. (Note, final analysis of the 18 to 22 month follow up data)

New Studies:

PREDICTION OF OUTCOME IN HYPOXIC ISCHEMIC ENCEPHALOPATHY USING AMPLITUDE INTEGRATED ELECTROENCEPHALOGRAPHY (Secondary Protocol To The Optimizing Cooling For HIE Trial noted above)

GFAP A BIOMARKER OF WHOLE BODY COOLING OUTCOME AND EFFICACY IN THE NEONATE WITH HIE (Secondary Protocol To The Optimizing Cooling For HIE Trial noted above)

A RANDOMIZED TRIAL OF TARGETED TEMPERATURE MANAGEMENT WITH WHOLE BODY HYPOTHERMIA FOR MODERATE AND SEVERE HYPOXIC-ISCHEMIC ENCEPHALOPATHY IN PREMATURE INFANTS 33-35 WEEKS GESTATIONAL AGE

Jenna Gabrio
RTI International
Public Health Analyst

701 13th St., NW Suite 750
Washington, DC 20005
Phone: 202-728-1946
Fax: 202-974-7855

From: Finer, Neil
To: Das, Abhik
Cc: Gantz, Marie; Vaucher, Yvonne; Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SGA in CPAP vs. surfactant groups
Date: Tuesday, November 08, 2011 11:12:38 AM

This is to me the most important point
SGA was not a per specified outcome so I would not overplay this
Neil

On Nov 8, 2011, at 6:45 AM, "Das, Abhik" <adas@rti.org> wrote:

> I forgot to add that the analysis only adjusting for the study design
> variables (center, GA stratum and clustering) should still be considered
> the primary analysis, particularly for outcomes on the entire trial
> cohort (such as death or NDI). Analyses adjusting for additional
> covariates such as SGA can be reported as secondary analyses.
>
> Thanks
>
> Abhik
>
> -----Original Message-----
> From: Das, Abhik
> Sent: Tuesday, November 08, 2011 9:44 AM
> To: Gantz, Marie; 'Vaucher, Yvonne'
> Cc: 'Higgins, Rosemary (NIH/NICHD)'; 'Finer, Neil'
> Subject: RE: SGA in CPAP vs. surfactant groups
>
> This seems to be the most reasonable course of action to us because we
> don't want to be in a position of contradicting results we reported
> earlier, and at the same time don't want to hide anything either.
>
> Thanks
>
> Abhik
>
> -----Original Message-----
> From: Gantz, Marie
> Sent: Tuesday, November 08, 2011 9:40 AM
> To: 'Vaucher, Yvonne'
> Cc: Higgins, Rosemary (NIH/NICHD); Finer, Neil; Das, Abhik
> Subject: RE: SGA in CPAP vs. surfactant groups
>
> Yvonne,
>
> Abhik and I discussed this and we agree that it makes sense to adjust
> for SGA in the analyses of all of the FU outcomes. I will get the new
> results to you ASAP. As far as the death outcome is concerned, we
> recommend simply stating that death at 18-22 months was not significant
> after adjusting for SGA and the usual design factors. If the reviewers
> want more information on the earlier death outcomes, they can ask for
> it.
>
> Marie

>
> Marie Gantz, Ph.D.
> Research Statistician
> RTI International
> mgantz@rti.org
> 828-254-6255
>
> -----Original Message-----
> From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]
> Sent: Tuesday, November 08, 2011 1:39 AM
> To: Gantz, Marie
> Cc: Higgins, Rosemary (NIH/NICHD); Finer, Neil; Vaucher, Yvonne
> Subject: RE: SGA in CPAP vs. surfactant groups
>
> Marie/Abhik,
>
> Since the % SGA was different between the CPAP and SURF groups it does
> make sense to adjust for it.
> Shouldn't we likewise adjust for SGA for all the NDI variables as it may
> also make a difference in the 24-25 week group comparison for these
> variables (esp. hearing)
> Re death by 36 weeks and by 18-22 mo: Can we note that the difference
> was no longer significant when adjusted for SGA status.
> We need your guidance as to how to correctly deal with this in the
> CPAP/SURF FUP paper.
>
> Yvonne
> _____
> From: Finer, Neil
> Sent: Monday, November 07, 2011 2:32 PM
> To: Vaucher, Yvonne
> Subject: FW: SGA in CPAP vs. surfactant groups
>
> Please look at these and review your paper relative the SGA issue
> Thanks
> Neil
>
> From: Gantz, Marie [mailto:mgantz@rti.org]
> Sent: Wednesday, October 19, 2011 2:11 PM
> To: Finer, Neil; wacarlo@uab.edu; Higgins, Rosemary (NIH/NICHD)
> Cc: Das, Abhik
> Subject: SGA in CPAP vs. surfactant groups
>
> Neil, Wally and Rose,
>
> In Table 1 create for the FU papers, there was a significant difference
> in the percentage of SGA infants between the CPAP and surfactant groups
> in the full SUPPORT population of 1316 infants. This difference was due
> in large part to an imbalance in the 24-25 week GA stratum. We had not
> recognized this imbalance before doing the analyses for the FU papers,
> because SGA was not one of the variables created for the primary SUPPORT
> analyses. In light of this difference between the CPAP and surfactant
> groups, Abhik and I decided to redo the analyses of death in the 24-25
> week GA stratum, controlling for SGA. The results are attached. After
> adding SGA as a covariate in the models to predict death at 36 weeks
> PMA, in-hospital, and at 18-22 months adjusted age, only the difference
> in death at 36 weeks PMA remained statistically significant. Although

> the other results are no longer statistically significant, they still
> provide some evidence (albeit weaker than before) that there were
> differences in death between the groups. Abhik and I thought we needed
> to let you know that we had looked at this and share the results with
> you.
>
> Marie
>
> Marie Gantz, Ph.D.
> Research Statistician
> RTI International
> mgantz@rti.org
> 828-254-6255

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Phelps, Dale"; "Nolen, Tracy"
Cc: "adas@rti.org"
Subject: RE: SUPPORT ROP Outcome Help
Date: Monday, November 07, 2011 4:39:00 PM

Wow
This is fabulous

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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higginsr@mail.nih.gov

From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Monday, November 07, 2011 4:39 PM
To: 'Nolen, Tracy'
Cc: adas@rti.org; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT ROP Outcome Help

Thank you all so much for these data.
Dale

From: Nolen, Tracy [mailto:tnolen@rti.org]
Sent: Monday, November 07, 2011 12:59 PM
To: Phelps, Dale
Cc: Das, Abhik; higginsr@mail.nih.gov; Wallace, Dennis; Gantz, Marie
Subject: FW: SUPPORT ROP Outcome Help

Hi Dale,

Please see below for the information from Marie. It looks like a very small number died after final ROP status (mature) but before 55 weeks).

Thanks Marie!

Tracy

From: Gantz, Marie
Sent: Monday, November 07, 2011 3:58 PM
To: Nolen, Tracy
Subject: RE: SUPPORT ROP Outcome Help

Hi Tracy,

5/859 infants with a final ROP status of "no severe ROP" (mature eyes) died before 55 weeks PMA (the deaths occurred between 47 and 52 weeks). In SUPPORT, we counted them as deaths in the death/ROP outcome, but we also counted any death that happened while hospitalized (so, many deaths were after 55 weeks).

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Nolen, Tracy
Sent: Monday, November 07, 2011 3:26 PM
To: Gantz, Marie
Subject: SUPPORT ROP Outcome Help

Hi Marie,

We are working on planning the next Inositol study and I need some estimates from SUPPORT that I'm hoping you can help with.

The current outcome for INS-2 was:

- Surgical ROP before 55 weeks or Death prior to final ROP status (e.g. before eye maturity or two assessments in zone 3).

The question the PIs have is whether it would be better to just do:

- Surgical ROP or Death before 55 weeks

This update means deaths after favorable final ROP status but before 55 weeks would now count as 'bad' outcomes where previously they would count as 'good' outcomes. Can you by any chance tell me how many infants would fall into this category in SUPPORT? Died before 55 weeks but after having favorable ROP outcome?

Tracy

From: Vaucher, Yvonne
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT CPAP Abstract
Date: Monday, November 07, 2011 3:44:24 PM

No problem to wait. Just wondered when to submit.

Yvonne

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, November 07, 2011 12:27 PM
To: Vaucher, Yvonne
Subject: RE: SUPPORT CPAP Abstract

It is sitting in NICHD clearance – can you wait a few days??
Thanks
rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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higginsr@mail.nih.gov

From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]
Sent: Monday, November 07, 2011 3:11 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: SUPPORT CPAP Abstract

Rose,

Should I submit the SUPPORT abstract to PAS yet? Have received no further comments since I sent it to you.

Yvonne

Yvonne E. Vaucher, M.D., M.P.H.
Division of Neonatal/Perinatal Medicine
Clinical Professor of Pediatrics
UCSD School of Medicine

tele: 619-543-3759
FAX: 619-543-3812

From: Rich, Wade
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Abstract again
Date: Monday, November 07, 2011 2:57:27 PM

Yes

wade

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, November 07, 2011 11:42 AM
To: Finer, Neil; 'Wally Carlo, M.D.'; Das, Abhik; 'Gantz, Marie'; 'kurt.schibler@cchmc.org'; 'mcw3@cwru.edu'; Rogers, Jill (NIH/NICHD) [E]; alaptook@WIHRI.org; 'Bradley Yoder'; nxs5@cwru.edu; Rich, Wade
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: Abstract again
Importance: High

Hi,
Please let me know by tomorrow November 8 if you want this to be submitted – I had only heard from one individual thus far.

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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higginsr@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Wednesday, October 19, 2011 9:10 AM
To: Finer, Neil; wcarlo@peds.uab.edu; 'Das, Abhik'; 'Gantz, Marie'; kurt.schibler@cchmc.org; mcw3@cwru.edu; Roger Faix; 'Laptook, Abbot'; Bradley Yoder; nxs5@cwru.edu; 'Rich, Wade'
Cc: yvaucher@ucsd.edu; MPeralta@PEDS.UAB.EDU; Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: Abstract again

HI,
See the note below from Neil – please send suggestions regarding submission or not.

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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higginsr@mail.nih.gov

From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Monday, October 17, 2011 7:19 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; 'WCarlo@peds.uab.edu'
Subject: Abstract again

Hi Rose and Wally
After reviewing this abstract and after our phone call I realized that the data in this abstract is the strongest data upon which to actually show that for all infants irrespective of CPAP vs SURF, while CPAP lowers mortality in the most immature, a high SpO2 range lowers death for each treatment arm in each strata
I reworked to emphasize this
I think this abstract provides useful information on this issue and for the specific gestational ages and the usual treatments used
Please relook and let me know
Be well
Neil

First Author: Neil N Finer, MD

Filename: 750127

Responsible Author: Neil N Finer, MD
Presenting Author: Neil N Finer, MD

Contact Person: Neil N Finer, MD

2012 PAS Annual Meeting

Subspecialty: Neonatology - General
Theme: Neonatal - Patient-Oriented Research

Contact Author: Neil N Finer, MD
Department/Institution/Address: Neonatology, Dept Pediatrics, UCSD, 200 W Arbor Dr, San Diego, Ca, 92103, United States
Phone: 1 619 543 3285 **Fax:** 1 619 543 3812 **E-mail:** nfiner@ucsd.edu

Reponsible Author: Neil N Finer, MD
Department/Institution/Address: 200 W Arbor Dr, San Diego, United States
Phone: 1 619 543 3285 **Fax:** 1 619 543 3812
Responsible Author E-mail: nfiner@ucsd.edu
Responsible Author Declaration: As the responsible author, I confirm that the individual listed as the sponsor has been contacted and given the opportunity to review the abstract and has subsequently agreed to sponsor this abstract.

Presenting Author: Neil N Finer, MD
Department/Institution/Address: Neonatology Pediarics, UCSD, 200 W Arbor Dr, San Diego, United States
Phone: 1 619 543 3285 **Fax:** 1 619 543 3812
Presenting Author E-mail: nfiner@ucsd.edu
The presenting author is member of these Alliance Societies:
Is Presenting Author a Trainee? No, Not a Trainee
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QUESTIONNAIRE INFORMATION
Eastern Society for Pediatric Research: No, Do not consider this abstract for the Eastern SPR
Pediatric Hospital Medicine: No, Do not consider this abstract for presentation at the Pediatric Hospital Medicine, July 19-22, 2012
Research Type: Clinical
Presentation Sabbath Conflict on: N/A
APA Special Interest Groups, Committees or Regions: None

AWARDS APPLIED FOR:
No awards selected

SPONSOR INFORMATION
Sponsoring Member for PAS/ASPR abstract:
Sponsor Name: Neil Norman Finer
Email: nfiner@ucsd.edu
Is the Sponsor an Author? Yes
Sponsoring Societies:
Society for Pediatric Research

Title: Early CPAP Versus Surfactant: The Effect Of A Lower SpO2 Range: Secondary Outcomes Of The SUPPORT Trial.

Neil N Finer, MD[UCSD], Waldemar Carlo, MD[University of A] and Support Group[NICHD]. [1]Neonatology, Pediatrics, University California San Diego, San Diego, Ca, 92103, United States.

Background: The SUPPORT Trial prospectively compared early CPAP and a limited ventilator strategy to early surfactant and randomized all infants to a lower (85-89%) versus a higher (91-95%) SpO2 range .(NEJM 2010). A prespecified secondary outcome was that infants randomized to CPAP and a low SpO2 strategy would have a lower rate of death/ROP.

Objective: This study evaluated the effect of the SpO2 range on the outcomes for infants in the 2 gestational age strata, 24-25 wks, and 26-27 weeks

Design/Methods: The surviving infants were assessed at 18 to 22 months for full neurodevelopmental evaluation, which included hearing, vision, and mental and motor outcomes using the Bayley 3. Tests for interaction were adjusted for GA center and family clustering.

Results: There were 1316 infants randomized and deaths prior to discharge, (16.4% vs 19.6%), and prior to follow-up (18.4% vs 21.9%) and the overall ROP rates among survivors (13.1% vs 13.7%) were not different between CPAP and Surf infants. ROP was less frequent in the 24-25wk strata, (22.2% vs 31.6%, p=0.04) whereas ROP was greater in CPAP infants in the 26-27 wk strata (7.3% vs 3.6% p=0.04). Death at follow-up for the 24-25 wk infants remained significantly lower for the CPAP infants (26.4% vs 35.5%, p=0.019). For the overall study and for the 26-27 wk strata there were no significant intercations between SpO2 group and the intervention groups for death/ROP or death/NDI for both strata. For the outcome of death or ROP, while no interaction was seen in the overall study, the 24-25wk infants in the Low SpO2 strata had a lower rate of ROP/death (p=.001),

Death/ROP for 24-25 wk Strata and 26-27 wk Strata - Low vs High SpO2

SpO2 Range	CPAP/Surf	Death - (24-25)	ROP	Death/ROP	Death - (26-27)	ROP	Death/ROP
Low	CPAP	37/142(26%)	11/95(12%)**	48/132(36%)*	25/194(13%)	8/153(5%)	33/178(19%)
	Surf	48/134(36%)	21/76(28%)**	69/124(56%)*	20/184(11%)	1/151(1%)	21/171(12%)
High	CPAP	31/143(22%)	33/103(32%)	64/134(48%)	15/185(9%)	15/160(9%)	31/176(18%)
	Surf	42/146(29%)	33/95(35%)	75/137(55%)	18/189(10%)	10/141(7%)	28/169(17%)

* p = 0.001, ** p=0.01

Conclusions: The lowest death rate was seen in both the CPAP and Surf infants in each strata treated with a high SpO2 approach whereas ROP was higher in the Low SpO2 arm. These results provide further evidence that the use of the higher SpO2 range is associated with decreased mortality in all infants and that these differences are magnified in the most immature infants

From: Newman, Nancy S
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Abstract again
Date: Monday, November 07, 2011 2:51:47 PM

I know- but it is just a long column- except for the table. I will try again. Thanks.

Nancy

Nancy Newman, BA, RN
Case Western Reserve University
Rainbow Babies and Children's Hospital
nxs5@case.edu

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, November 07, 2011 2:50 PM
To: Newman, Nancy S
Subject: RE: Abstract again

SCROLL DOWN – its in the email

Rosemary D. Higgins, MD
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higginsr@mail.nih.gov

From: Newman, Nancy S [mailto:Nancy.Newman2@UHhospitals.org]
Sent: Monday, November 07, 2011 2:50 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Abstract again

Hi Rose- I am not able to view this abstract. Not sure why. Sorry

Nancy

Nancy Newman, BA, RN
Case Western Reserve University
Rainbow Babies and Children's Hospital
nxs5@case.edu

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, November 07, 2011 2:42 PM
To: Finer, Neil; 'Wally Carlo, M.D.'; Das, Abhik; 'Gantz, Marie'; 'kurt.schibler@cchmc.org'; 'mcw3@cwru.edu'; Rogers, Jill (NIH/NICHD) [E]; alaptook@WIHRI.org; 'Bradley Yoder'; nxs5@cwru.edu; 'Rich, Wade'
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Cc: yvaucher@ucsd.edu; MPeralta@PEDS.UAB.EDU; Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: Abstract again

Hi,
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Subject: Abstract again

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I think this abstract provides useful information on this issue and for the specific gestational ages and the usual treatments used
Please relook and let me know
Be well
Neil

First Author: Neil N Finer, MD **Filename:** 750127

Responsible Author: Neil N Finer, MD
Presenting Author: Neil N Finer, MD
Contact Person: Neil N Finer, MD

2012 PAS Annual Meeting

Subspecialty: Neonatology - General
Theme: Neonatal - Patient-Oriented Research

Contact Author: Neil N Finer, MD
Department/Institution/Address: Neonatology, Dept Pediatrics, UCSD, 200 W Arbor Dr, San Diego, Ca, 92103, United States
Phone: 1 619 543 3285 **Fax:** 1 619 543 3812 **E-mail:** nfiner@ucsd.edu

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Responsible Author E-mail: nfiner@ucsd.edu
Responsible Author Declaration: As the responsible author, I confirm that the individual listed as the sponsor has been contacted and given the opportunity to review the abstract and has subsequently agreed to sponsor this abstract.

Presenting Author: Neil N Finer, MD
Department/Institution/Address: Neonatology Pediarics, UCSD, 200 W Arbor Dr, San Diego, United States
Phone: 1 619 543 3285 **Fax:** 1 619 543 3812
Presenting Author E-mail: nfiner@ucsd.edu
The presenting author is member of these Alliance Societies:
Is Presenting Author a Trainee? No, Not a Trainee
Presenter Copyright Declaration:
I certify that any material I will use, display, distribute, reproduce or have reproduced or distributed in connection with my above noted presentation for which I do not have permission to use, is my original work and/or is public information or another type of material which does not require securing permission from another party to use, display, distribute, reproduce or have reproduced or distributed.

QUESTIONNAIRE INFORMATION
Eastern Society for Pediatric Research: No, Do not consider this abstract for the Eastern SPR
Pediatric Hospital Medicine: No, Do not consider this abstract for presentation at the Pediatric Hospital Medicine, July 19-22, 2012
Research Type: Clinical
Presentation Sabbath Conflict on: N/A
APA Special Interest Groups, Committees or Regions: None

AWARDS APPLIED FOR:

No awards selected

SPONSOR INFORMATION
Sponsoring Member for PAS/ASPR abstract:
Sponsor Name: Neil Norman Finer
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Is the Sponsor an Author? Yes
Sponsoring Societies:
Society for Pediatric Research

Title: Early CPAP Versus Surfactant: The Effect Of A Lower SpO2 Range: Secondary Outcomes Of The SUPPORT Trial.

Neil N Finer, MD[UCSD], Waldemar Carlo, MD[University of A] and Support Group[NICHD]. [1]Neonatology, Pediatrics, University California San Diego, San Diego, Ca, 92103, United States.

Background: The SUPPORT Trial prospectively compared early CPAP and a limited ventilator strategy to early surfactant and randomized all infants to a lower (85-89%) versus a higher (91-95%) SpO2 range .(NEJM 2010). A prespecified secondary outcome was that infants randomized to CPAP and a low SpO2 strategy would have a lower rate of death/ROP.

Objective: This study evaluated the effect of the SpO2 range on the outcomes for infants in the 2 gestational age strata, 24-25 wks, and 26-27 weeks

Design/Methods: The surviving infants were assessed at 18 to 22 months for full neurodevelopmental evaluation, which included hearing, vision, and mental and motor outcomes using the Bayley 3. Tests for interaction were adjusted for GA center and family clustering.

Results: There were 1316 infants randomized and deaths prior to discharge, (16.4% vs 19.6%), and prior to follow-up (18.4% vs 21.9%) and the overall ROP rates among survivors (13.1% vs 13.7%) were not different between CPAP and Surf infants. ROP was less frequent in the 24-25wk strata, (22.2% vs 31.6%, p=0.04) whereas ROP was greater in CPAP infants in the 26-27 wk strata (7.3% vs 3.6% p=0.04). Death at follow-up for the 24-25 wk infants remained significantly lower for the CPAP infants (26.4% vs 35.5%, p=0.019). For the overall study and for the 26-27 wk strata there were no significant intercations between SpO2 group and the intervention groups for death/ROP or death/NDI for both strata. For the outcome of death or ROP, while no interaction was seen in the overall study, the 24-25wk infants in the Low SpO2 strata had a lower rate of ROP/death (p=.001),

Death/ROP for 24-25 wk Strata and 26-27 wk Strata - Low vs High SpO2

SpO2 Range	CPAP/Surf	Death - (24-25)	ROP	Death/ROP	Death - (26-27)	ROP	Death/ROP
Low	CPAP	37/142(26%)	11/95(12%)**	48/132(36%)*	25/194(13%)	8/153(5%)	33/178(19%)
	Surf	48/134(36%)	21/76(28%)**	69/124(56%)*	20/184(11%)	1/151(1%)	21/171(12%)
High	CPAP	31/143(22%)	33/103(32%)	64/134(48%)	15/185(9%)	15/160(9%)	31/176(18%)
	Surf	42/146(29%)	33/95(35%)	75/137(55%)	18/189(10%)	10/141(7%)	28/169(17%)

* p = 0.001, ** p=0.01

Conclusions: The lowest death rate was seen in both the CPAP and Surf infants in each strata treated with a high SpO2 approach whereas ROP was higher in the Low SpO2 arm. These results provide further evidence that the use of the higher SpO2 range is associated with decreased mortality in all infants and that these differences are magnified in the most immature infants

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From: Phelps, Dale
To: "yvaucher@ucsd.edu"; Finer, Neil
Cc: Archer, Stephanie (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: CONFIDENTIAL SUPPPORT FU PAPER
Date: Friday, November 04, 2011 10:50:47 PM
Attachments: Vaucher SUPPORT FU CPAP PAPER.boilerplate.UofR.docx

Hi Dr. Vaucher,

Thank you for the well written, compact and meaningful manuscript. I enjoyed reading it. I really do not have any concerns and wish you well with it.

Dale Phelps, MD

PS
The boilerplate for Univ. of Rochester is out of date and I will attach edits and copy Stephanie Archer.

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, October 27, 2011 11:07 AM
To: 'yvaucher@ucsd.edu'; 'MPeralta@PEDS.UAB.EDU'; 'wcarlo@peds.uab.edu'; 'Finer, Neil'; 'alaptook@WIHRI.org'; 'kurt.schibler@cchmc.org'; 'mcw3@cwru.edu'; 'Gantz, Marie'; 'Bradley Yoder'; 'Roger Faix'; 'Abhik Das'; 'Rich, Wade'; 'nxs5@cwru.edu'; 'vohr'; 'Kim Yolton'; 'Roy.Heyne@utsouthwestern.edu'; (b)(6) @aol.com'; 'golds005@mc.duke.edu'; 'Evans, Patricia W'; 'Acarregui, Michael'; 'Adams-Chapman, Ira'; 'Susan Hintz'; 'apappas@med.wayne.edu'; 'Poindexter, Brenda B'; 'emcgowan@tuftsmedicalcenter.org'; 'Ehrenkranz, Richard'; 'abodnar@utah.gov'; 'Bauer, Charles R'; 'JaFuller@salud. unm. edu (JaFuller@salud.unm.edu)'; Myers, Gary; 'Michael O`Shea'
Cc: 'Pablo.Sanchez@UTSouthwestern.edu'; 'Seetha Shankaran'; 'Barbara Stoll'; 'vohr'; 'Krisa VanMeurs'; 'Kathleen.A.Kennedy@uth.tmc.edu'; 'goldb008@mc.duke.edu'; Phelps, Dale; 'edward-bell@uiowa.edu'; 'Kristi Watterberg'; 'Frantz, Ivan'; Archer, Stephanie (NIH/NICHD) [E]; 'Duara, Shahnaz'
Subject: RE: CONFIDENTIAL SUPPPORT FU PAPER

Here is the other paper. Please send comments back to Yvonne by November 4.
Thanks
Rose

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Sent: Thursday, October 27, 2011 9:23 AM

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I have attached the SUPPORT Oximetry FU paper – I have cc'd the SUPPORT PI's from the steering committee during the SUPPORT Study recruitment also on the list even though this is a FU paper.
Please send you comments to Dr. Peralta by November 4.
I expect to have the CPAP/surf paper shortly
Thanks
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From: Myriam Peralta, M.D. [mailto:MPeralta@peds.uab.edu]
Sent: Tuesday, October 25, 2011 7:03 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Support NDI_10-21-2011

Rose here is the last version of the manuscript I had added comments from everyone who send this to me. I know I can add more to the discussion perhaps we can talk more on the meeting, Thank you

Early CPAP versus Surfactant in Extremely Preterm Infants: Neurodevelopmental Outcomes in Early Childhood

Yvonne E. Vaucher, MD MPH[1]; Myriam Peralta-Carcelen, MD MPH[2]; Neil N. Finer, MD[1]; Waldemar A. Carlo, MD[2]; Michele C. Walsh, MD MS[3]; Marie G. Gantz, PhD[4]; Abbot R. Laptook, MD[5]; Bradley A. Yoder, MD[6]; Roger G. Faix, MD[6]; Abhik Das, PhD[7]; Kurt Schibler, MD[8]; Wade Rich, RRT[2]; Nancy S. Newman, RN[4]; Betty R. Vohr, MD[5]; Kimberly Yolton, PhD[8]; Roy J. Heyne, MD[9]; Deanne E. Wilson-Costello, MD[4]; Patricia W. Evans, MD[10]; Ricki F. Goldstein, MD[11]; Michael J. Acarregui, MD[12]; Ira Adams-Chapman, MD[13]; Athina Pappas, MD[14]; Susan R. Hintz, MD MS Epi[15]; Anna M. Dusick, MD FAAP[16]; Elisabeth C. McGowan, MD[17]; Richard A. Ehrenkranz, MD[18]; Anna Bodnar, MD[6]; Charles R. Bauer, MD[19]; Janell Fuller, MD[20]; T. Michael

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O'Shea, MD MPH[21]; Gary J. Myers, MD[22]; Rosemary D. Higgins, MD[23] for the SUPPORT Study Group of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network

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University of Rochester Medical Center, Golisano Children's Hospital (U10 HD40521, M01 RR44) – Nirupama Laroia, MD; Dale L. Phelps, MD; Gary David Markowitz, MD; Linda J. Reubens, RN CCRC; Diane Hust, MS RN CS; Lisa Augostino; Julie Babish Johnson, MSW; Erica Burnell, RN; ~~Harris Gelbard, MD PhD;~~ Rosemary L. Jensen; Emily Kushner, MA; Joan Merzbach, LMSW; ~~Jonathan Mink, MD PhD; Carlos Torres, MD; David Wang, MD;~~ Kelley Yost, PhD.

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[22] Department of Pediatrics, University of Rochester Medical Center, Rochester, NY
[23] *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD

From: Phelps, Dale
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Cc: vohr; Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: CONFIDENTIAL SUPPPORT FU PAPER
Date: Friday, November 04, 2011 10:10:19 PM
Attachments: Support NDI 10-21-2011.edits.DLP (2).doc

Dr. Peralta,
Thank you for bringing this paper together so nicely. I enjoyed learning what happened to these children. There are a couple of points that need clarification, but overall it is good.

In the introduction to the abstract on p4 you state that the hypothesis was that the reduced oxygen saturation group would have a lower rate of NDI. My understanding was that everyone has been concerned that the lower oxygen saturation group would have a HIGHER rate of NDI... indeed in the rest of your manuscript, that is the way you put it (especially p6 and p15 in the conclusions).

You may not want to go into it, but the kids who had early surgery for their acute ROP may not have more blindness, but they probably have visual acuity that is less favorable. You can see this in 6 year follow up in the ETROP study (published this year) and the 15 year CRYO-ROP study. Laser is effective in reducing poor visual outcomes, but not as effective in improving rates of normal visual outcomes. It shifts kids from bad to 'not-so-bad', but not to normal.

It appears that you do not have the causes of eye surgery recorded. I suspect that the reviewers may question this. You can wait, or you can put a bit more detail in the methods about what information you did collect.

I am also attaching a copy of the paper with several minor points for you to address in the final editing.

Thanks again.
Dale Phelps

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
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From: Myriam Peralta, M.D. [mailto:MPeralta@peds.uab.edu]
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To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Support NDI_10-21-2011

Rose here is the last version of the manuscript I had added comments from everyone who send this to me. I know I can add more to the discussion perhaps we can talk more on the meeting, Thank you

Parts that I have highlighted in yellow are grammatically incorrect, or there has been a cut and paste error.

[redacted]

Neurodevelopmental Outcome of Extremely Preterm Infants in a Trial of Different Oxygen Saturation Targets

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Word Count

Abstract: 248

Text: 1,148

ABSTRACT

BACKGROUND

Targeting lower (vs. higher) oxygen saturations in the SUPPORT Trial decreased severe retinopathy of prematurity but increased mortality before discharge. We hypothesized that the effects lower oxygen saturations target will [redacted] – [redacted]

METHODS

Infants born at 24 to 27 week gestation were randomized to higher (91-95%) or lower oxygen saturation targets (85-89%) from birth to 36 weeks corrected age. The outcome of this follow up study was a composite of death or neurodevelopment impairment at 18 to 22 months corrected age. Neurodevelopmental impairment (NDI) was defined as a Bayley III cognitive composite score of less than 70, modified Gross Motor Function Classification System ≥2, presence of moderate to severe cerebral palsy, permanent hearing loss, and/or bilateral blindness. Results were adjusted for gestational age stratum, center and familial clustering.

RESULTS

The primary outcome was determined for 1234/1316 (93.8%) of infants enrolled in SUPPRT; 990 survivors were evaluated at 18 to 22 months corrected age. Death or NDI occurred in 185 (30.2%) infants in the lower oxygen saturation group and 171 (27.5%) infants in the higher oxygen saturation group (relative risk 1.12; 95% confidence interval 0.94, 1.32; p=0.21). Death occurred in 140 (22.1%) of the children in the lower oxygen saturation group and in 118 (18.2%) in the higher oxygen saturation group (relative risk 1.25; 95% confidence interval 1, 1.55,

p=0.05). NDI was present in 9.5% (45/472) of the lower oxygen saturation group and 10.5 % (53/504) of the higher oxygen saturation group survivors (relative risk 0.87, 95% confidence interval 0.6, 1.28; p=0.49); and blindness was present in 1% (5/479) of the lower oxygen saturation group and 1.2% (6/511) of the higher oxygen saturation group (relative risk 0.9; 95% confidence interval 0.28, 2.9, p= 0.86).

CONCLUSIONS

Among extremely preterm infants targeted at different levels of oxygen saturation, no significant difference in death or neurodevelopmental impairment was observed at 18 to 22 months. Mortality remained significantly higher in the lower oxygen target group at 18 to 22 months.

Oxygen supplementation is a vital therapy for survival of many preterm infants with respiratory disorders. However, oxygen supplementation may increase the risk of retinopathy of prematurity, bronchopulmonary dysplasia, [1] periventricular leukomalacia,[2] and cerebral palsy [3] Restrictive oxygen therapy decreases retinopathy but has resulted in increased deaths in randomized controlled trials. [4,5,6,7]

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development SUPPORT Trial demonstrated no significant difference in a composite outcome including retinopathy of prematurity and death between a lower oxygen saturation target group (85-89%) and a higher saturation target group (91-95%). However, mortality prior to discharge was increased (in 19.9% of infants vs. 16.2%; relative risk 1.27; 95% CI 1.01 to 1.06; p=0.04) and severe retinopathy of prematurity was reduced (8.6% vs. 17.9%; relative risk 0.52; 95% CI 0.37 to 0.73; p<0.001) in the lower oxygen saturation target group compared to the higher saturation target group. [8] A recent meta-analysis that included the SUPPORT Trial and two other concurrent multi-center randomized controlled trials with a total of 3631 infants showed that infants randomized to an oxygen saturation target of 91-95% % had a lower mortality rate than infants randomized to oxygen saturation targets of 85-89% (17.3% versus 14.4%, P=0.015). [7] The effects of oxygen on the immature brain are not clearly understood. [9] [redacted] [10] However, in two non randomized studies of oxygen saturation targeting,[1,3] neurodevelopmental outcome did not differ by oxygen targets.

This study evaluated the composite outcome of death or neurodevelopmental impairment at 18 to 22 months corrected age in the subjects enrolled in the SUPPORT trial and randomized to lower (85-89%) or higher oxygen saturation targets (91-95%) from birth to 36 weeks corrected age.

METHODS

Study Design

Extremely preterm infants (24 weeks 0 days to 27 weeks 6 days) born between February 2005 and February 2009 at 20 centers in the United States participating in the Neonatal Research Network of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development were enrolled immediately following delivery in the prospective, randomized, controlled SUPPORT trial. Permuted block randomization was used, with stratification according to center and gestational age (24 weeks 0 days to 25 weeks 6 days or 26 weeks 0 days to 27 weeks 6 days). The infants were randomly assigned in the delivery room to a target range of oxygen saturation of 85% to 89% (the lower oxygen saturation group) or 91 to 95% (the higher oxygenation group). Using a 2-by-2 factorial design, participants were also randomly assigned to receive either CPAP immediately following delivery and a limited ventilation strategy if subsequent intubation was required or intubation with surfactant administration within an hour after birth. Procedures for enrollment, intervention and data collection have been previously reported. [8]. The study was approved by the institutional review board at each participating site and at RTI International which is the independent data coordinating center for the Neonatal Research Network. Written informed consent was obtained from the parents or guardians of each child before delivery.

Assessments

A comprehensive neurodevelopmental assessment was performed on survivors at 18-22 months corrected age by neurologic examiners and neurodevelopmental testers who were unaware of the treatment assignments and had been trained annually for reliability of assessments during a 2-day workshop. Developmental status was assessed using The Bayley Scales for Infant Development 3rd edition (BSID III) [11]. Cognitive Composite Scores are reported as a standardized score with a mean of 100 and a standard deviation of 15. The modified Gross Motor Function Classification System (GMFCS) [12] describes the gross motor performance and has a range from 0 (normal) to 5 (most impaired). Examiners also recorded the presence of cerebral palsy defined as a non-progressive disorder of the central nervous system and characterized by abnormal muscle tone in at least one arm or leg associated with abnormal control of movement or posture with delayed attainment of motor milestones.[13] Cerebral palsy was classified depending on severity into mild (GMFCS $\leq$1), moderate (GMFCS 2 or 3) or severe (GMFCS $\geq$ 4). Hearing and visual impairment were determined based on parent report and examination.

Certified research nurses collected demographic and neonatal data using standardized definitions. Data collection included gestational age, birth weight, gender, multiple gestation, race/ethnicity, ROP status, BPD status, history of medical or surgical NEC, history of late onset sepsis, use of postnatal steroids, re-hospitalizations, interim medical history, surgeries, insurance status, maternal marital status, maternal education, household income, language spoken at home, and whether living with biological parents. Socioeconomic data from the neonatal period were used and when not available data updated at the 18-22 month visit were used.

Outcome

The composite of death or neurodevelopmental impairment at 18 to 22 months corrected age for prematurity was the pre-specified primary follow up outcome for the SUPPORT trial. This composite outcome was selected because (a) the data are available on the entire randomized trial cohort, (b) infants who died before 18 months could not be classified as having neurodevelopmental impairment and (c) death can be considered as a competing outcome to neurodevelopmental impairment among survivors. Neurodevelopmental impairment was defined as having any of the following: BSID III cognitive composite score less than 70, GMFCS $\geq$ 2, presence of moderate or severe cerebral palsy, permanent hearing loss that does not permit the child to understand directions of the examiner and communicate despite amplification with hearing aids, or bilateral visual impairment (vision < 20/200).

Analysis

Data was entered in standard forms and was transmitted to the Neonatal Research Network Data Coordinating Center at RTI International which stored, managed and analyzed the data for this study. Details regarding sample size calculations for the SUPPORT trial has been previously reported [6]. All analyses were performed according to the intention to treat principle. Unadjusted comparisons of neonatal and demographic characteristics between treatment groups were conducted using chi-square tests for categorical variables and t tests for continuous variables. The primary analysis focused on the percentage of infants in each group for whom the primary outcome of death or NDI at 18 to 22 months corrected age could be assigned. Analysis of this

and all other categorical outcomes was performed with the used of robust Poisson regression in a generalized-estimating-equation model to obtain adjusted relative risks with 95% confidence intervals. The denominator that was used to calculate the rate of each outcome was the number of infants for whom the outcome was known. Continuous outcomes were analyzed with the use of mixed-effects linear models to obtain adjusted means and standard errors. Pre-specified subgroup analyses were also conducted within each gestational age strata.

In the analysis of all outcomes, the results were adjusted, as pre-specified, for gestational-age strata, center and familial clustering (because multiple births from the same mother were randomized to the same treatment group). Two-sided p values of less than 0.05 were considered to indicate statistical significance, and no adjustments have been made for multiple comparisons.

RESULTS

Characteristics of the Study Sample

The SUPPORT trial enrolled 1316 infants (see flowchart in Figure 1). Five hundred twenty four infants in the lower oxygen saturation group and 555 in the higher oxygen saturation group survived to discharge or transfer from the hospital. The baseline characteristics of the entire group have been reported previously[8] Ten children in the lower oxygen saturation group and 11 children in the higher oxygen saturation group died after discharge from the nursery and prior to the 18 to 22 month corrected age follow up visit. Thirty five children in the lower saturation group and 33 children in the higher saturation group were lost to follow up. However 14/35 in the lower saturation group and 19/33 in the higher saturation group were known to be alive at 18 to 22 months corrected age. Neurodevelopmental assessment was performed in 990/1058 of

infants who were not known to have died (93.6%). Of those who were evaluated at the 18 to 22 months corrected age, neurodevelopmental status was determined in 976 children. From the entire cohort the pre- specified outcome of death or neurodevelopmental impairment could be determined in 93.8% (1234/1316) of enrolled children. There were no significant differences in the baseline characteristics of the cohort that was followed up and those lost to follow up. The mothers of infants lost to follow up were less likely to be married (31 vs. 47% p=0.01) and more likely to have public health insurance (69 vs. 52% p=0.008)

Baseline characteristics of the follow up cohort and the entire trial cohort are presented in Table 1. Among children who were followed up, the percentage of infants who were small for gestational age was greater in the higher oxygen saturation target group compared to the lower saturation target group. In addition, as reported previously the incidence of severe retinopathy of prematurity was higher incidence in the higher oxygen saturation group compared to the lower saturation group. No other significant differences were found in the baseline characteristics of infants with follow up.

Primary Outcome

The mean corrected age for neurodevelopmental evaluation was similar between both groups (Lower oxygen saturation, 19.9 $\pm$ 2.4 months vs. higher oxygen saturation 20.2 $\pm$ 2.7 months, p=0.08). Prevalence of the composite primary outcome of death or neurodevelopmental impairment was not significantly different (relative risk 1.12, 95% confidence interval 0.94, 1.32; p=0.21) between the lower (185/612, 30%) and higher oxygen saturation target groups (171/662, 27.5%). (Table 2) On the age strata between 24 weeks gestation to 25 weeks gestation, primary outcome data was available for 261 of 276 children in the lower saturation

group and 276 of 289 in the higher saturation group. For the age strata between 26 weeks gestation to 27 weeks gestation outcome data was available for 351 of 378 of the lower oxygen saturation group and 346 of 373 of the higher oxygen saturation group. Similar to the entire cohort there were no significant differences in the prevalence of death or neurodevelopmental impairment within both gestational age strata as shown in table 2.

Components of the Primary Outcome

Death prior to the 18 to 22 month adjusted age visit was significantly higher among infants in the lower oxygen saturation target group compared to those in the higher saturation target group. (Lower oxygen saturation, 140/633, 22.1% vs. higher oxygen saturation, 118/648, 18.2%; relative risk 1.25, 95% CI 1, 1.55, p=0.05). However death at 18 to 22 months corrected age was not significantly different within either gestational age strata (table 2)

The rate of neurodevelopmental impairment among survivors followed at 18 to 22 month corrected age visit was similar between the lower and the higher oxygen saturation target groups. Rates of neurodevelopmental impairment were not significantly different in either of the gestational age stratum.

Other outcomes among survivors at follow up

The percentage of children with Bayley III cognitive scores below 70 was not significantly different between the lower and higher oxygen saturation group, nor was the percentage of children with cognitive scores below 85. Adjusted means of cognitive composite scores are presented in table 3.

Rates of severe retinopathy of prematurity and eye surgery among survivors to follow up were higher in the higher oxygen target group compared to the lower oxygen target group; however the rate of blindness was not significantly different at the 18 to 22 month adjusted age visit. Other visual outcomes are presented in Table 3.

DISCUSSION

In this multicenter, follow up study of infants randomized to a lower target range of oxygen saturation (85 to 89%) or to higher target oxygen saturation (91 to 95%) there were not a significant difference in the pre-specified outcome of death or neurodevelopmental impairment at 18-22 months corrected age. To our knowledge this is the only large comprehensive study that has included neurodevelopmental impairment as an outcome for evaluating effects of different oxygen target saturation levels in extremely premature babies within a randomized multicenter trial. There has been a concern about using lower oxygen saturation targets because of potentially increased mortality in extremely premature infants [10]. We found that death prior to discharge in the SUPPORT trial was increased among children who were assigned to lower target saturation levels, and this difference persisted at 18 to 22 months corrected age follow up. We had reported previously that our lower saturation oxygen target was associated with a large reduction in the incidence of severe retinopathy of prematurity among survivors. [8] It has been previously reported that severe ROP may be associated with poor visual outcomes even with treatment [14,15] Although our study was not powered to detect small differences in eye disorders or visual function at 18 to 22 months of age we found that there were no significant differences in the report of unilateral and bilateral blindness between the two groups. Eye surgery was higher

in the group with a higher oxygen saturation target and was likely related to higher incidence of severe retinopathy of prematurity in this group and our criteria used to define severe retinopathy of prematurity. Additional analysis regarding specific visual outcomes of eye function after the presence of retinopathy of prematurity were not included in the outcome data collected in this trial however we did not find a significant difference in other reported visual outcomes like nystagmus, strabismus or use of corrective lenses.

[redacted] However NDI as we defined in this study was not found to be significantly different between the lower and higher oxygen saturation groups.

In addition Cerebral Palsy was not significantly different between the two groups, though it is noteworthy that the incidence of CP was lower than previously reported in other outcome studies.[16]

It has been recognized that higher oxygen levels can be associated with lung disease, however we found no difference in the use of postnatal corticosteroids or diuretics at 18 to 22 months corrected age, or long term use of oxygen as well as rehospitalization between the two groups.

A limitation of this study is that it reports only follow up to 18 to 22 months corrected age, which may had not been enough time to detect the presence of minor but important disabilities. However, it is to note here that when we used the cutoff of Bayley III scores less than 85 we also did not find significant differences between the groups. There is an ongoing follow up SUPPORT study that will be reporting in the future the follow up outcome of these children at

school age. These children were enrolled in tertiary care centers therefore generalizibility is a concern, however we included 20 centers around the country.

In summary we found no significant differences in death or neurodevelopmental impairment at 18 to 22 months corrected age in extremely premature infants who were randomized to a lower target oxygen saturation or higher target oxygen saturation. The increased death rate at discharge that was previously reported in the lower target oxygen saturation group was still present at 18 to 22 months corrected age. Although severe retinopathy of prematurity was associated with higher oxygen saturation target levels, blindness was not significantly different among survivors at 18 to 22 months.

Table 1. Baseline characteristics of the SUPPORT group

Characteristics	Trial Cohort	
	Lower Oxygen Saturation	Higher Oxygen Saturation
	N=654	N=662
Birth weight – g	835.5± 193.4	824.8± 193
Gestational age – wk	26.2 ± 1.1	26.1 ± 1.1
Small for gestational age – no./total no. (%)	41/654 (6.3)	55/662 (8.3)
Male sex – no./total no. (%)	341/654 (52.1)	371/662 (56)
Race or ethnic group – no./total no. (%)		
Non Hispanic Black	257/654 (39.3)	232/662 (35)
Non Hispanic White	242/654 (37)	279/662 (42.1)
Hispanic	132/654 (20.2)	127/662 (19.2)
Other or unknown	23/654 (3.5)	24/662 (3.6)
Multiple births – no./total no. (%)	161/654 (24.6)	176/662 (26.6)
Maternal educational level <high school no./total no. (%)	148/594 (24.9)	165/612 (27)

Public Health Insurance only – no./total no. (%)	356/650 (54.8)	348/660 (52.7)
Mother married – no./total no. (%)	284/652 (43.6)	308/661 (46.6)
Lives with both biological parents – no./total no. (%)	354/508 (69.7)	364/547 (66.5)
Household income < $30,000/year – no./total no.(%)	247/474 (52.1)	291/528 (55.1)
English as primary language – no./total no. (%)	402/477 (84.3)	429/513 (83.6)
Cesarean section – no./total no. (%)	441/654 (67.4)	442/662 (66.8)
Antenatal steroids – no./total no. (%)	633/654 (96.8)	632/661 (95.6)
Severe retinopathy of prematurity – no./total no. (%)	41/475 (8.6)**	91/509 (17.9)**
Bronchopulmonary dysplasia – no./total no. (%)	205/540 (38)	237/568 (41.7)
Intraventricular hemorrhage grade 3 or 4 or Periventricular leukomalacia – no./total no. (%)	98/630 (15.6)	100/640 (15.6)
Necrotizing enterocolitis – no./total no. (%)	76/641 (11.9)	70/649 (10.8)
Late onset sepsis/meningitis – no./total no. (%)	228/624 (36.5)	226/634 (35.6)
155/479 (32.4)	166/511 (32.5)	
Post natal steroids – no./total no. (%)	61/636 (9.6)	69/644 (10.7)
41/477 (8.6)	48/507 (9.5)	
CPAP – no./total no. (%)	336/654 (51.4)	327/662 (49.4)
254/479(53)	257/511 (50.3)	

Surfactant – no./total no. (%)	318/654 (48.6)	335/662 (50.6)
	225/479 (47)	254/511 (49.7)

*p<0.05, **p<0.001

Table 2. Primary Outcomes at 18-22 Months Corrected Age

	Lower Oxygen Saturation	Higher (Satur
Lower oxygenation saturation vs higher oxygen saturation	N=654	N=(
Outcome determined for death or NDI – no./total no. (%)	612/654 (93.6)	622/66
Neurodevelopmental impairment or death – no./total no. (%)	185/612 (30.2)	171/622
Died by 18-22 months – no./total no. (%)	140/633 (22.1)	118/648
Survivors at follow-up		
Neurodevelopmental impairment – no./total no. (%)	45/472 (9.5)	53/504
Bayley III cognitive composite score < 70 – no./total no. (%)	34/471 (7.2)	38/503
Gross motor function level ≥ 2 – no./total no. (%)	26/479 (5.4)	23/511
Moderate/severe cerebral palsy – no./total no. (%)	20/479 (4.2)	20/511
Blindness – no./total no. (%)	5/479 (1)	6/511
Deafness – no./total no. (%)	12/479 (2.5)	12/511
24 0/7 to 25 6/7 weeks gestational age strata	276	28
Neurodevelopmental impairment or death – no./total no. (%)	115/261 (44.1)	112/276
Died by 18-22 months – no./total no. (%)	91/267(34.1)	79/283
Survivors at follow-up		
Neurodevelopmental impairment – no./total no. (%)	24/170 (14.1)	33/197
Bayley III cognitive composite score < 70 – no./total no. (%)	17/169 (10.1)	22/196
Gross motor function level ≥ 2 – no./total no. (%)	13/173 (7.5)	13/200
Moderate/severe cerebral palsy – no./total no. (%)	10/173 (5.8)	12/20(

Blindness – no./total no. (%)	1/173 (0.6)	3/200
Deafness – no./total no. (%)	4/173 (2.3)	10/200
26 0/7 to 27 6/7 weeks gestational age strata	378	37
Neurodevelopmental impairment or death – no./total no. (%)	70/351(19.9)	59/346
Died by 18-22 months – no./total no. (%)	49/366(13.4)	39/365
Survivors at follow-up		
Neurodevelopmental impairment – no./total no. (%)	21/302(7.0)	20/307
Bayley III cognitive composite score < 70 – no./total no. (%)	17/302 (5.6)	16/307
Gross motor function level ≥ 2 – no./total no. (%)	13/306(4.2)	10/311
Moderate/severe cerebral palsy – no./total no. (%)	10/306(3.3)	8/311
Blindness – no./total no. (%)	4/306 (1.3)	3/311
Deafness – no./total no. (%)	8/306 (2.6)	2/311

Table 3. Other Outcomes at 18 to 22 months corrected Age by Group

Outcome	Low SpO2 (N=479)	High SpO2 (N=510)	Relative Risk Low SpO2 High SpO (95% CI)
Bayley Scales of Infant Development III			
Cognitive composite < 70	34/471 (7.2)	38/503 (7.6)	0.91 (0.58, 1
Cognitive composite <85	105/471 (22.3)	132/503 (26.2)	0.85 (0.68, 1
Adjusted mean cognitive composite scores ± standard error	92.2 ± 0.8	90.5 ± 0.7	
Median cognitive composite scores Scores	90 (85, 100)	90 (80, 100)	
Neurologic findings			
Mild cerebral palsy vs. none	23/459 (5.0)	21/490 (4.3)	1.16 (0.66, 2
Moderate cerebral palsy vs. none	11/447 (2.5)	10/479 (2.1)	1.19 (0.52, 2
Severe cerebral palsy vs. none	9/445 (2.0)	10/479 (2.1)	0.95 (0.39, 2
Any cerebral palsy	43/479 (9.0)	41/510 (8.0)	1.12 (0.76, 1
Abnormal neurologic exam	108/479 (22.5)	114/511 (22.3)	1.02 (0.82, 1
Vision findings			
Strabismus	46/478 (9.6)	41/510 (8)	1.2 (0.8, 1.

Nystagmus	22/479 (4.6)	13/510 (2.4)	1.81 (0.89, 3
Tracks 180 degrees [3]	462/476 (97.1)	492/506 (97.2)	1 (0.98, 1.0
Corrective lenses both eyes	21/468 (4.5)	20/493 (4.1)	1.14 (0.62, 2
Blind, some function, both eyes vs. normal	3/450 (0.7)	2/475 (0.4)	1.57 (0.27, 8
Blind, no useful vision, both eyes vs. normal	2/449 (0.4)	4/477 (0.8)	0.54 (0.1, 2.
Other abnormal vision vs. normal	6/453 (1.3)	12/485 (2.5)	0.55 (0.21, 1
Eye surgery	31/477 (6.5)	67/509 (13.2)	0.52 (0.35, 0
Medicines			
Bronchodilators	159/475 (33.5)	185/506 (36.6)	0.92 (0.78, 1
Steroids	95/475 (20.0)	108/506 (21.3)	0.92 (0.72, 1
Diuretics	15/475 (3.2)	14/506 (2.8)	1.17 (0.58,2.
Anticonvulsants	12/478 (2.5)	12/511 (2.3)	1.08 (0.49, 2
Readmission	210/478 (43.9)	239/511 (46.8)	0.94 (0.82, 1
Readmission for respiratory reason	110/470 (23.4)	127/503 (25.2)	0.93 (0.74, 1
Readmission for growth/nutrition	12/470 (2.6)	13/503 (2.6)	1.05 (0.49, 2

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From: Stevens, Timothy
To: "Newman, Jamie"; "Das, Abhik"; Higgins, Rosemary (NIH/NICHD) [E]; D"Angio, Carl
Subject: Breathing Outcomes Update
Date: Sunday, October 23, 2011 8:54:19 PM
Attachments: Breathing Outcomes Update-Oct-23-11.doc

Hi

Here is the Breathing Outcomes update for later this week.

Thanks

Tim

Breathing Outcomes Update
October 23, 2011
Tim Stevens

Brief Update: 944 subjects are enrolled in the Breathing Outcomes secondary to SUPPORT. Data cleaning is underway. Missing data have been identified as outlined below. I'm working with Lei Li (analyst) and RTI to obtain missing data and finalize the dataset in preparation for analysis.

Goal is to have preliminary analyses prepared by end of November.

Table I. Demographics of the 18-22 month Breathing Outcomes Follow-up Population

	CPAP N=486	Surfactant N=452	High SpO2 N=491	Low SpO2 N=447
Birth Weight (g, mean ± s.d.)	852.4 ± 183.6	852.2 ± 186.8	842.7 ± 186.9	862.7 ± 182.7
Gestational Age (w, mean ± s.d.)	25.9 ± 1	25.9 ± 1	25.9 ± 1	25.9 ± 1
Gestational Age - no. (%)				
24 wk 0 days–25 wk 6 days	179 (37.7)	154 (35.3)	179 (37.7)	154 (35.3)
26 wk 0 days–27 wk 6 days	296 (62.3)	282 (64.7)	296 (62.3)	282 (64.7)
Male Sex - no. (%)	232 (48.8)	239 (54.7)	254 (53.5)	217 (49.7)
Race or ethnic group — no. (%)				
Non-Hispanic black	173 (37.9)	147 (34.7)	155 (33.8)	165 (39.1)
Non-Hispanic white	193 (42.3)	202 (47.6)	224 (48.9)	171 (40.5)
Hispanic	90 (19.7)	75 (17.7)	79 (17.2)	86 (44.1)
Length of NICU Hospitalization (median, range)	91,1-365	92,1-365	93,1-365	90,1-365
BPD (oxygen at 36w BPD_T) - no. (%)	184 (39.4)	192 (44.5)	220 (47.1)	156 (36.2)
BPD (physiologic definition BPD_P) - no. (%)	151 (39.4)	139 (38.5)	162 (41.3)	128 (36.4)
Discharged home on oxygen - no. (%)	108 (23.3)	104 (24.2)	110 (23.7)	102 (23.8)
Discharged home on respiratory medications - - no. (%)	109 (28.2)	92 (26.1)	102 (27.1)	99 (27.3)
Discharged home October – March - no. (%)	226 (48.6)	221 (51.6)	220 (47.5)	227 (52.8)
First degree relative with asthma - no. (%)	152 (31.3)	149 (33.0)	159 (32.4)	142 (31.8)

Notes: including only 944 infants with consents in enrollment log. Missing data are listed below.
GA: 27 wks , 28 wks 1, 29 wks 1, unknown 26
Male Sex: unknown 26
Race/ethnicity: unknown 27, others 31
BPD_T: unknown 40
BPD_P: unknown 194
Discharged home on oxygen: 45
Discharged home on respiratory medications: 199
Discharged home October-March: 45
Birth weight: 26
Length of hospitalization: 26
? 26 infants were in enrollment log but not in GDB.
? Six infants were not assigned a treatment.

From: Phelps, Dale
To: Kennedy, Kathleen A; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Wrage, Lisa Ann (wrage@rti.org)
Subject: RE: "Final" version
Date: Thursday, October 13, 2011 7:19:51 PM
Attachments: ROP Natural History PAS Abstract.DLP.10.13.doc

Hi Kathleen,

The numbers all sync now, and it flows well.

I had to stop and re-read my old nemesis sentence a few times, but it is ok.

I have added the word "severe" in one place to prevent ambiguity in a different sentence. (highlighted in red) I hope you have room for it. ☺

Can you make the phrase in the table:

ROP type (number of infants)

Appear a line lower? That way no one will be trying to figure out if it applies to the percents.

Nice work !

Remember, you have to put the table tag into the text to have it show up. I put it there and highlighted in red.

Dale

From: Kennedy, Kathleen A [mailto:Kathleen.A.Kennedy@uth.tmc.edu]
Sent: Thursday, October 13, 2011 1:49 PM
To: Phelps, Dale; Higgins, Rosemary (NIH/NICHD)
Cc: Wrage, Lisa Ann (wrage@rti.org)
Subject: "Final" version

I think this is looking good. Lisa and I have finished arm wrestling about the numbers. If you (Dale and Rose) are ok with it, I think we can call it final, send it back to the SUPPORT Subcommittee and onto the NICHD for clearance.

Kathleen A. Kennedy, MD, MPH
Richard W. Mithoff Professor of Pediatrics
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713 500-6708

Evaluating the Retinopathy of Prematurity (ROP) Screening GUIDELINES ~~Interval~~ for 24-27 Week Gestation Infants

Kathleen A. Kennedy MD MPH, Lisa Wrage, MPH, Dale L. Phelps MD, Rosemary D. Higgins on behalf of the SUPPORT Subcommittee for the NICHD Neonatal Research Network

Background:
Timely detection of treatable ROP is important to assure optimal outcomes for infants who meet the criteria for treatment. Current screening guidelines are based on natural history data from randomized trials that enrolled infants between 1986-1997: screening should begin by 31 weeks postmenstrual age(PMA) and continue until the vessels have reached zone III at ≥ 35 weeks, or, for infants without prethreshold ROP, until a PMA~~postmenstrual age~~ of 45 weeks. Since the 1980s, survival of lower gestational age(GA) infants has increased, and earlier treatment of ROP (Type 1 ROP: stage 3 or ROP with plus disease in zone ~~1~~ I or stage 2-3 with plus disease in zone II ~~2~~) is recommended. The timing of onset of ROP is related most closely to postmenstrual age (PMA = gestational age at birth + postnatal age).

Objective:
To validate current screening recommendations for detection of treatable ROP in 24-27 week gestational age infants.

Design/Methods:
In the NICHD Network SUPPORT trial, severe ROP (Type 1 ROP or treatment with laser, cryotherapy or bevacizumab) or death was the primary outcome for the O_2 saturation target arm of the factorial design. Infants 24 0/7 to 27 6/7 weeks gestation (no birth weight limits) and consented prior to delivery were eligible for this study. ROP examinations were conducted according to current screening recommendations and recorded using the international classification of ROP. Results of each exam were prospectively collected for all enrolled infants~~. Study eye exam data were recorded~~ until a study endpoint was reached: ROP treatment, full vascularization to the ora serrata, vascularization in zone III in 2 consecutive exams, or the infant was 55 weeks PMA.

Results:
1316 infants were enrolled. 1091 (83%) of infants survived to the age of ROP determination. 997 (91%) of these infants had a definitive ROP outcome and 986 (90%) had sufficient exam data (no missing or delayed exams before diagnosis) to determine the diagnosis and age of onset of ROP. 644 infants developed ROP (138 met severe ROP criteria); 353 infants did not. As expected, infants with severe ROP were less mature [mean (SD) 25.5 (0.9) wks vs 26.8 (0.9) wks, p<0.0001], lower birth weight [mean (SD) 708 (148)g vs 942 (173)g, p<0.0001], and more likely to be White race (44% vs 35%, p=0.07) than infants with no ROP. For the 633 infants with ROP and known age of onset, the PMA for selected cumulative %iles is shown in the table:
see e-mail about discrepant numbers all highlighted--dlp

ROP type (number of infants)	Cumulative %tile with Diagnosis of ROP						
	1%	5%	25%	50%	75%	95%	99%
	Postmenstrual Age (weeks)						
Diagnosis of any ROP (n=633)	30.4	31.4	32.7	33.9	35.1	37.9	41.0
Diagnosis of severe (Type 1/Treated) ROP (n=128)	32.7	33.9	35.1	36.4	38.6	43.3	45.0

The PMA at onset of severe ROP ranged from 32.1 to 53.1 weeks. In this referral center cohort of 997 infants, 0.5% were diagnosed with severe ROP after back transfer to another NICU; 1.0% of the cohort (7% of infants with severe ROP) reached severe ROP criteria after discharge to home.

Our data are consistent with the 2006 ROP screening guidelines. In this cohort of 997 infants born at 24-27 weeks, we did not observe ROP needing treatment before 32 weeks PMA; only 1 infant was diagnosed with severe ROP after 45 weeks PMA. A limitation of this study is that infants < 24 weeks gestational age were not enrolled and these data may not be generalizable to less mature infants at the highest risk for ROP.

From: Roger Faix
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: Oximetry targets manuscript
Date: Wednesday, November 02, 2011 7:41:17 PM
Attachments: Support NDI 09-26-2011.doc

FYI

From: Roger Faix
Sent: Wednesday, November 02, 2011 5:37 PM
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Subject: Oximetry targets manuscript

Hi Miryam!

It is evident that you have worked hard on long on the draft manuscript. I have included a few suggested changes and comments embedded on the attached manuscript. Suggested changes are in bold red font, while comments are in bold purple. I hope these are useful for you.

Roger

Neurodevelopmental Outcome of Extremely Preterm Infants in a Trial of Different Oxygen Saturation Targets

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Word Count

Abstract: 248

Text: 1,148

ABSTRACT

BACKGROUND

Targeting lower (vs. higher) oxygen saturations in the SUPPORT Trial decreased severe retinopathy of prematurity but increased mortality before discharge. We hypothesized that the effects of different oxygen levels on long term neurodevelopmental intact survival were not significant.

METHODS

We followed 1211 of 1316 (92%) infants born at 24 to 27 week gestation and randomized to higher (91-95%) or lower oxygen saturation targets (85-89%) from birth to 36 weeks corrected age. The outcome of this follow up study was a composite of death or neurodevelopment impairment at 18 to 22 months corrected age. Neurodevelopmental impairment was defined as a Bayley III cognitive composite score of less than 70, modified Gross Motor Function Classification System $\geq$2, presence of moderate to severe cerebral palsy, permanent hearing loss, and/or bilateral blindness.

RESULTS

Death or neurodevelopmental impairment occurred in 185 (30.2%) infants in the lower oxygen saturation group and 171 (27.5%) infants in the higher oxygen saturation group (relative risk 1.12; confidence interval 0.94, 1.32; p=0.21). Death occurred in 140 (22.1%) of the children in the lower oxygen saturation group and in 118 (18.2%) in the higher oxygen saturation group

(relative risk 1.25; confidence interval 1, 1.55, p=0.05). **Should we include findings re: blindness/visual morbidity in abstract, since the lack of apparent difference attributable to ROP on follow-up is one of the major points of this article, in my opinion.**

CONCLUSIONS

Among extremely preterm infants targeted at different levels of oxygen saturation, no significant difference in death or neurodevelopmental impairment was observed at 18 to 22 months. Mortality remained elevated in the lower oxygen target group at 18 to 22 months, though the trend was only borderline statistically significant.

Oxygen supplementation is a vital therapy for survival of many preterm infants with respiratory disorders. However, oxygen supplementation may increase the risk of retinopathy of prematurity, bronchopulmonary dysplasia,[Tin et al, 2001] periventricular leukomalacia,[Chow et al, 2003] and cerebral palsy.[Anderson et al, 2004] Restrictive oxygen therapy decreases retinopathy but has resulted in increased deaths in randomized controlled trials.[Bolton DP et al, 1997; Askie et al, 2009; Carlo et al, 2010, Stenson et al, 2011]

Comment [WC1]: These references are quoted in my NEJM paper

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development SUPPORT Trial demonstrated no significant difference in a composite outcome including retinopathy of prematurity and death between a lower oxygen saturation group (85-89%) and the higher saturation target group (91-95%). However, mortality was increased and severe retinopathy of prematurity was reduced in the lower oxygen saturation group compared to the higher saturation target group. A recent meta-analysis that included the SUPPORT Trial and two other subsequently multi-center randomized controlled trials with a total of 3631 infants showed that infants randomized to an oxygen saturation of 91-95% % had a lower mortality rate than infants randomized to oxygen saturation targets of 85-89% (17.3% versus 14.4%, P=0.015).[Stenson, NEJM 2011] There has been keen interest in determining whether oxygen supplementation can reduce neurodevelopmental impairment. However, in two non randomized studies of oxygen saturation targeting,[Tin et al, 2001; Bradley et al, 1993] neurodevelopmental outcome did not differ by oxygen targets.

Comment [WC2]: Spell out

This study evaluated the composite outcome of death or neurodevelopmental impairment at 18 to 22 months corrected age in the subjects enrolled in the SUPPORT trial and randomized to two

groups of extremely preterm infants randomized to lower (85-89%) or higher oxygen saturation targets (91-95%) from birth to 36 weeks corrected age.

METHODS

Study Design

1316 extremely preterm infants (24 weeks 0 days to 27 weeks 6 days) born between February 2005 and February 2009 at 20 centers in the United States participating in the Neonatal Research Network of the Eunice Kennedy Shriver National Institute of Child Health and Human Development were enrolled immediately following delivery in the prospective, randomized, controlled SUPPORT trial. Permuted block randomization was used, with stratification according to center and gestational age (24 weeks 0 days to 25 weeks 6 days or 26 weeks 0 days to 27 weeks 6 days). The infants were randomly assigned before birth to a target range of oxygen saturation of 85% to 89% (the lower oxygen saturation group) or 91 to 95% (the higher oxygenation group). Using a 2-by-2 factorial design, participants were also randomly assigned to receive either CPAP immediately following delivery and a limited ventilation strategy if subsequent intubation was required or intubation with surfactant administration within an hour after birth. Procedures for enrollment, intervention and data collection have been previously reported. (Carlo NEJM) . The study was approved by the institutional review board at each participating site and RTI international **(Does RTI stand for Research Triangle International? If so, the extra International after RTI is redundant.)** which is the independent data coordinating center for the Neonatal Research Network. Written informed consent was obtained from the parent(s) or guardian (s) of each child before delivery.

Assessments

All infants who survived to 36 weeks corrected age were eligible to participate in the prospective follow up cohort of the SUPPORT trial. A comprehensive neurodevelopmental assessment was performed at 18-22 months of corrected age by neurologic examiners and neurodevelopmental testers who were unaware of the treatment assignments and had been trained annually for reliability of assessments during a 2-day workshop. Developmental assessment was assessed using The Bayley Scales for Infant Development 3rd edition (BSID III) (ref). Cognitive Composite Scores are reported as a standardized score with a mean of 100 and a standard deviation of 15. The modified Gross Motor Function Classification System (GMFCS) (ref) describes the gross motor performance and has a range from 0 (normal) to 5 (most impaired). Examiners also recorded the presence of cerebral palsy defined as a nonprogressive disorder of the central nervous system and characterized by abnormal muscle tone in at least one arm or leg associated with abnormal control of movement or posture with delayed attainment of motor milestones. Cerebral palsy was classified depending on severity into mild (GMFCS $\leq$1) (**This seems to imply that a GMFCS of zero would be categorized as mild.**), moderate (GMFCS 2 or 3) or severe (GMFCS $\geq$ 4). Hearing and visual impairment were determined based on parental history and examination.

Certified research nurses collected demographic and neonatal **data** using standardized definitions in the trial's manual of operations. Data collection included (but was not limited to) gestational age, birthweight, gender, multiple gestation, race/ethnicity, ROP status, BPD status, history of medical or surgical NEC, history of late onset sepsis, use of postnatal steroids, rehospitalizations, interim medical history, surgeries, insurance status, marital status, maternal education, household

income, language spoken at home, whether living with biological parents. Socioeconomic data was updated during the 18-22 month visit and if not available, data during the neonatal period was included.

Outcome

The composite of death or neurodevelopmental impairment at 18 to 22 months corrected age for prematurity was the primary neurodevelopmental outcome. This composite outcome was selected because infants who died before 18 months could not be classified as having neurodevelopmental impairment. Neurodevelopmental impairment was defined as having any of the following: BSID III cognitive composite score less than 70, GMFCS $\geq$ 2, presence of moderate or severe cerebral palsy, permanent hearing loss that does not permit the child to understand directions of the examiner and communicate despite amplification with hearing aids or cochlear implants, or bilateral visual impairment (vision < 20/200).

Analysis

Data was entered in standard forms and was transmitted to RTI International **(see previous comment)** which stored, managed and analyzed the data for this study. Details regarding sample size calculations for the SUPPORT trial have been previously reported (ref finer). All analyses were performed according to the intention to treat principle. The denominator that was used to calculate the rate of each outcome was the number of infants for whom the outcome was known. The primary analysis focused on the percentage of infants in each group for whom the primary

outcome of death or NDI at 18 to 22 months corrected age could be assigned. Analysis of this and all other categorical outcomes was performed with the used of robust Poisson regression in a generalized-estimating-equation model to obtain adjusted relative risks with 95% confidence intervals. **(Move description of factors adjusted for from next paragraph to here)** Continuous outcomes were analyzed with the use of mixed-effects linear models to obtain adjusted means and standard errors.

In the analysis of all outcomes, the results were adjusted, as pre-specified, for gestational-age strata, center and familial clustering **(Move this sentence to previous paragraph).** Two-sided p value of less than 0.05 were considered to indicate statistical significance, and no adjustments have been made for multiple comparisons. RESULTS

Characteristics of the Study Sample

The SUPPORT trial enrolled 1316 study in the study (see flowchart in Figure 1). Five hundred twenty four infants in the lower oxygen saturation group and 555 in the higher oxygen saturation group survived to discharge from the hospital. The baseline characteristics of the entire group have been reported previously[(Carlo NEJM)] Ten children in the lower oxygen saturation group and 11 children in the higher oxygen saturation group died after discharge from the nursery prior to the 18 to 22 month adjusted age follow up visit. Thirty five children in the lower saturation group and 33 children in the higher saturation group were lost to follow up. However 9/35 in the lower saturation group and 11/33 in the higher saturation group were known to be alive at 18 to 22 months adjusted age. Neurodevelopmental assessment was performed in 990/1058 eligible infants (93.6%). Of those who were evaluated at the 18 to 22 months adjusted age, neurodevelopmental impairment was determined in 976 children. From the entire cohort the pre-

specified outcome of death or neurodevelopmental impairment was able to be determined in 93.8% (1234/1316). There were no significant differences in the baseline characteristics of the cohort that was followed up and then lost to follow up. The mothers **at the of those** lost to follow up were more likely to be married and more likely to have public health insurance. (*add numbers, Marie not sure if I have these ones, I could not find them)*

We looked at the baseline characteristics of the follow up cohort and the entire trial cohort which is presented in Table 1. The percentage of infants who were small for gestational age in the higher saturation target group was higher compared to the infants who were in the lower saturation target group in the follow up cohort group. In addition, as reported previously, severe retinopathy of prematurity had a higher incidence in the higher oxygen saturation group compared to the lower saturation group. No other significant differences were reported in the baseline characteristics of the eligible infants for follow up.

Primary Outcome

The mean corrected age for neurodevelopmental evaluation was similar between both groups (low SpO2 19.9 m $\pm$ 2.4 vs. High SpO2 20.2 $\pm$ 2.7 mo, p=0.076). Prevalence of the composite primary outcome of death or neurodevelopmental impairment was not significantly different between the lower and higher oxygen saturation target groups. (Table 2) Similar results were observed within both gestational age strata (Low SpO2 115/261, 44.1% vs. High SpO2 112/276, 40.6%, P= 0.4201 for the 24 0/7-25 6/7 wks ga; and Low SpO2 70/351, 19.9% vs High SpO2 59/346, 17.1%, p=0.33 for the 26 0/7 – 27 6/7 wks GA). Death prior to the 18 to 22 month adjusted age visit was higher among infants in the lower oxygen saturation target group compared to those in the higher saturation target group. (Low SpO2 140/633, 22.1% vs. high

SpO2 118/648 , 18.2%, relative risk 1.25 95% CI 1, 1.55, p=0.0462). However death at 18 to 22 months adjusted age was not significantly different within both gestational age strata (low SpO2 91/267, 34.1% vs. High SpO2 79/283, 27.9%, relative risk 1.23 95% CI 0.95, 1.59 P=0.118 for the 24 0/7-25 6/7 wks GA; and Low SpO2 49/366, 13.4% vs. High SpO2 39/365, 10.7%, relative risk 1.28 95% CI 0.86, 1.89, p=0.2195).

The rate of neurodevelopmental impairment among survivors followed at 18 to 22 month adjusted age visit was similar between the lower and the higher oxygen saturation target groups. Rates for neurodevelopmental impairment were not significantly different in either of the gestational age strata groups.

Outcomes among survivors at follow up

The percentage of children with Bayley III cognitive scores below 70 was not significantly different between the lower and higher oxygen saturation group. In addition we looked into the percentage of children with Bayley cognitive scores below 85 and these were not significantly different between the groups. Mean scores of the Bayley Scales of Cognitive Composite are presented in table 3.

The rate of retinopathy of prematurity as well as infants, who required eye surgery, was higher in the higher oxygen target group compared to the lower oxygen target group; however the rate of blindness was not significantly different at the 18 to 22 month adjusted age visit. Other visual outcomes are presented in table 3. **(Any point worth adding re: contrast/comparisons with CPAP vs Surf part of study?)**

DISCUSSION

In this multicenter, follow up study of infants randomized to a lower target range of oxygen saturation (85 to 89%) or to a higher target oxygen saturation (91 to 95%) there were no significant difference in the prespecified outcome of death or neurodevelopmental impairment. To our knowledge this is the only large comprehensive study that has included neurodevelopmental impairment as an outcome for evaluating effects on different oxygen target saturation levels. There has been a previous concern of using lower saturation target and increased mortality in extreme premature infants (ref) In addition we found that death prior to discharge in the SUPPORT trial showed increased mortality among children who were assigned to lower target saturation levels,. **however I In** this follow up study, death at 18 to 22 months of age was not significantly different between the two target groups or at the different gestational age stratification levels.

We had reported previously that our lower saturation oxygen target was associated with a large reduction in the incidence of severe retinopathy of prematurity among survivors. (ref) It has been previously reported that severe ROP may be associated with poor visual outcomes even with treatment(ref) Although our study was not powered to detect small differences in eye disorders or visual function at 18 to 22 months of age, we did find that there were no significant differences in the report of unilateral and bilateral blindness among the two groups. Eye surgery was reported higher in our group with a higher oxygen saturation target more likely related to higher incidence of severe retinopathy of prematurity, although data regarding specifics of eye surgery **was were** not collected (*Marie I think we actually did this but did not have it in the*

table). Additional analysis regarding eye findings and its association with presence of severe retinopathy of prematurity is needed.

There had been concerns that lower saturation oxygen saturation targets are associated with effects on long term neurdevelopmental impairment (ref). However NDI as we defined in this study was not found to be significant in the lower or higher oxygen saturation assigned group.

In addition Cerebral Palsy was not significant in both groups. it is **to note notable** that the incidence of CP was lower as previously reported in other outcome studies.

It has been recognized that higher oxygen levels can be associated with lung disease, however we found no difference in the use of postnatal corticosteroids, diuretics or long term use of oxygen as well as rehospitalization between the two groups.

This study has some limitations,. tThis study reports only follow up to 18 to 22 months of age, which may had not been enough time to detect the presence of other minor **however but** important disabilities. However **it is to note here notable that** when we used the cutoff of Bayley III to less than 85 we also did not find significant differences between the groups. In addition there is an ongoing follow up SUPPORT study that will be reporting in the future the follow up outcome of these children at school age. These children were enrolled in tertiary care centers therefore generalizibility is a concern, however we include 20 centers around the country. **(This last sentence is awkward.)**

In summary we found no significant differences in death or Neurodevelopmental impairment, at 18 to 22 months corrected age in extremely premature infants that were randomized to receive lower target oxygen saturation or higher target oxygen saturation. Increased death at discharge

that was found on our previous report associated with lower target oxygen saturation was still present at 18 to 22 months adjusted age. Although retinopathy of prematurity was associated with higher oxygen saturation target levels, blindness was not significantly different among survivors.

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Comment [bb3]: Check references

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Table 1. Baseline characteristics of the SUPPORT group

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Characteristics	Trial Cohort		Cohort with Follow-up Visit	
	Lower Oxygen Saturation	Higher Oxygen Saturation	Lower Oxygen Saturation	Higher Oxygen Saturation
	N=654	N=662	N=479	N=510
Birth weight – g	835.5± 193.4	824.8± 193	857.8 ± 186.3	843.9± 191.6
Gestational age – wk	26.2 ± 1.1	26.1 ± 1.1	26.3 ± 1.1	26.2 ± 1
Small for gestational age – no./total no. (%)	41/654 (6.3)	55/662 (8.3)	17/479 (3.5)*	38/511 (7.4)*
Male sex – no./total no. (%)	341/654 (52.1)	371/662 (56)	240/479 (50.1)	281/510 (55.1)
Race or ethnic group – no./total no. (%)				
Non Hispanic Black	257/654 (39.3)	232/662 (35)	201/479 (42)	176/510 (34.5)
Non Hispanic White	242/654 (37)	279/662 (42.1)	178/479 (37.2)	217/510 (42.5)

Hispanic	132/654 (20.2)	127/662 (19.2)	86/479 (18)	97/510 (19)
Other or unknown	23/654 (3.5)	24/662 (3.6)	14/479 (2.9)	20/510 (3.9)
Multiple births – no./total no. (%)	161/654 (24.6)	176/662 (26.6)	124/479 (25.9)	128/510 (25.1)
Maternal educational level <high school no./total no. (%)	148/594 (24.9)	165/612 (27)	115/471 (24.4)	129/504 (25.6)
Public Health Insurance only – no./total no. (%)	356/650 (54.8)	348/660 (52.7)	253/479 (52.8)	266/511 (52.1)
Mother married – no./total no. (%)	284/652 (43.6)	308/661 (46.6)	222/479 (46.3)	243/511 (47.6)
Lives with both biological parents – no./total no. (%)	354/508 (69.7)	364/547 (66.5)	332/478 (69.5)	345/511 (67.5)
Household income < $30,000/year – no./total no.(%)	247/474 (52.1)	291/528 (55.1)	239/456 (52.4)	272/498 (54.6)
English as primary language – no./total no. (%)	402/477 (84.3)	429/513 (83.6)	402/477 (84.3)	427/511 (83.6)
Cesarean section – no./total no. (%)	441/654 (67.4)	442/662 (66.8)	332/479 (69.3)	335/511 (65.6)
Antenatal steroids – no./total no. (%)	633/654 (96.8)	632/661 (95.6)	462/479 (96.5)	487/511 (95.3)
Retinopathy of prematurity – no./total no. (%)	41/475 (8.6)**	91/509 (17.9)**	38/442 (8.6)**	82/471 (17.4)**

Bronchopulmonary dysplasia – no./total no. (%)	205/540 (38)	237/568 (41.7)	177/479 (37)	203/511 (39.7)
Intraventricular hemorrhage grade 3 or 4 or Periventricular leukomalacia – no./total no. (%)	98/630 (15.6)	100/640 (15.6)	56/478 (11.7)	60/510 (11.8)
Necrotizing enterocolitis – no./total no. (%)	76/641 (11.9)	70/649 (10.8)	42/479 (8.8)	44/511 (8.6)
Late onset sepsis/meningitis – no./total no. (%)	228/624 (36.5)	226/634 (35.6)	155/479 (32.4)	166/511 (32.5)
Post natal steroids – no./total no. (%)	61/636 (9.6)	69/644 (10.7)	41/477 (8.6)	48/507 (9.5)
CPAP – no./total no. (%)	336/654 (51.4)	327/662 (49.4)	254/479(53)	257/511 (50.3)
Surfactant – no./total no. (%)	318/654 (48.6)	335/662 (50.6)	225/479 (47)	254/511 (49.7)

*p<0.05, **p<0.001

Table 2. Primary Outcomes at 18-22 Months Adjusted AGe

	Lower Oxygen Saturation N=654	Higher Oxygen Saturation N=662	Adjusted Relative Risk	p value
Death prior to discharge – no./total no. (%)	130/654 (19.9)	107/662 (16.2)		
Outcome determined by death or NDI – no./total no. (%)	612/654 (93.6)	622/662 (94)	1 (0.97, 1.03)	0.7927
Died by 18-22 months – no./total no. (%)	140/633 (22.1)	118/648 (18.2)	1.25 (1, 1.55)	0.0462
Neurodevelopmental impairment or death – no./total no. (%)	185/612 (30.2)	171/662 (27.5)	1.12 (0.94, 1.32)	0.2098
Survivors at follow-up				
Neurodevelopmental impairment – no./total no. (%)	45/472 (9.5)	53/504 (10.5)	0.87 (0.6, 1.28)	0.4920
Bayley III cognitive composite score < 70 – no./total no. (%)	34/471 (7.2)	38/503 (7.6)	0.91 (0.58, 1.43)	0.6870
Gross motor function level ≥ 2 – no./total no. (%)	26/479 (5.4)	23/511 (4.5)	1.17 (0.68, 2.01)	0.5597
Moderate/severe cerebral palsy – no./total no. (%)	20/479 (4.2)	20/511 (3.9)	1 (0.54, 1.83)	0.9971
Blindness – no./total no. (%)	5/479 (1)	8/511 (1.6)	0.67 (0.22. 2.02)	0.4789
Deafness – no./total no. (%)	12/479 (2.5)	12/511 (2.3)	1.16 (0.54, 2.49)	0.7013

Table 3. Medical Outcomes by Group

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Outcome	Low SpO2 (N=479)	High SpO2 (N=510)	Relative Risk for Low SpO2 vs. High SpO2 (95% CI)	Adjusted difference in means (95% CI)	Adjusted P-value
Bayley Scales of Infant Development III					
Cognitive composite < 70					
Cognitive composite <85	105/471 (22.3)	131/502 (26.1)	0.86 (0.69, 1.07)		0.1831
Mean Scores					0.2940
Median Scores					
					0.8121
					0.3016
Neurologic findings					0.8948
Mild cerebral palsy	23/459 (5.0)	21/490 (4.3)	1.16 (0.66, 2.02)		0.6105

Moderate cerebral palsy	11/447 (2.5)	10/479 (2.1)	1.19 (0.52, 2.71)	0.6873
Severe cerebral palsy	9/445 (2.0)	10/479 (2.1)	0.95 (0.39, 2.27)	0.9026
Any cerebral palsy	43/479 (9.0)	41/510 (8.0)	1.12 (0.76, 1.65)	0.5766
Abnormal neurologic exam	108/479 (22.5)	114/510 (22.4)	1.02 (0.82, 1.27)	0.8606
Vision findings				
Strabismus	46/478 (9.6)	41/509 (8.1)	1.2 (0.7, 1.8)	0.3845
Nystagmus	22/479 (4.6)	12/509 (2.4)	1.95 (0.94, 4.07)	0.0737
Tracks 180 degrees	462/476 (97.1)	492/506 (97.2)	1 (0.98, 1.02)	0.9330
Corrective lenses both eyes vs. normal both eyes	21/468 (4.5)	20/492 (4.1)	1.14 (0.62, 2.08)	0.6774
Blind, some function, both eyes	3/450 (0.7)	2/474 (0.4)	1.56 (0.27, 8.95)	0.6151
Blind, no useful vision, both eyes	2/449 (0.4)	4/476 (0.8)	0.54 (0.1, 2.95)	0.4789
Other abnormal vision	6/453 (1.3)	12/484 (2.5)	0.55 (0.21, 1.46)	0.2301
Eye surgery	31/477 (6.5)	67/508 (13.2)	0.52 (0.35, 0.78)	0.0014
Medicines				
Bronchodilators	159/475 (33.5)	185/505 (36.6)	0.92 (0.78, 1.09)	0.3583
Steroids	95/475 (20.0)	108/505 (21.4)	0.92 (0.72, 1.18)	0.5016

Diuretics	15/475 (3.2)	14/505 (2.8)	1.16 (0.58,2.34)	0.6717
Anticonvulsants	12/478 (2.5)	12/510 (2.4)	1.08 (0.49, 2.37)	0.8514
Readmission	210/478 (43.9)	238/510 (46.7)	0.94 (0.82, 1.08)	0.4111
Readmission for respiratory reason	110/470 (23.4)	127/503 (25.2)	0.93 (0.74, 1.16)	0.5114
No Readmission for growth/nutrition	12/470 (2.6)	13/503 (2.6)	1.05 (0.49, 2.25)	0.8953

From: Roger Faix
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: CONFIDENTIAL SUPPPORT FU PAPER
Date: Wednesday, November 02, 2011 6:59:09 PM
Attachments: Vaucher SUPPORT FU CPAP PAPERwith FigureTables123_10272001_forFUP_PIs.docx

Copy was sent directly to Yvonne as well.

Roger

From: Roger Faix
Sent: Wednesday, November 02, 2011 4:54 PM
To: yvaucher@ucsd.edu
Subject: FW: CONFIDENTIAL SUPPPORT FU PAPER

Hi Yvonne!

I have a few suggested changes and comments on the manuscript (on which you CLEARLY worked very hard). Comments and suggested changes are embedded in the attached manuscript. Proposed changes are in red bold font, while comments and questions are in purple bold font. I hope they are useful for you.

Roger

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]
Sent: Thursday, October 27, 2011 12:06 PM
To: 'yvaucher@ucsd.edu'; 'MPeralta@PEDS.UAB.EDU'; 'wcarlo@peds.uab.edu'; 'Finer, Neil'; 'alaptook@WIHRI.org'; 'kurt.schibler@cchmc.org'; 'mcw3@cwru.edu'; 'Gantz, Marie'; Bradley Yoder; Roger Faix; 'Abhik Das'; 'Rich, Wade'; 'nxs5@cwru.edu'; 'vohr'; 'Kim Yolton'; 'Roy.Heyne@utsouthwestern.edu'; (b)(6) @aol.com'; 'golds005@mc.duke.edu'; 'Evans, Patricia W'; 'Acarregui, Michael'; 'Adams-Chapman, Ira'; 'Susan Hintz'; 'apappas@med.wayne.edu'; 'Poindexter, Brenda B'; 'emcgowan@tuftsmedicalcenter.org'; 'Ehrenkranz, Richard'; 'abodnar@utah.gov'; 'Bauer, Charles R'; 'JaFuller@salud. unm. edu (JaFuller@salud.unm.edu)'; 'gary_myers@URMC.Rochester.edu'; 'Michael O`Shea'
Cc: 'Pablo.Sanchez@UTSouthwestern.edu'; 'Seetha Shankaran'; 'Barbara Stoll'; 'vohr'; 'Krisa VanMeurs'; 'Kathleen.A.Kennedy@uth.tmc.edu'; 'goldb008@mc.duke.edu'; 'Phelps, Dale'; 'edward-bell@uiowa.edu'; 'Kristi Watterberg'; 'Frantz, Ivan'; Archer, Stephanie (NIH/NICHD) [E]; 'Duara, Shahnaz'
Subject: RE: CONFIDENTIAL SUPPPORT FU PAPER

Here is the other paper. Please send comments back to Yvonne by November 4.

Thanks

Rose

Rosemary D. Higgins, MD
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From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Thursday, October 27, 2011 9:23 AM

To: 'yvaucher@ucsd.edu'; 'MPeralta@PEDS.UAB.EDU'; 'wcarlo@peds.uab.edu'; 'Finer, Neil'; 'alaptook@WIHRI.org'; 'kurt.schibler@cchmc.org'; 'mcw3@cwru.edu'; 'Gantz, Marie'; Bradley Yoder; Roger Faix; Abhik Das; 'Rich, Wade'; 'nxs5@cwru.edu'; vohr; 'Kim Yolton'; 'Roy.Heyne@utsouthwestern.edu'; (b)(6) @aol.com'; 'golds005@mc.duke.edu'; 'Evans, Patricia W'; Acarregui, Michael; Adams-Chapman, Ira; Susan Hintz; 'apappas@med.wayne.edu'; Poindexter, Brenda B; 'emcgowan@tuftsmedicalcenter.org'; 'Ehrenkranz, Richard'; abodnar@utah.gov; 'Bauer, Charles R'; 'JaFuller@salud. unm. edu (JaFuller@salud.unm.edu)'; 'gary_myers@URMC.Rochester.edu'; 'Michael O`Shea'
Cc: 'Pablo.Sanchez@UTSouthwestern.edu'; Seetha Shankaran; Barbara Stoll; vohr; 'Krisa VanMeurs'; 'Kathleen.A.Kennedy@uth.tmc.edu'; 'goldb008@mc.duke.edu'; Phelps, Dale; 'edward-bell@uiowa.edu'; Kristi Watterberg; Frantz, Ivan; Archer, Stephanie (NIH/NICHD) [E]; Duara, Shahnaz
Subject: CONFIDENTIAL SUPPPORT FU PAPER

Hi,

I have attached the SUPPORT Oximetry FU paper – I have cc'd the SUPPORT PI's from the steering committee during the SUPPORT Study recruitment also on the list even though this is a FU paper.

Please send you comments to Dr. Peralta by November 4.

I expect to have the CPAP/surf paper shortly

Thanks

Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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higginsr@mail.nih.gov

From: Myriam Peralta, M.D. [mailto:MPeralta@peds.uab.edu]
Sent: Tuesday, October 25, 2011 7:03 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Support NDI_10-21-2011

Rose here is the last version of the manuscript I had added comments from everyone who send this to me. I know I can add more to the discussion perhaps we can talk more on the meeting, Thank you

From: Vaucher, Yvonne
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Please forward to SUPPORT subcommittee
Date: Tuesday, November 01, 2011 12:44:06 PM

To the SUPPORT subcommittee,

Thank you all for your very helpful and insightful suggestions on the SUPPORT CPAP paper and PAS abstract. I really appreciated your feedback and I hope I was able to successfully incorporate/accommodate all of them. If not let me know!

Yvonne

From: Vaucher, Yvonne
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Revised SUPPORT CPAP AbstractPAS 2012
Date: Monday, October 31, 2011 11:40:59 PM
Attachments: SUPPORTCPAPvsSURFAbstractPAS2012rev_10312011YEV.docx

Rose,

I belatedly found Laptook's recommendations which I just so added. Use this one instead.

Yvonne E. Vaucher, M.D., M.P.H.
Division of Neonatal/Perinatal Medicine
Clinical Professor of Pediatrics
UCSD School of Medicine

tele: 619-543-3759
FAX: 619-543-3812

Draft Preview of Abstract #750265
THIS COPY IS A DRAFT ONLY. YOUR FINAL PRINTOUT WILL BE AVAILABLE AT TIME OF SUBMISSION

First Author: Yvonne E Vaucher, MD,MPH
Responsible Author: Yvonne E Vaucher, MD,MPH
Presenting Author: Yvonne E Vaucher, MD,MPH
Contact Person: Yvonne E Vaucher, MD. MPH

Filename: 750265

2012 Eastern SPR Annual Meeting

Subspecialty: Neonatal Epidemiology & Follow-Up
Theme: Neonatal Medicine: Clinical Trials

Contact Author: Yvonne E Vaucher, MD. MPH
Department/Institution/Address: Pediatrics,Division of Neonatology, Univ California, San Diego, 200 West Arbor Drive MC 8774, San Diego, CA, 92103, United States
Phone: 1-619-543-3759 **Fax:** 1-619-543-3812 **E-mail:** yvaucher@ucsd.edu

Reponsible Author: Yvonne E Vaucher, MD,MPH
Department/Institution/Address: Pediatrics, Div. of neonatology, Univ of California, San Diego, 200 West Arbor Drive MC 8774, San Diego, CA, 92037-8774, United States
Phone: 1-619-543-3759 **Fax:** 1-619-543-3759
Responsible Author E-mail: yvaucher@ucsd.edu
Responsible Author Declaration: As the responsible author, I confirm that the individual listed as the sponsor has been contacted and given the opportunity to review the abstract and has subsequently agreed to sponsor this abstract.

Presenting Author: Yvonne E Vaucher, MD,MPH
Department/Institution/Address: Pediatrics, Div of Neonatology, 200 West Arbor Drive MC 8774, San Diego, CA, 92103-8774, United States
Phone: 1-619-543-3759 **Fax:** 1-619-543-3812
Presenting Author E-mail: yvaucher@ucsd.edu
The presenting author is member of these Alliance Societies:
Is Presenting Author a Trainee? No, Not a Trainee
Presenter Copyright Declaration:
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QUESTIONNAIRE INFORMATION

Eastern Society for Pediatric Research: Yes, Consider for Eastern SPR ONLY (not PAS/ASPR)
Pediatric Hospital Medicine: No, Do not consider this abstract for presentation at the Pediatric Hospital Medicine, July 19-22, 2012
Research Type: Clinical
Presentation Sabbath Conflict on: N/A
APA Special Interest Groups, Committees or Regions: None

AWARDS APPLIED FOR:

No awards selected

SPONSOR INFORMATION

Sponsoring Member for Eastern SPR abstract:

Sponsor Name:
Email:
Is the Sponsor an Author? Not yet indicated

Title: Neurodevelopmental Outcome of Extremely Premature Infants Enrolled in the SUPPORT trial: Early CPAP versus Intubation with Surfactant Administration

Yvonne E Vaucher, MD,MPH[1], Marie Gantz, PhD[2], Neil N Finer, MD[1] and SUPPORT Study Group[3]. [1]Division of Neonatology, Department of Pediatrics, University of California,, San Diego, CA, United States; [2]Statistics and Epidemiology, RTI International, Research Triangle Park, NC, United States and [3]Neonatal research Network, Eunice Kennedy Shriver National Institute of Child Health and Human Development, Bethesda, MD, United States.

Background: The multicenter SUPPORT randomized, controlled trial demonstrated that initial treatment with non-invasive CPAP is an alternative to early surfactant administration after intubation and is associated with similar rates of death or BPD in infants born at 24 to 27 weeks gestation.

Objective: We hypothesized that, compared to treatment with surfactant administration after intubation, treatment with early CPAP would decrease the composite outcome of death or neurodevelopmental impairment (NDI).

Design/Methods: The SUPPORT Trial enrolled 1316 extremely premature infants, 24 to 27 weeks gestation, randomized to receive either CPAP in the delivery room with a limited ventilation for strategy for two weeks (CPAP) or intubation with surfactant administration within one hour after birth (SURF). Infants were randomized within each center by gestational age strata (24 0/7-25 6/7 and 26 0/7-27 6/7 weeks). A standardized neurodevelopmental assessment was performed at 18-22 months corrected age. The primary, pre-specified composite outcome was death or NDI including at least one of the following: BSID-III cognitive score < 70, Gross Motor Function Classification Score (GMFCS) ≥2, moderate/severe cerebral palsy, bilateral blindness or permanent hearing impairment. Results were adjusted for gestational age, center and familial clustering.

Results: Death or NDI was determined for 1234/1316 (93.8%) enrolled infants. Death or NDI occurred in 27.9% (173/621) of CPAP and 29.9% (183/613) of SURF infants (p=0.39). Rates of death (CPAP-18.4 vs. SURF-21.9%, p=0.10), NDI alone (CPAP-0.9 vs. SURF 9.1%, p=0.44), cognitive score < 70 (CPAP-7.2 vs. SURF-7.6%, p=0.84), moderate/severe cerebral palsy (CPAP-4.1 vs. SURF-4.0%, p=0.82), GMFCS ≥2 (CPAP-5.1 vs. SURF 4.8%, p=0.95); blindness (CPAP-0.8 vs. SURF 1.5%, p=0.31), and permanent hearing impairment (CPAP-3.3 vs. SURF-1.5%, p=0.06) were similar in both treatment arms. There were fewer deaths in the most immature GA stratum [CPAP-26.4% (73/277) vs. SURF-35.5% (97/273), p=0.02], but no significant differences in neurodevelopmental outcomes between CPAP and SURF groups within each GA stratum.

Conclusions: We found no significant difference in the composite outcome of death or neurodevelopmental impairment at 18-22 months corrected age between extremely premature infants randomized to treatment with either early CPAP or intubation and surfactant administration.

Other Previews:
Abstract Disclosure Info:

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Wally Carlo, M.D."; "Finer, Neil"; "kurt.schibler@cchmc.org"; "mcw3@cwru.edu"; "Laptook, Abbot"; "Bradley Yoder"; "Das, Abhik"; "Gantz, Marie"; "Roger Faix"; "nxs5@cwru.edu"; "Rich, Wade"
Subject: FW: Please forward to SUPPORT subcommittee
Date: Tuesday, November 01, 2011 12:49:00 PM

From Yvonne--

Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
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higginsr@mail.nih.gov

-----Original Message-----
From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]
Sent: Tuesday, November 01, 2011 12:44 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Please forward to SUPPORT subcommittee

To the SUPPORT subcommittee,

Thank you all for your very helpful and insightful suggestions on the SUPPORT CPAP paper and PAS abstract. I really appreciated your feedback and I hope I was able to successfully incorporate/accommodate all of them. If not let me know!

Yvonne

From: Vaucher, Yvonne
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: SUPPORT CPAP Abstract
Date: Monday, October 31, 2011 11:21:02 PM
Attachments: SUPPORTCPAPvsSURFAbstractPAS2012_10312011YEV.docx

Rose,

Attached

Yvonne

Yvonne E. Vaucher, M.D., M.P.H.
Division of Neonatal/Perinatal Medicine
Clinical Professor of Pediatrics
UCSD School of Medicine

tele: 619-543-3759
FAX: 619-543-3812

First Author: Yvonne E Vaucher, MD,MPH
Responsible Author: Yvonne E Vaucher, MD,MPH
Presenting Author: Yvonne E Vaucher, MD,MPH
Contact Person: Yvonne E Vaucher, MD. MPH

Filename: 750265

2012 Eastern SPR Annual Meeting

Subspecialty: Neonatal Epidemiology & Follow-Up
Theme: Neonatal Medicine: Clinical Trials

Contact Author: Yvonne E Vaucher, MD. MPH
Department/Institution/Address: Pediatrics,Division of Neonatology, Univ California, San Diego, 200 West Arbor Drive MC 8774, San Diego, CA, 92103, United States
Phone: 1-619-543-3759 **Fax:** 1-619-543-3812 **E-mail:** yvaucher@ucsd.edu

Reponsible Author: Yvonne E Vaucher, MD,MPH
Department/Institution/Address: Pediatrics, Div. of neonatology, Univ of California, San Diego, 200 West Arbor Drive MC 8774, San Diego, CA, 92037-8774, United States
Phone: 1-619-543-3759 **Fax:** 1-619-543-3759
Responsible Author E-mail: yvaucher@ucsd.edu
Responsible Author Declaration: As the responsible author, I confirm that the individual listed as the sponsor has been contacted and given the opportunity to review the abstract and has subsequently agreed to sponsor this abstract.

Presenting Author: Yvonne E Vaucher, MD,MPH
Department/Institution/Address: Pediatrics, Div of Neonatology, 200 West Arbor Drive MC 8774, San Diego, CA, 92103-8774, United States
Phone: 1-619-543-3759 **Fax:** 1-619-543-3812
Presenting Author E-mail: yvaucher@ucsd.edu
The presenting author is member of these Alliance Societies:
Is Presenting Author a Trainee? No, Not a Trainee
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QUESTIONNAIRE INFORMATION

Eastern Society for Pediatric Research: Yes, Consider for Eastern SPR ONLY (not PAS/ASPR)
Pediatric Hospital Medicine: No, Do not consider this abstract for presentation at the Pediatric Hospital Medicine, July 19-22, 2012
Research Type: Clinical
Presentation Sabbath Conflict on: N/A
APA Special Interest Groups, Committees or Regions: None

AWARDS APPLIED FOR:

No awards selected

SPONSOR INFORMATION

Sponsoring Member for Eastern SPR abstract:
Sponsor Name:
Email:
Is the Sponsor an Author? Not yet indicated

Title: Neurodevelopmental Outcome of Extremely Premature Infants Enrolled in the SUPPORT trial: Early CPAP versus Intubation with Surfactant Administration

Yvonne E Vaucher, MD,MPH[1], Marie Gantz, PhD[2], Neil N Finer, MD[1] and SUPPORT Study Group[3]. [1]Division of Neonatology, Department of Pediatrics, University of California,, San Diego, CA, United States; [2]Statistics and Epidemiology, RTI International, Research Triangle Park, NC, United States and [3]Neonatal research Network, Eunice Kennedy Shriver National Institute of Child Health and Human Development, Bethesda, MD, United States.

Background: The multicenter SUPPORT randomized, controlled trial demonstrated that initial treatment with non-invasive CPAP is an alternative to early surfactant administration after intubation and is associated with similar rates of death or BPD in infants born at 24 to 27 weeks gestation.

Objective: We hypothesized that, compared to treatment with surfactant administration after intubation, treatment with early CPAP would decrease the composite outcome of death or neurodevelopmental impairment (NDI).

Design/Methods: The SUPPORT Trial enrolled 1316 extremely premature infants, 24 to 27 weeks gestation, randomized to receive treatment with either CPAP in the delivery room with limited ventilation if needed (CPAP) or intubation with surfactant administration within one hour after birth (SURF). Infants were randomized within each center by gestational age strata (24 0/7-25 6/7 and 26 0/7-27 6/7 weeks). A standardized neurodevelopmental assessment was performed at 18-22 months corrected age. The primary composite outcome was death or NDI which included at least one of the following: BSID-III cognitive score < 70, Gross Motor Function Classification Score (GMFCS) ≥2, moderate/severe cerebral palsy, bilateral blindness or permanent hearing impairment. Results were adjusted for gestational age, center and familial clustering.

Results: Death or NDI was determined for 1234/1316 (93.8%) infants enrolled in SUPPORT. Death or NDI occurred in 27.9% (173/621) of CPAP and in 29.9% (183/613) of SURF infants (p=0.39). Rates of death (CPAP-18.4 vs. SURF-21.9%, p=0.10), NDI alone (CPAP-0.9 vs. SURF 9.1%, p=0.44), cognitive score < 70 (CPAP-7.2 vs. SURF-7.6%, p=0.84), moderate/severe cerebral palsy (CPAP-4.1 vs. SURF-4.0%, p=0.82), GMFCS ≥2 (CPAP-5.1 vs. SURF 4.8%, p=0.95); blindness (CPAP-0.8 vs. SURF 1.5%, p=0.31), and permanent hearing impairment (CPAP-3.3 vs. SURF-1.5%, p=0.06) were similar in both treatment arms. There were fewer deaths in the most immature GA stratum [CPAP-26.4% (73/277) vs. SURF-35.5% (97/273), p=0.02], but no significant differences in neurodevelopmental outcomes between CPAP and SURF groups within each GA stratum.

Conclusions: We found no significant difference in the composite outcome of death or neurodevelopmental impairment at 18-22 months corrected age between extremely premature infants randomized to treatment with either early CPAP or intubation and surfactant administration.

Other Previews:
Abstract Disclosure Info:

From: Susan Hintz
To: Stephens, Bonnie
Cc: Vohr, Betty; Bann, Carla M.; Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT numbers
Date: Monday, October 31, 2011 6:06:54 PM

Did they have 18-22 month screening too? I don't recall - I should look back!

Thanks

Susan
On Oct 31, 2011, at 1:33 PM, Stephens, Bonnie wrote:

> Epicure saw 219 of 307 survivors at 11 years
>
> ---
>
> **From:** Susan Hintz [srhintz@stanford.edu]
> **Sent:** Monday, October 31, 2011 8:11 AM
> **To:** Vohr, Betty
> **Cc:** Bann, Carla M.; Stephens, Bonnie; Higgins, Rosemary (NIH/NICHD) [E]
> **Subject:** Re: SUPPORT numbers
>
> Thanks very much Carla!
>
> Bonnie - how does that number compare to other cohort with 18 mo autism screening and early School age follow up in this EGA range?
>
> Thanks
>
> Susan
>
> Sent from my iPhone
>
> On Oct 31, 2011, at 6:33 AM, "Vohr, Betty" <BVohr@WIHRI.org> wrote:
>
> > Carla,
> > Sounds good.
> > Betty
> >
> > ---
> >
> > **From:** Bann, Carla M. [mailto:cmb@rti.org]
> > **Sent:** Monday, October 31, 2011 9:25 AM
> > **To:** Susan Hintz; Stephens, Bonnie
> > **Cc:** Vohr, Betty; Higgins, Rosemary (NIH/NICHD) [E]
> > **Subject:** RE: SUPPORT numbers
> >
> > Susan and Bonnie,
> >
> > Based on the information Jenny gave me, 112 of those in the SUPPORT neuroimaging secondary who survived to discharge were also in the autism protocol. Of these 112, 27 (24%) failed one or more of the 3 autism screeners.
> >
> > Carla
> >
> > ---
> >
> > **From:** Bann, Carla M.

Sent: Wednesday, October 12, 2011 12:45 PM
To: 'Susan Hintz'; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Vohr, Betty; Stephens, Bonnie
Subject: RE: SUPPORT numbers

Susan,

You are right. Those numbers are the ones that were randomized into the SUPPORT trial. I will check with Jenny about figuring out which ones are in the neuroimaging secondary.

Carla

From: Susan Hintz [mailto:srhintz@stanford.edu]
Sent: Wednesday, October 12, 2011 11:54 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Vohr, Betty; Stephens, Bonnie; Bann, Carla M.
Subject: Re: SUPPORT numbers

One more thing Carla - As I think about the email below further, I just want to make sure we are talking about the same numbers. We need the number of patients in the autism protocol who are in the SUPPORT Neuroimaging secondary (not just randomized into SUPPORT trial) AND survived to discharge. Jenny Auman has that info, as well as those who had successful 18-22 month follow up visits.

Thanks

S

Sent from my iPhone

On Oct 12, 2011, at 8:14 AM, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> wrote:

> This may be the biggest group out there with imaging, medical outcomes, 18-22 month outcomes and school age information.
>
> Rose
>
> Rosemary D. Higgins, MD
> Program Scientist for the *Eunice Kennedy Shriver*
> NICHD Neonatal Research Network
> Pregnancy and Perinatology Branch
> CDBPM, NIH
> 6100 Executive Blvd., Room 4B03
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> Bethesda, MD 20892
> For overnight delivery use Rockville, MD 20852

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301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Vohr, Betty [mailto:BVohr@WIHRI.org]
Sent: Wednesday, October 12, 2011 11:08 AM
To: Stephens, Bonnie; Bann, Carla M.
Cc: srhintz@stanford.edu; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT numbers

Great !!

From: Stephens, Bonnie
Sent: Wednesday, October 12, 2011 11:04 AM
To: Bann, Carla M.
Cc: srhintz@stanford.edu; Vohr, Betty; Rosemary [E] Higgins
Subject: Re: SUPPORT numbers

Wow, not bad.

On Oct 11, 2011, at 3:12 PM, "Bann, Carla M." <cmb@rti.org> wrote:

> Hi Bonnie,
>
> It looks like 194 of the children from the autism protocol were randomized into the SUPPORT trial. Of those 194, 41 were positive on at least 1 of the 3 autism screeners.
>
> Carla

Carla M. Bann, Ph.D.
Fellow, Statistics and Psychometrics
Associate Editor, *Quality of Life Research*
Statistics and Epidemiology Unit
RTI International
P.O. Box 12194
Research Triangle Park, NC 27709-2194
Phone: (919) 485-2773
Fax: (919) 541-6722
E-mail: cmb@rti.org

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: SUPPORT PAS CPAP abstract
Date: Monday, October 31, 2011 3:43:00 PM
Attachments: PAS 2012SUPPORTCPAPAbstract09292011 AD MG WC RH YV ver3.0.docx

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]
Sent: Thursday, September 29, 2011 2:12 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: SUPPORT PAS CPAP abstract

Rose,

Could you look at the authors section and advise me how to list/arrange /change it?

Thanks.

Yvonne

Yvonne E. Vaucher, M.D., M.P.H.
Division of Neonatal/Perinatal Medicine
Clinical Professor of Pediatrics
UCSD School of Medicine

tele: 619-543-3759
FAX: 619-543-3812

PAS 2012 Abstract

Title: Neurodevelopmental Outcome after Early CPAP versus Intubation with Surfactant Administration in Extremely Preterm Infants Enrolled in the SUPPORT Trial

Yvonne E Vaucher, MD,MPH[1], Myriam Peralta-Carcelen, MD,MPH[2], Marie G Gantz, PhD[3], Neil N Finer, MD[1], Waldemar A Carlo, MD[2], Rose D Higgins, MD[4], NRN Follow-up PIs and SUPPORT Study Group. [1]Div.ision of Neonatology, Department of Pediatrics, University of California,, San Diego, CA, United States; [2]Division of Neonatology, University of Alabama at Birmingham, Birmingham, AL, United States; [3]Statistics and Epidemiology, RTI International, Research Triangle Park, NC, United States and [4]Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network, Bethesda, MD, United States.

Background: The recent multicenter SUPPORT randomized, controlled trial demonstrated that initial treatment with early, non-invasive CPAP is an alternative to early surfactant administration after intubation and is associated with similar rates of death or BPD in infants born at 24 to 27 weeks gestation.

Objective: We hypothesized that, compared to treatment with surfactant administration after intubation, treatment with early CPAP would decrease the composite outcome of mortality or neurodevelopmental impairment by 18-22 months corrected age.

Design/Methods: The SUPPORT trial enrolled 1316 infants, 24 to 27 weeks gestation, who were randomized to receive either CPAP in the delivery room with limited ventilation as needed (CPAP) or intubation with surfactant administration within one hour after birth (SURF). Infants were randomized within each center by two gestational age strata (24 0/7-25 6/7 and 26 0/7-27 6/7 weeks). A standardized neurodevelopmental assessment was performed on survivors at 18-22 months corrected age. The primary composite outcome was death or neurodevelopmental impairment (NDI) which included at least one of the following: Bayley Scales of Infant Development, 3rd ed., cognitive composite score < 70, Gross Motor Function Classification score of ≥2, moderate/severe cerebral palsy, bilateral blindness or permanent hearing impairment. Results were adjusted for gestational age stratum, center and familial clustering.

Results: Death or NDI was determined for 1234/1316 (93.8%) of infants enrolled in SUPPORT; 990 children were evaluated at 18-22 months corrected age. Death or NDI occurred in 27.9% (173/621) of the CPAP and in 29.9% (183/613) of the SURF infants (p=0.39). Rates of death (CPAP-18.4 vs. SURF-21.9%, p=0.10), and outcomes among survivors, including NDI alone (CPAP-10.9 vs. SURF 9.1%, p=0.44), cognitive score < 70 (CPAP-7.2 vs. SURF-7.6%, p=0.84), moderate/severe cerebral palsy (CPAP-4.1 vs. SURF-4.0%, p=0.82), blindness (CPAP-0.8 vs. SURF 1.5%, p=0.31), and permanent hearing impairment (CPAP-3.3 vs. SURF-1.5%, p=0.06) were similar in both treatment arms. Except for fewer deaths in the most immature GA stratum [CPAP-26.4% (73/277) vs. SURF-35.5% (97/273), aRR 0.73 (0.57,0.96), p=0.022], there were no statistically significant differences in these outcomes between CPAP and SURF groups within each GA stratum.

Conclusions: In extremely premature children born at 24-27 weeks gestation, there were no significant differences in death or neurodevelopmental outcomes at 18-22months corrected age between those treated with early CPAP in the delivery room and those treated with intubation and surfactant administration.

From: D"Angio, Carl
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Breathing Outcomes
Date: Friday, October 28, 2011 5:07:57 PM

Sounds fine.

Carl

Carl T. D'Angio, MD
Associate Professor of Pediatrics and Medical Humanities
Director, Neonatal Clinical Research
Director, Pediatric Clinical Research Office
Division of Neonatology
Golisano Children's Hospital
University of Rochester Medical Center
601 Elmwood Avenue, Box 651
Rochester, NY 14642
Phone (585) 273-4911, Fax (585) 461-3614
carl_dangio@urmc.rochester.edu

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, October 28, 2011 5:06 PM
To: D'Angio, Carl; Stevens, Timothy
Subject: Re: Breathing Outcomes

They are posted following the meeting (usually within a week or so)

From: D'Angio, Carl <Carl_Dangio@URMC.Rochester.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]; Stevens, Timothy <Timothy_Stevens@URMC.Rochester.edu>
Sent: Fri Oct 28 14:51:08 2011
Subject: RE: Breathing Outcomes

Rose,

What I remembered seeing were respiratory meds and readmissions, as you note. I couldn't recall whether other respiratory items were there, as well. I didn't see the slides from the talk at the Follow-up session yesterday up on the web yet. Which section will the be under when posted? Thanks.

Carl

Carl T. D'Angio, MD
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Director, Neonatal Clinical Research
Director, Pediatric Clinical Research Office
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University of Rochester Medical Center
601 Elmwood Avenue, Box 651
Rochester, NY 14642
Phone (585) 273-4911, Fax (585) 461-3614
carl_dangio@urmc.rochester.edu

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, October 28, 2011 2:45 PM
To: Stevens, Timothy
Cc: D'Angio, Carl
Subject: RE: Breathing Outcomes

Tim
We do have some readmission data and medication information in the FU papers, but the focus is not pulmonary. Is this what you are referring to? Also, the SUPPORT subcommittee will be involved in the breathing outcomes analyses and manuscripts.

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Stevens, Timothy [mailto:Timothy_Stevens@URMC.Rochester.edu]
Sent: Friday, October 28, 2011 2:25 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: D'Angio, Carl
Subject: Breathing Outcomes

Hi Rose,

Carl mentioned that the 18-22 month follow-up studies for SUPPORT may include pulmonary as well as neurologic outcomes. For Breathing Outcomes, the primary outcome is respiratory symptoms at 18-22 months with med and health care utilization as important secondary outcomes.

How do you think presentation of the pulmonary outcome data should be coordinated between SUPPORT Follow-up and Breathing Outcomes?

Thanks

Tim

From: Vaucher, Yvonne
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Finer, Neil; Vaucher, Yvonne
Subject: SUPPORTCAPAPvsSurfactant ND Outcome
Date: Thursday, October 27, 2011 1:41:13 PM
Attachments: Vaucher SUPPORT FU_CPAP PAPERwith FigureTables123_10272001_forFUP_PIs.docx

Here it is.

Yvonne

Yvonne E. Vaucher, M.D., M.P.H.
Division of Neonatal/Perinatal Medicine
Clinical Professor of Pediatrics
UCSD School of Medicine

tele: 619-543-3759
FAX: 619-543-3812

From: Finer, Neil
To: Jerold Lucey; Higgins, Rosemary (NIH/NICHD) [E]; Martinez, Fernando; Karen Bidus
Subject: RE: Dr. Finer - Hot Topics
Date: Thursday, October 27, 2011 1:35:12 AM

Thanks Jerry
Neil

From: Jerold Lucey [mailto:(b)(6)@yahoo.com]
Sent: Wednesday, October 26, 2011 7:21 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Martinez, Fernando; Karen Bidus
Cc: Finer, Neil
Subject: Re: Dr. Finer - Hot Topics

He should come as a speaker and guest discussant.... Jerry

Jerold F. Lucey MD. FAAP
Prof. of Pediatrics, Emeritus
University of Vermont
Editor-in-Chief, Pediatrics, Emeritus

email: (b)(6)@yahoo.com
(b)(6)
(b)(6) (Winter-Spring)
(b)(6)
(b)(6) (Summer-Fall)

From: "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>
To: "'Martinez, Fernando'" <fmartinez@ucsd.edu>; 'Gail M. Murphy' <info@hottopics.org>; 'Jerold Lucey' (b)(6)@yahoo.com>; Karen Bidus <kbidus@nemours.org>
Cc: "Finer, Neil" <nfiner@ucsd.edu>
Sent: Wednesday, October 26, 2011 4:18 PM
Subject: RE: Dr. Finer - Hot Topics

Fernando-
I have included Gail, Jerry and Karen on the email as they would need to answer your question

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research

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Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Martinez, Fernando [mailto:fmartinez@ucsd.edu]
Sent: Wednesday, October 26, 2011 3:36 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Finer, Neil
Subject: Dr. Finer - Hot Topics

Dear Dr. Higgins,

I hope this e-mail finds you well.

I am writing on behalf of Dr. Finer, who is planning on presenting SUPPORT at the Hot Topics meeting in December. He asked me to contact you regarding the registration for the meeting – we would be grateful if you could please let us know if he needs to pay the fee.

Many thanks for your time.

Kind regards,
Fernando

Fernando I. Martinez
Administrative Supervisor
Assistant to Division Director, Dr. Neil N. Finer
UC San Diego School of Medicine
UC San Diego Medical Center, Hillcrest
Department of Pediatrics
Division of Neonatal-Perinatal Medicine
402 Dickinson St., MPF 1-140
San Diego, CA 92103-8774
Telephone: 619.543.3759
Facsimile: 619.543.3812

Please consider the environment and don't print this e-mail unless you really need to.

From: Finer, Neil
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Dr. Finer - Hot Topics
Date: Wednesday, October 26, 2011 4:53:03 PM

Thanks Rose
I will pay if necessary
Neil

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, October 26, 2011 1:37 PM
To: Finer, Neil
Subject: RE: Dr. Finer - Hot Topics

I will let them know you were one of the mail trial PI's

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Wednesday, October 26, 2011 4:36 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Dr. Finer - Hot Topics

Yes
I just needed to know if I need to pay to come to Hot Topics
Thanks
Neil

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, October 26, 2011 1:29 PM
To: Martinez, Fernando; Finer, Neil
Subject: FW: Dr. Finer - Hot Topics

Is Yvonne presenting?

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH

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301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Bidus, Karen [mailto:kbidus@NEMOURS.ORG]
Sent: Wednesday, October 26, 2011 4:27 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Dr. Finer - Hot Topics

Dr. Higgins-

I am confused - I have Dr. Peralta and Dr. Vaucher presenting? if we are talking about the NICHD Support Trail outcomes piece?

Karen Bidus
Director, Office of CME
Alfred I. duPont Hospital for Children
302-651-6752

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, October 26, 2011 4:18 PM
To: 'Martinez, Fernando'; 'Gail M. Murphy'; 'Jerold Lucey'; Bidus, Karen
Cc: Finer, Neil
Subject: RE: Dr. Finer - Hot Topics

Fernando-
I have included Gail, Jerry and Karen on the email as they would need to answer your question

Thanks
Rose

Rosemary D. Higgins, MD

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Many thanks for your time.

Kind regards,
Fernando

Fernando I. Martinez
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Assistant to Division Director, Dr. Neil N. Finer
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San Diego, CA 92103-8774
Telephone: 619.543.3759
Facsimile: 619.543.3812

Please consider the environment and don't print this e-mail unless you really need to.

From: Martinez, Fernando
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Dr. Finer - Hot Topics
Date: Wednesday, October 26, 2011 4:18:49 PM

Many thanks, Dr. Higgins.

Fernando

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, October 26, 2011 1:18 PM
To: Martinez, Fernando; 'Gail M. Murphy'; 'Jerold Lucey'; Karen Bidus
Cc: Finer, Neil
Subject: RE: Dr. Finer - Hot Topics

Fernando-
I have included Gail, Jerry and Karen on the email as they would need to answer your question

Thanks
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Sent: Wednesday, October 26, 2011 3:36 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
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Telephone: 619.543.3759
Facsimile: 619.543.3812

Please consider the environment and don't print this e-mail unless you really need to.

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "pbarnes@stanford.edu"
Cc: "srhintz@stanford.edu"
Subject: Re: Fwd: SPR absract SUPPORT Trial
Date: Friday, October 21, 2011 10:54:32 AM

I told folks to get back to me by monday

Thanks
Rose

----- Original Message -----
From: Patrick David Barnes M.D. <pbarnes@stanford.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: 'srhintz@stanford.edu' <srhintz@stanford.edu>
Sent: Fri Oct 21 10:53:45 2011
Subject: Re: Fwd: SPR absract SUPPORT Trial

Deadline is 10-27-11 next thursday 11:59 pm EDT.
PB

----- Original Message -----
From: Rosemary Higgins (NIH/NICHD) [E] <higginsr@mail.nih.gov>
To: 'pbarnes@stanford.edu' <pbarnes@stanford.edu>, 'srhintz@stanford.edu' <srhintz@stanford.edu>
Sent: Fri, 21 Oct 2011 05:39:03 -0700 (PDT)
Subject: Re: Fwd: SPR absract SUPPORT Trial

What is the deadline?
Thanks
Rose

----- Original Message -----
From: Patrick David Barnes M.D. <pbarnes@stanford.edu>
To: Susan Hintz <srhintz@stanford.edu>
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Fri Oct 21 00:40:03 2011
Subject: Re: Fwd: SPR absract SUPPORT Trial

Thanks so much.
Pat Barnes

----- Original Message -----
From: Susan Hintz <srhintz@stanford.edu>
To: Rosemary Higgins <higginsr@mail.nih.gov>, Pat Barnes <pbarnes@stanford.edu>
Sent: Thu, 20 Oct 2011 21:36:10 -0700 (PDT)
Subject: Fwd: SPR absract SUPPORT Trial

Hi Rose,

Below is Pat's abstract draft for the Society for Pediatric Radiology. It is similar to the last year PAS abstract I presented, and Pat has not added any additional data (particularly NO outcomes data), so I am hoping it will be able to move through clearance as quickly as possible. He has already sent to Dorothy and Tom. As a co-author, please feel free to make suggested changes to the text Pat has

included below. I am also attaching a disclosure for your completion and e-signature.

Pat - I am attaching my completed disclosure. I also made a few other little comments/suggestions in addition to what I sent you before. If you have more space, you could make a comment regarding "Cerebellar injury and moderate-severe WMA by brain MRI was more common among the more premature infants (24-25 weeks EGA)."

Rose - I assume Pat should just send the abstract to the other co-authors and for their disclosure completion. Pat - The other email addresses:

wrage@rti.org
hcheng@rti.org
adas@rti.org
nfiner@ucsd. edu
higginsr@mail.nih.gov

Thanks,

Susan

Begin forwarded message:

> From: Susan Hintz <srhintz@stanford.edu>
> Date: October 20, 2011 9:07:42 PM PDT
> To: "Patrick David Barnes M.D." <pbarnes@stanford.edu>
> Cc: Dorothy Bulas <dbulas@cnmc.org>, Tom Slovis
> <tslovis@med.wayne.edu>
> Subject: Re: SPR absract SUPPORT Trial
>
> Hi Pat
>
> I suspect you are up against space issues - I guess the radiology
> abstracts are even more restrictive than the pediatric societies. I
> have suggested some changed below in red. Also, just to be clear,
> there were more patients with early and late US and MRI, it is just
> that only 480 had MRI and late CUS within 2 weeks of each other, so
> we had to limit the comparative analysis of the cohort to that group.
>
> I would recommend changing the order of the authors so all you
> radiology experts are up front for this submission. I will take up
> the rear, in the senior author position.
>
> Pat, I will send this to Rose, and also send you other email
> addresses.
>
> Susan
>
> On Oct 20, 2011, at 7:57 PM, Patrick David Barnes M.D. wrote:
>
>> Dear Dorothy and Tom - please see draft SPR abstract below; please
>> also complete attached disclosure form (e-signature) and return to
>> me asap.
>> Thanks,
>> Pat Barnes

>>
>>
>> Control ID: 1260741 Contact Name: Patrick Barnes Current Character
>> Count: 1180 out of 2200
>>
>> PD Barnes, D Bulas, TL Slovis, LA Wrage, H Cheng, RD Higgins, N
>> Finer, A Das, SR Hintz, for the SUPPORT Subcommittee and the NICHD
>> Neonatal Research Network
>>
>>
>> Title
>> Magnetic Resonance Imaging (MRI) and Ultrasonography (US) of the
>> Extreme Preterm Brain
>>
>>
>>
>> Purpose or Case Report
>> To compare near-term brain MRI with early and late brain US in a
>> large cohort of extreme preterm newborns.
>>
>>
>> Methods & Materials
>> A prospective secondary study was done of near-term MRI (mean PMA
>> 37.9 wk) as compared with early (4-14 days postnatal age) and late
>> (34-42 weeks PMA) US in extremely preterm infants (mean 25.9 weeks
>> EGA) as part of the multi-center, NICHD Neonatal Research Network
>> (NRN) Surfactant Positive Airway Pressure and Oximetry Trial
>> (SUPPORT). The cohort comprises 480 infants who had early CUS, and
>> late US and MRI within 2 weeks of each other. Independent MRI and
>> US central readers were masked to the clinical and other
>> neuroimaging findings.
>>
>>
>> Results
>> 306 (89.5%) of 342 infants with normal late US had normal near term
>> MRI or only mild white matter abnormalities (WMA) (Inder TE, et.
>> al., J Peds, 2003); the remaining 36 (10.5%) had moderate-severe
>> WMA. All 18 infants with late US findings of moderate-severe
>> ventriculomegaly (VMG) had MRI findings of moderate-severe WMA,
>> moderate-severe VMG, or cystic lesions. 76% of 46 infants with
>> grade 3 or 4 hemorrhage on early US had moderate-severe WMA on
>> MRI. On MRI, cerebellar abnormalities were present in 79 (16.5%)
>> and cerebral gray matter abnormalities were present in 6 (1%).
>> Posterior fossa lesions were seen on US in 1.6%, but mastoid views
>> were included in only about 50% of the centrally read US.
>>
>> Conclusions
>> In the largest extreme preterm cohort to date with near-term MRI
>> and serial US, 19% had mod-severe WMA on brain MRI, similar to
>> previous reports. Cerebellar abnormalities were detected more
>> frequently by MRI than by US. Neurodevelopmental outcomes at 18-22
>> months and school age will assess the relative and combined values
>> of MRI and US as outcome predictors.
>

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Susan Hintz"
Cc: "Patrick David Barnes M.D."
Subject: RE: SPR abstract SUPPORT Trial
Date: Friday, October 21, 2011 9:32:00 AM

I found it on the web - pretty easy as you have given me the society name -
Take care
Rose

Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
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For overnight delivery use Rockville, MD 20852
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301-496-3790 (FAX)
higginsr@mail.nih.gov

-----Original Message-----
From: Susan Hintz [mailto:srhintz@stanford.edu]
Sent: Friday, October 21, 2011 9:31 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Patrick David Barnes M.D.
Subject: Re: SPR abstract SUPPORT Trial

It is Pediatric Radiology - but I see you have that all set in subsequent emails!

Thanks

S

Sent from my iPhone

On Oct 21, 2011, at 6:06 AM, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> wrote:

> Just to be sure - is this for the Society of PEDIATRIC Research Annual meeting in San Francisco - April 16-20??
> Let me know and I can send to the subcommittee/steering committee for approval.
> Thanks
> Rose
>
> Rosemary D. Higgins, MD
> Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network
> Pregnancy and Perinatology Branch
> CDBPM, NIH
> 6100 Executive Blvd., Room 4B03
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> 301-435-7909

> 301-496-5575
> 301-496-3790 (FAX)
> higginsr@mail.nih.gov
>
>
> -----Original Message-----
> From: Patrick David Barnes M.D. [mailto:pbarnes@stanford.edu]
> Sent: Friday, October 21, 2011 12:40 AM
> To: Susan Hintz
> Cc: Higgins, Rosemary (NIH/NICHD) [E]
> Subject: Re: Fwd: SPR absract SUPPORT Trial
>
> Thanks so much.
> Pat Barnes
>
> ----- Original Message -----
> From: Susan Hintz <srhintz@stanford.edu>
> To: Rosemary Higgins <higginsr@mail.nih.gov>, Pat Barnes <pbarnes@stanford.edu>
> Sent: Thu, 20 Oct 2011 21:36:10 -0700 (PDT)
> Subject: Fwd: SPR absract SUPPORT Trial
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> Hi Rose,
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> Pat - I am attaching my completed disclosure. I also made a few other
> little comments/suggestions in addition to what I sent you before. If
> you have more space, you could make a comment regarding "Cerebellar
> injury and moderate-severe WMA by brain MRI was more common among the
> more premature infants (24-25 weeks EGA)."
>
> Rose - I assume Pat should just send the abstract to the other co-
> authors and for their disclosure completion. Pat - The other email
> addresses:
>
> wrage@rti.org
> hcheng@rti.org
> adas@rti.org
> nfiner@ucsd. edu
> higginsr@mail.nih.gov
>
> Thanks,
>
> Susan
>
> Begin forwarded message:
>
>> From: Susan Hintz <srhintz@stanford.edu>
>> Date: October 20, 2011 9:07:42 PM PDT
>> To: "Patrick David Barnes M.D." <pbarnes@stanford.edu>

>> Cc: Dorothy Bulas <dbulas@cnmc.org>, Tom Slovis
>> <tslovis@med.wayne.edu>
>> Subject: Re: SPR absract SUPPORT Trial
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>> Hi Pat
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>>
>> I would recommend changing the order of the authors so all you
>> radiology experts are up front for this submission. I will take up
>> the rear, in the senior author position.
>>
>> Pat, I will send this to Rose, and also send you other email
>> addresses.
>>
>> Susan
>>
>> On Oct 20, 2011, at 7:57 PM, Patrick David Barnes M.D. wrote:
>>
>>> Dear Dorothy and Tom - please see draft SPR abstract below; please
>>> also complete attached disclosure form (e-signature) and return to
>>> me asap.
>>> Thanks,
>>> Pat Barnes
>>>
>>>
>>> Control ID: 1260741 Contact Name: Patrick Barnes Current Character
>>> Count: 1180 out of 2200
>>>
>>> PD Barnes, D Bulas, TL Slovis, LA Wrage, H Cheng, RD Higgins, N
>>> Finer, A Das, SR Hintz, for the SUPPORT Subcommittee and the NICHD
>>> Neonatal Research Network
>>>
>>>
>>> Title
>>> Magnetic Resonance Imaging (MRI) and Ultrasonography (US) of the
>>> Extreme Preterm Brain
>>>
>>>
>>>
>>> Purpose or Case Report
>>> To compare near-term brain MRI with early and late brain US in a
>>> large cohort of extreme preterm newborns.
>>>
>>>
>>> Methods & Materials
>>> A prospective secondary study was done of near-term MRI (mean PMA
>>> 37.9 wk) as compared with early (4-14 days postnatal age) and late
>>> (34-42 weeks PMA) US in extremely preterm infants (mean 25.9 weeks
>>> EGA) as part of the multi-center, NICHD Neonatal Research Network
>>> (NRN) Surfactant Positive Airway Pressure and Oximetry Trial
>>> (SUPPORT). The cohort comprises 480 infants who had early CUS, and

>>> late US and MRI within 2 weeks of each other. Independent MRI and
>>> US central readers were masked to the clinical and other
>>> neuroimaging findings.
>>>
>>>
>>> Results
>>> 306 (89.5%) of 342 infants with normal late US had normal near term
>>> MRI or only mild white matter abnormalities (WMA) (Inder TE, et.
>>> al., J Peds, 2003); the remaining 36 (10.5%) had moderate-severe
>>> WMA. All 18 infants with late US findings of moderate-severe
>>> ventriculomegaly (VMG) had MRI findings of moderate-severe WMA,
>>> moderate-severe VMG, or cystic lesions. 76% of 46 infants with
>>> grade 3 or 4 hemorrhage on early US had moderate-severe WMA on
>>> MRI. On MRI, cerebellar abnormalities were present in 79 (16.5%)
>>> and cerebral gray matter abnormalities were present in 6 (1%).
>>> Posterior fossa lesions were seen on US in 1.6%, but mastoid views
>>> were included in only about 50% of the centrally read US.
>>>
>>> Conclusions
>>> In the largest extreme preterm cohort to date with near-term MRI
>>> and serial US, 19% had mod-severe WMA on brain MRI, similar to
>>> previous reports. Cerebellar abnormalities were detected more
>>> frequently by MRI than by US. Neurodevelopmental outcomes at 18-22
>>> months and school age will assess the relative and combined values
>>> of MRI and US as outcome predictors.
>>
>
>

From: Finer, Neil
To: Gantz, Marie; wacarlo@uab.edu; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik
Subject: RE: SGA in CPAP vs. surfactant groups
Date: Wednesday, October 19, 2011 7:05:59 PM

HI Marie
Thanks for sending these
I would not make a special case of this
The difference in death at 36 weeks remains and the differences all favor the CPAP infants
Neil

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Wednesday, October 19, 2011 2:11 PM
To: Finer, Neil; wacarlo@uab.edu; Higgins, Rosemary (NIH/NICHD)
Cc: Das, Abhik
Subject: SGA in CPAP vs. surfactant groups

Neil, Wally and Rose,

In Table 1 create for the FU papers, there was a significant difference in the percentage of SGA infants between the CPAP and surfactant groups in the full SUPPORT population of 1316 infants. This difference was due in large part to an imbalance in the 24-25 week GA stratum. We had not recognized this imbalance before doing the analyses for the FU papers, because SGA was not one of the variables created for the primary SUPPORT analyses. In light of this difference between the CPAP and surfactant groups, Abhik and I decided to redo the analyses of death in the 24-25 week GA stratum, controlling for SGA. The results are attached. After adding SGA as a covariate in the models to predict death at 36 weeks PMA, in-hospital, and at 18-22 months adjusted age, only the difference in death at 36 weeks PMA remained statistically significant. Although the other results are no longer statistically significant, they still provide some evidence (albeit weaker than before) that there were differences in death between the groups. Abhik and I thought we needed to let you know that we had looked at this and share the results with you.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-8255

From: Kennedy, Kathleen A
To: dale_phelps@urmc.rochester.edu; Wrage, Lisa Ann (wrage@rti.org); Higgins, Rosemary (NIH/NICHD) [E]
Subject: Yet another abstract revision
Date: Tuesday, October 18, 2011 4:23:01 PM
Attachments: ROP Natural History PAS Abstract.doc

Thanks to Ed Bell for noticing that the PAS decreased the abstract limit by 35%. I should have known the previous generous allocation was too good to be true. We were at about 80% of the old limit, it went up to 140%, and I've now whacked it back to 99%. It's not as nicely worded as it was before but most of the content is still there. I took out the white vs non-white comparison and a few of the population flow numbers, but mostly I did it by whacking out words and using a few more abbreviations. Please let me know if you think I've removed anything too important or if it doesn't make sense now.

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Evaluating the Retinopathy of Prematurity (ROP) Screening Guidelines for 24-27 Week Gestational Age (GA) Infants

Kathleen A. Kennedy MD MPH, Lisa Wrage, MPH, Dale L. Phelps MD, Rosemary D. Higgins on behalf of the SUPPORT Subcommittee for the NICHD Neonatal Research Network

Background:
Timely detection of treatable ROP is important for optimal outcomes. The 2006 screening guidelines are based on data from infants born in 1986-1997: screening should begin by 31 wks postmenstrual age (PMA = GA + postnatal age) and continue until the vessels have reached zone III at ≥ 35 wks or, for infants without prethreshold ROP, until a PMA of 45 wks. Since the 1980s, survival of lower GA infants has increased and earlier treatment of ROP (Type 1 ROP: stage 3 or ROP with plus disease in zone I or stage 2-3 with plus disease in zone II) is recommended.

Objective:
To validate current recommendations for ROP screening in 24-27 wk GA infants.

Design/Methods:
In the NICHD Network SUPPORT trial, severe ROP (Type 1 ROP or treatment with laser, cryotherapy, or bevacizumab) or death was the primary outcome for the O_2 saturation target arm of the factorial trial. Infants 24 0/7 to 27 6/7 wks GA with consent prior to delivery were eligible. Examinations followed current screening recommendations and used the international classification of ROP. Exam results were collected until a study endpoint was reached: ROP treatment, full vascularization to the ora serrata, vascularization in zone III in 2 consecutive exams, or 55 wks PMA.

Results:
1316 infants were enrolled. 1091 (83%) survived to the age of ROP determination. 997 (91%) of these infants had a definitive ROP outcome. 644 infants developed ROP of any severity (138 met criteria for severe ROP); 353 had no ROP. Among infants with ROP, 642/644 (99.7%) of infants with any ROP and 128/138 (93%) of infants with severe ROP had sufficient data (no missing or delayed exams before diagnosis) to determine the age of onset of ROP. As expected, infants with severe ROP were less mature [mean(SD) 25.5(0.9) wks vs 26.8(0.9) wks, p<0.0001], lower birth weight [mean(SD) 708(148)g vs 942(173)g, p<0.0001], and more likely to be White race (44% vs 35%, p=0.07) than infants with no ROP. For the infants with ROP and known age of onset, the PMAs at which selected percentiles reached diagnosis are shown in the table:

ROP type (number of infants)	Cumulative % with Diagnosis of ROP						
	1%	5%	25%	50%	75%	95%	99%
	Postmenstrual Age (weeks)						
Diagnosis of any ROP (n=642)	30.4	31.4	32.7	33.9	35.1	37.9	41.0
Diagnosis of severe (Type 1/Treated) ROP (n=128)	32.7	33.9	35.1	36.4	38.6	43.3	45.0

The PMA at onset of severe ROP ranged from 32.1 to 53.1 wks. In this referral center cohort of 997 infants, 0.5% were diagnosed with severe ROP after back transfer; 1.0% (7% of infants with severe ROP) reached severe ROP criteria after discharge.

Our data are consistent with the 2006 ROP screening guidelines. In these 997 infants, we did not observe ROP needing treatment before 32 wks PMA; only 1 infant was diagnosed with severe ROP after

45 wks PMA. A limitation of this study is that infants < 24 wks GA were not enrolled and these data may not be generalizable to less mature infants.

From: Finer, Neil
To: Higgins, Rosemary (NIH/NICHD) [E]; 'wcarlo@peds.uab.edu'
Subject: RE: Abstract again
Date: Monday, October 17, 2011 7:47:38 PM

Absolutely
Thanks
Neil

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, October 17, 2011 4:23 PM
To: Finer, Neil; 'wcarlo@peds.uab.edu'
Subject: Re: Abstract again

Neil/Wally
Shall I send to the subcommittee for input?
Thanks
Rose

From: Finer, Neil <nfiner@ucsd.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]; 'WCarlo@peds.uab.edu' <WCarlo@peds.uab.edu>
Sent: Mon Oct 17 19:19:26 2011
Subject: Abstract again

Hi Rose and Wally
After reviewing this abstract and after our phone call I realized that the data in this abstract is the strongest data upon which to actually show that for all infants irrespective of CPAP vs SURF, while CPAP lowers mortality in the most immature, a high SpO2 range lowers death for each treatment arm in each strata
I reworked to emphasize this
I think this abstract provides useful information on this issue and for the specific gestational ages and the usual treatments used
Please relook and let me know
Be well
Neil

First Author: Neil N Finer, MD **Filename:** 750127

Responsible Author: Neil N Finer, MD
Presenting Author: Neil N Finer, MD
Contact Person: Neil N Finer, MD

2012 PAS Annual Meeting

Subspecialty: Neonatology - General
Theme: Neonatal - Patient-Oriented Research

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Responsible Author Declaration: As the responsible author, I confirm that the individual listed as the sponsor has been contacted and given the opportunity to review the abstract and has subsequently agreed to sponsor this abstract.

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The presenting author is member of these Alliance Societies:
Is Presenting Author a Trainee? No, Not a Trainee
Presenter Copyright Declaration:
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QUESTIONNAIRE INFORMATION
Eastern Society for Pediatric Research: No, Do not consider this abstract for the Eastern SPR
Pediatric Hospital Medicine: No, Do not consider this abstract for presentation at the Pediatric Hospital Medicine, July 19-22, 2012
Research Type: Clinical
Presentation Sabbath Conflict on: N/A
APA Special Interest Groups, Committees or Regions: None

AWARDS APPLIED FOR:
No awards selected

SPONSOR INFORMATION
Sponsoring Member for PAS/ASPR abstract:
Sponsor Name: Neil Norman Finer
Email: nfiner@ucsd.edu
Is the Sponsor an Author? Yes
Sponsoring Societies:
Society for Pediatric Research

Title: Early CPAP Versus Surfactant: The Effect Of A Lower SpO2 Range: Secondary Outcomes Of The SUPPORT Trial.

Neil N Finer, MD[UCSD], Waldemar Carlo, MD[University of A] and Support Group[NICHD]. [1]Neonatology, Pediatrics, University California San Diego, San Diego, Ca, 92103, United States.

Background: The SUPPORT Trial prospectively compared early CPAP and a limited ventilator strategy to early surfactant and randomized all infants to a lower (85-89%) versus a higher (91-95%) SpO2 range .(NEJM 2010). A prespecified secondary outcome was that infants randomized to CPAP and a low SpO2 strategy would have a lower rate of death/ROP.

Objective: This study evaluated the effect of the SpO2 range on the outcomes for infants in the 2 gestational age strata, 24-25 wks, and 26-27 weeks

Design/Methods: The surviving infants were assessed at 18 to 22 months for full neurodevelopmental evaluation, which included hearing, vision, and mental and motor outcomes using the Bayley 3. Tests for interaction were adjusted for GA center and family clustering.

Results: There were 1316 infants randomized and deaths prior to discharge, (16.4% vs 19.6%), and prior to follow-up (18.4% vs 21.9%) and the overall ROP rates among survivors (13.1% vs 13.7%) were not different between CPAP and Surf infants. ROP was less frequent in the 24-25wk strata, (22.2% vs 31.6%, p=0.04) whereas ROP was greater in CPAP infants in the 26-27 wk strata (7.3% vs 3.6% p=0.04). Death at follow-up for the 24-25 wk infants remained significantly lower for the CPAP infants (26.4% vs 35.5%, p=0.019). For the overall study and for the 26-27 wk strata there were no significant intercations between SpO2 group and the intervention groups for death/ROP or death/NDI for both strata. For the outcome of death or ROP, while no interaction was seen in the overall study, the 24-25wk infants in the Low SpO2 strata had a lower rate of ROP/death (p=.001),

Death/ROP for 24-25 wk Strata and 26-27 wk Strata - Low vs High SpO2

SpO2 Range	CPAP/Surf	Death - (24-25)	ROP	Death/ROP	Death - (26-27)	ROP	Death/ROP
Low	CPAP	37/142(26%)	11/95(12%)**	48/132(36%)*	25/194(13%)	8/153(5%)	33/178(19%)
	Surf	48/134(36%)	21/76(28%)**	69/124(56%)*	20/184(11%)	1/151(1%)	21/171(12%)
High	CPAP	31/143(22%)	33/103(32%)	64/134(48%)	15/185(9%)	15/160(9%)	31/176(18%)
	Surf	42/146(29%)	33/95(35%)	75/137(55%)	18/189(10%)	10/141(7%)	28/169(17%)

* p = 0.001, ** p=0.01

Conclusions: The lowest death rate was seen in both the CPAP and Surf infants in each strata treated with a high SpO2 approach whereas ROP was higher in the Low SpO2 arm. These results provide further evidence that the use of the higher SpO2 range is associated with decreased mortality in all infants and that these differences are magnified in the most immature infants

From: Susan Hintz
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: SUPPORT maternal education
Date: Friday, October 14, 2011 7:29:02 PM

Hi Rose

I looked at Yvonne's paper and see that for the patients in the follow up cohort, there was only ~3-4% missing maternal education data. However, if you look at the ENTIRE cohort, there was much more (see her Table 1). I think that is further reinforcement for the points we discussed on the phone today, and that you thought would be a good idea to address.

THANKS!

S

From: Phelps, Dale
To: "Kennedy, Kathleen A"; Wrage, Lisa Ann
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik
Subject: RE: ROP Natural History Abstract
Date: Friday, October 14, 2011 4:46:19 PM

That's a good idea Kathleen.

I studied carefully the most recent flow sheet which Lisa sent to me today.
Of the 10 infants who had severe ROP with 'unknown time of onset', I believe there are two that could be reclassified with a known date of diagnosis that would still fall within our criteria -- maybe.
It would require a discussion with an ROP ophthalmologist and a careful look at the particulars of the infants' forms, but it seems to me it's possible.
We may wish to consider that as we prepare the manuscript.

Dale Phelps

From: Kennedy, Kathleen A [mailto:Kathleen.A.Kennedy@uth.tmc.edu]
Sent: Friday, October 14, 2011 7:54 AM
To: Wrage, Lisa Ann; Phelps, Dale
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik
Subject: RE: ROP Natural History Abstract

Thanks, Lisa. When the dust settles from the PAS abstracts, I'd really like to get an updated summary, in 1 document, of all the information that went back and forth in the PAS emails, as well as the additional data that has been previously requested, and the following that was recently requested by Michele Walsh:

The PMAs for percentiles (1, 5, 25, 50, 75, 95,99) for diagnosis/onset of prethreshold ROP (if we have it or can construct if from what we have).
The latest occurrence (PMA) of prethreshold ROP among babies who subsequently met severe ROP criteria.

Once we get that, I think we should be in good shape to get the manuscript written fairly quickly.

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Richard W. Mithoff Professor of Pediatrics
Director, MS in Clinical Research Degree Program
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From: Wrage, Lisa Ann [mailto:wrage@rti.org]
Sent: Friday, October 14, 2011 9:47 AM
To: Phelps, Dale
Cc: Kennedy, Kathleen A; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik
Subject: RE: ROP Natural History Abstract

Hi Dale,
This is the latest one that I sent (early last month) except I've made a correction to last box.

Lisa

From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Thursday, October 13, 2011 11:18 PM
To: Wrage, Lisa Ann
Cc: 'Kennedy, Kathleen A'; 'Higgins, Rosemary (NIH/NICHD) [E]'; Das, Abhik
Subject: RE: ROP Natural History Abstract

Hi Lisa,

Can you please provide your new or current flow chart?

Dale

From: Wrage, Lisa Ann [mailto:wrage@rti.org]
Sent: Thursday, October 13, 2011 10:00 AM
To: Kennedy, Kathleen A
Cc: Phelps, Dale; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik
Subject: RE: ROP Natural History Abstract

Hi,
I have attached Kathleen's latest version with some changes/comments. One of the reasons some of the numbers were confusing is because of the 138 infants with severe ROP we know age of onset of "Any ROP" for 137 of them (since they had less severe ROP before severe ROP) and we know age of onset of 'Severe ROP" for 128 of them. SO, overall we know age of onset of 'Any ROP' for 642 of the 644 who developed any type of ROP. You did not have this number. I think that in future versions of the flowchart I will flow the 'severe ROP' group out of the 'Any ROP' group so that these numbers will be in the flowchart. Anyway, I have fixed the associated numbers in the abstract draft. I also changed the cohort number back to 997 because that is less confusing and I changed some text that refers to the severe ROP group as the 'treated' group, I still find that confusing because 1) some are not treated and 2) the PMA given is for onset (diagnosis) of {severe} ROP rather than treatment. I made those types of changes so now the groups are referred to consistently throughout, at least for me this is less confusing. I made all changes in track changes. I also think the table is looking better.
Lisa

From: Kennedy, Kathleen A [mailto:Kathleen.A.Kennedy@uth.tmc.edu]
Sent: Thursday, October 13, 2011 12:01 PM
To: Wrage, Lisa Ann
Subject: RE: ROP Natural History Abstract

I've rearranged the results section because it seemed to confuse people. I have enough space so I was able to put more of the numbers in there. Please use this one if you're checking the data.

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From: Wrage, Lisa Ann [mailto:wrage@rti.org]
Sent: Thursday, October 13, 2011 10:41 AM
To: Kennedy, Kathleen A; Phelps, Dale
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: ROP Natural History Abstract

Fyi I am going through the numbers, etc. now and will send an updated version of the abstract with my comments shortly.

From: Kennedy, Kathleen A [mailto:Kathleen.A.Kennedy@uth.tmc.edu]
Sent: Wednesday, October 12, 2011 6:46 PM
To: Phelps, Dale
Cc: Wrage, Lisa Ann; 'Higgins, Rosemary (NIH/NICHD) [E]'
Subject: RE: ROP Natural History Abstract

About Lisa's response:
I think we're all saying the same thing (understanding that "severe ROP" conceptually means "should be treated" and that our operational definition was treated or Type 1 ROP. (Your previous email said threshold rather Type 1 but we don't use that term anymore so I think you meant Type 1). You're also correct that it would be very unlikely for a baby to get diagnosed with Type 1 ROP before discharge and then get treated after discharge. It sounds like there was 1 baby diagnosed with Type 1 ROP after discharge who was not treated. I've added that 1 to the abstract, but just wanted to verify.

I re-ran the numbers a little too quickly before running off to class. Now I see where there's a problem and why my last version did agree with my previous calculations.

Lisa, in the flow diagram in the document you sent in September, there are 506 infants with ROP that did not meet Type 1 criteria and regressed without treatment. Beneath that, it says that 505 had known age of onset and 3 did not. That doesn't add up. I think it's because there are 2 babies who had some missing exams and they were moved from the "regressed ROP" to the "no ROP" category, but they were left in the box for unknown age of onset. So that box should really be 1, not 3. Is that correct?

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From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Wednesday, October 12, 2011 4:18 PM
To: Kennedy, Kathleen A
Cc: Wrage, Lisa Ann (wrage@rti.org); 'Higgins, Rosemary (NIH/NICHD) [E]'

Subject: RE: ROP Natural History Abstract

Hi Kathleen,

Thank you for the good revisions: we are getting there. I am still struggling with numbers, but I'm sure you and Lisa can figure these out.

Per the abstract:
1316 enrolled and 1091 survived to ROP age.
997 had a definitive ROP outcome, and 986 of those had sufficient data to determine age of onset of ROP.

So to me your key group is those 986. In the text and conclusions subsequently, you say 984,
644 developed ROP
of those 138 met the severe ROP criteria

Your sentence says that "644 infants developed ROP (138 met severe ROP criteria); 353 did not."
138 + 353 = 491, not the 644 (or 633) that you say developed ROP.
This was my confusion. What about the other 644-491 = 153 with ROP?
But I just figured it out (I think)

Is this what you meant? (seems obvious in retrospect):
644 infants developed ROP (138 of those met severe ROP criteria); 353 did not develop ROP.
644 with ROP + 353 without ROP = 997 infants... not the 984 (or 986) you say you have.
Or reverse it for clarity in the abstract (with corrected numbers) ?
353 infants did not develop ROP; 644 did (138 of those met severe ROP criteria).

In the table you report age of onset of ROP for 633 infants. Why the discrepancy between 644 and 633 ?
In the table you report PMA for onset of severe ROP for 128 infants. Why the discrepancy between 128 and 138 ?

In the title of the table, I think you have to revise a bit to say.
Cumulative Percentile with Diagnosis of ROP or Cumulative %tile with Diagnosis of ROP
But I'm not certain of this (Lisa/Marie help), but I think "%" is different than "percentile". If RTI says "no" you can leave it.

Title of the Abstract (has to be all caps)
I would say "...SCREENING GUIDELINES...." rather than "...SCREENING INTERVAL...."
The guidelines don't really talk about an interval, so I don't think you are testing an interval.

[I have put in some specific responses to you questions below, in square brackets—DLP]

and put in some minor edits or suggestions in green highlight in the attached copy of the text.

Dale

From: Kennedy, Kathleen A [mailto:Kathleen.A.Kennedy@uth.tmc.edu]
Sent: Wednesday, October 12, 2011 10:57 AM
To: Phelps, Dale
Cc: Wrage, Lisa Ann (wrage@rti.org); Higgins, Rosemary (NIH/NICHD)
Subject: RE: ROP Natural History Abstract

Thanks for the careful review. I tried to make most of these suggested changes (along with most of the suggestion in in the 16 other emails since Mon).

I have verified twice that the demographic comparisons are for severe ROP vs no ROP. Do you see something about that data that makes you think I've quoted it incorrectly?

I'm also struggling with the sentence that says what's in the table.

I think the min ages of diagnoses would be good to include and they are still consistent with the statement that treatable ROP was not diagnosed before 32 weeks. But a 0%ile really doesn't make sense, so I'm thinking we should put that in the text rather than the table. I've also added the late onset one to the text below the table because I don't think it makes sense to replace 99%ile with the 100%ile for such an extreme value.

[I agree with keeping the 99th%tile in the table and putting the range in the text. –DLP]

I haven't addressed Michelle's comment (at what point you can say a baby without prethreshold is no longer at risk to need treatment), although I think it's important, because we need more data and I doubt that we can get it before the deadline. A simple solution (not exactly the same thing but close) would be to add a line to the table for PMAs at which cumulative %iles of prethreshold were diagnosed. We can do that for the presentation/manuscript.

[I don't think we really need to address this. It is a clinical judgement made by the ophthalmologists and we are not ophthalmologists. Let's not go there. The guidelines say that stopping examinations depends on the eye findings. Let it go. There is not a 100% safe answer, especially for a neonatologist. –DLP]

I added the information about treatment after discharge. I just want to verify (quadruple check) that it was initial treatment (not "touch-up of previous laser treatment or vitrectomy or scleral buckle). What did you do with the ones where the date was uncertain? You should have the date of the first exam after treatment because that's when they met study outcome, right? If there was a long interval between that exam and the previous one, they would have been removed before because of uncertain timing of onset, right?

[As I count up the SUPPORT data: 132 infants were treated. 5 after discharge and 9 after transfer = 14.

14/132 is 10% of infants went on to treatment after leaving the primary hospital, ~1/3 of those after discharge to home. It is a real problem everyone needs to be aware of. –DLP]

I've attached a new version. The changes (except for moving things around) are in yellow.

Kathleen A. Kennedy, MD, MPH
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From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Sunday, October 09, 2011 4:56 PM
To: Kennedy, Kathleen A; wcarlo@peds.uab.edu; Das, Abhik; Roger.Faix@hsc.utah.edu; nfiner@ucsd.edu; Gantz, Marie; alaptook@WIHRI.org; nxs5@cwru.edu; wrich@ucsd.edu; kurt.schibler@cchmc.org; Michele.Walsh@UHhospitals.org; Bradley.Yoder@hsc.utah.edu
Cc: Wrage, Lisa Ann (wrage@rti.org); Archer, Stephanie (NIH/NICHD) [E] (archerst@mail.nih.gov); Higgins, Rosemary (NIH/NICHD)
Subject: RE: ROP Natural History Abstract

Thank you for your hard work on this Kathleen,
I have been through the abstract again, and discovered some things we had missed.. probably because we're too familiar with the material already. Just some clarifications, no real substantive changes. I have edited the abstract in the attached word file. (They are not track changes because my old laptop seems to confuse others when I use them.

Thanks again!
Dale

From: Kennedy, Kathleen A [mailto:Kathleen.A.Kennedy@uth.tmc.edu]
Sent: Saturday, October 08, 2011 9:56 AM
To: wcarlo@peds.uab.edu; Das, Abhik; Roger.Faix@hsc.utah.edu; nfiner@ucsd.edu; Gantz, Marie; alaptook@WIHRI.org; nxs5@cwru.edu; wrich@ucsd.edu; kurt.schibler@cchmc.org; Michele.Walsh@UHhospitals.org; Bradley.Yoder@hsc.utah.edu
Cc: Wrage, Lisa Ann (wrage@rti.org); Phelps, Dale; Archer, Stephanie (NIH/NICHD) [E] (archerst@mail.nih.gov); Higgins, Rosemary (NIH/NICHD)
Subject: ROP Natural History Abstract

SUPPORT Subcommittee: I've attached a draft of the PAS abstract for the ROP Natural History Secondary Study that uses data from the SUPPORT trial. Comments and suggestions are welcome. I hope to get the missing data before the deadline. If anyone knows how to navigate the submission process (how to include the NICHD without entering the NICHD as an author and then being required to submit a bunch of CME/COI disclosures for the NICHD), I'd appreciate the help.

Stephanie, could you please check to make sure I haven't missed anyone on the SUPPORT Subcommittee?

Lisa, if we could get the data for treatment after back transfer and after discharge, that would be great. If you can tabulate the 0 and 100%iles and they look reasonable (no extreme outliers), we could replace the 1 and 99%iles in the table with 0 and 100%iles.

Kathleen A. Kennedy, MD, MPH
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713 500-6708

From: Phelps, Dale
To: "Kennedy, Kathleen A"; wcarlo@peds.uab.edu; Das, Abhik; Roger.Faix@hsc.utah.edu; nfiner@ucsd.edu; Gantz, Marie; alaptook@WIHRI.org; nxs5@cwru.edu; wrich@ucsd.edu; kurt.schibler@cchmc.org; Michele.Walsh@UHhospitals.org; Bradley.Yoder@hsc.utah.edu
Cc: Wrage, Lisa Ann (wrage@rti.org); Archer, Stephanie (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Revised ROP Natural History Abstract
Date: Friday, October 14, 2011 4:42:23 PM

This has matured very nicely and is a very interesting abstract. Thank you Kathleen.
I agree it is ready to go to NICHD for approval.
Dale

From: Kennedy, Kathleen A [mailto:Kathleen.A.Kennedy@uth.tmc.edu]
Sent: Friday, October 14, 2011 6:50 AM
To: wcarlo@peds.uab.edu; Das, Abhik; Roger.Faix@hsc.utah.edu; nfiner@ucsd.edu; Gantz, Marie; alaptook@WIHRI.org; nxs5@cwru.edu; wrich@ucsd.edu; kurt.schibler@cchmc.org; Michele.Walsh@UHhospitals.org; Bradley.Yoder@hsc.utah.edu
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Subject: Revised ROP Natural History Abstract

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From: Phelps, Dale
To: "Wrage, Lisa Ann"; Kennedy, Kathleen A
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik
Subject: RE: ROP Natural History Abstract
Date: Friday, October 14, 2011 3:08:07 PM

Hi Kathleen and Lisa,

I will be happy to assist you in selecting the algorithm for "prethreshold ROP". The component parts that define it should be available from the 'lowest zone with ROP" and "highest stage of ROP in the lowest zone" and the "highest stage in any zone" and whether there is plus disease.

Dale

From: Wrage, Lisa Ann [mailto:wrage@rti.org]
Sent: Friday, October 14, 2011 9:02 AM
To: Kennedy, Kathleen A; Phelps, Dale
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik
Subject: RE: ROP Natural History Abstract

Yes, will do.
Lisa

From: Kennedy, Kathleen A [mailto:Kathleen.A.Kennedy@uth.tmc.edu]
Sent: Friday, October 14, 2011 10:54 AM
To: Wrage, Lisa Ann; Phelps, Dale
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik
Subject: RE: ROP Natural History Abstract

Thanks, Lisa. When the dust settles from the PAS abstracts, I'd really like to get an updated summary, in 1 document, of all the information that went back and forth in the PAS emails, as well as the additional data that has been previously requested, and the following that was recently requested by Michele Walsh:

The PMAs for percentiles (1, 5, 25, 50, 75, 95,99) for diagnosis/onset of prethreshold ROP (if we have it or can construct if from what we have).
The latest occurrence (PMA) of prethreshold ROP among babies who subsequently met severe ROP criteria.

Once we get that, I think we should be in good shape to get the manuscript written fairly quickly.

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From: Wrage, Lisa Ann [mailto:wrage@rti.org]
Sent: Friday, October 14, 2011 9:47 AM

To: Phelps, Dale
Cc: Kennedy, Kathleen A; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik
Subject: RE: ROP Natural History Abstract

Hi Dale,
This is the latest one that I sent (early last month) except I've made a correction to last box.
Lisa

From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Thursday, October 13, 2011 11:18 PM
To: Wrage, Lisa Ann
Cc: 'Kennedy, Kathleen A'; 'Higgins, Rosemary (NIH/NICHD) [E]'; Das, Abhik
Subject: RE: ROP Natural History Abstract

Hi Lisa,

Can you please provide your new or current flow chart?

Dale

From: Wrage, Lisa Ann [mailto:wrage@rti.org]
Sent: Thursday, October 13, 2011 10:00 AM
To: Kennedy, Kathleen A
Cc: Phelps, Dale; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik
Subject: RE: ROP Natural History Abstract

Hi,
I have attached Kathleen's latest version with some changes/comments. One of the reasons some of the numbers were confusing is because of the 138 infants with severe ROP we know age of onset of "Any ROP" for 137 of them (since they had less severe ROP before severe ROP) and we know age of onset of 'Severe ROP" for 128 of them. SO, overall we know age of onset of 'Any ROP' for 642 of the 644 who developed any type of ROP. You did not have this number. I think that in future versions of the flowchart I will flow the 'severe ROP' group out of the 'Any ROP' group so that these numbers will be in the flowchart. Anyway, I have fixed the associated numbers in the abstract. draft. I also changed the cohort number back to 997 because that is less confusing and I changed some text that refers to the severe ROP group as the 'treated' group, I still find that confusing because 1) some are not treated and 2) the PMA given is for onset (diagnosis) of {severe} ROP rather than treatment. I made those types of changes so now the groups are referred to consistently throughout, at least for me this is less confusing. I made all changes in track changes. I also think the table is looking better.
Lisa

From: Kennedy, Kathleen A [mailto:Kathleen.A.Kennedy@uth.tmc.edu]
Sent: Thursday, October 13, 2011 12:01 PM
To: Wrage, Lisa Ann
Subject: RE: ROP Natural History Abstract

I've rearranged the results section because it seemed to confuse people. I have enough space so I

was able to put more of the numbers in there. Please use this one if you're checking the data.

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From: Wrage, Lisa Ann [mailto:wrage@rti.org]
Sent: Thursday, October 13, 2011 10:41 AM
To: Kennedy, Kathleen A; Phelps, Dale
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: ROP Natural History Abstract

Fyi I am going through the numbers, etc. now and will send an updated version of the abstract with my comments shortly.

From: Kennedy, Kathleen A [mailto:Kathleen.A.Kennedy@uth.tmc.edu]
Sent: Wednesday, October 12, 2011 6:46 PM
To: Phelps, Dale
Cc: Wrage, Lisa Ann; 'Higgins, Rosemary (NIH/NICHD) [E]'
Subject: RE: ROP Natural History Abstract

About Lisa's response:
I think we're all saying the same thing (understanding that "severe ROP" conceptually means "should be treated" and that our operational definition was treated or Type 1 ROP. (Your previous email said threshold rather Type 1 but we don't use that term anymore so I think you meant Type 1). You're also correct that it would be very unlikely for a baby to get diagnosed with Type 1 ROP before discharge and then get treated after discharge. It sounds like there was 1 baby diagnosed with Type 1 ROP after discharge who was not treated. I've added that 1 to the abstract, but just wanted to verify.

I re-ran the numbers a little too quickly before running off to class. Now I see where there's a problem and why my last version did agree with my previous calculations.

Lisa, in the flow diagram in the document you sent in September, there are 506 infants with ROP that did not meet Type 1 criteria and regressed without treatment. Beneath that, it says that 505 had known age of onset and 3 did not. That doesn't add up. I think it's because there are 2 babies who had some missing exams and they were moved from the "regressed ROP" to the "no ROP" category, but they were left in the box for unknown age of onset. So that box should really be 1, not 3. Is that correct?

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From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Wednesday, October 12, 2011 4:18 PM
To: Kennedy, Kathleen A
Cc: Wrage, Lisa Ann (wrage@rti.org); 'Higgins, Rosemary (NIH/NICHD) [E]'
Subject: RE: ROP Natural History Abstract

Hi Kathleen,

Thank you for the good revisions: we are getting there. I am still struggling with numbers, but I'm sure you and Lisa can figure these out.

Per the abstract:
1316 enrolled and 1091 survived to ROP age.
997 had a definitive ROP outcome, and 986 of those had sufficient data to determine age of onset of ROP.

So to me your key group is those 986. In the text and conclusions subsequently, you say 984,
644 developed ROP
of those 138 met the severe ROP criteria

Your sentence says that "644 infants developed ROP (138 met severe ROP criteria); 353 did not."
138 + 353 = 491, not the 644 (or 633) that you say developed ROP.
This was my confusion. What about the other 644-491 = 153 with ROP?
But I just figured it out (I think)

Is this what you meant? (seems obvious in retrospect):
644 infants developed ROP (138 of those met severe ROP criteria); 353 did not develop ROP.

644 with ROP + 353 without ROP = 997 infants... not the 984 (or 986) you say you have.

Or reverse it for clarity in the abstract (with corrected numbers) ?
353 infants did not develop ROP; 644 did (138 of those met severe ROP criteria).

In the table you report age of onset of ROP for 633 infants. Why the discrepancy between 644 and 633 ?
In the table you report PMA for onset of severe ROP for 128 infants. Why the discrepancy between 128 and 138 ?

In the title of the table, I think you have to revise a bit to say.
Cumulative Percentile with Diagnosis of ROP or Cumulative %tile with Diagnosis of ROP
But I'm not certain of this (Lisa/Marie help), but I think "%" is different than "percentile". If RTI says "no" you can leave it.

Title of the Abstract (has to be all caps)
I would say "...SCREENING GUIDELINES...." rather than "...SCREENING INTERVAL...."
The guidelines don't really talk about an interval, so I don't think you are testing an interval.

[I have put in some specific responses to you questions below, in square brackets—DLP]

and put in some minor edits or suggestions in green highlight in the attached copy of the text.

Dale

From: Kennedy, Kathleen A [mailto:Kathleen.A.Kennedy@uth.tmc.edu]
Sent: Wednesday, October 12, 2011 10:57 AM
To: Phelps, Dale
Cc: Wrage, Lisa Ann (wrage@rti.org); Higgins, Rosemary (NIH/NICHD)
Subject: RE: ROP Natural History Abstract

Thanks for the careful review. I tried to make most of these suggested changes (along with most of the suggestion in in the 16 other emails since Mon).

I have verified twice that the demographic comparisons are for severe ROP vs no ROP. Do you see something about that data that makes you think I've quoted it incorrectly?

I'm also struggling with the sentence that says what's in the table.

I think the min ages of diagnoses would be good to include and they are still consistent with the statement that treatable ROP was not diagnosed before 32 weeks. But a 0%ile really doesn't make sense, so I'm thinking we should put that in the text rather than the table. I've also added the late onset one to the text below the table because I don't think it makes sense to replace 99%ile with the 100%ile for such an extreme value.

[I agree with keeping the 99th%tile in the table and putting the range in the text. –DLP]

I haven't addressed Michelle's comment (at what point you can say a baby without prethreshold is no longer at risk to need treatment), although I think it's important, because we need more data and I doubt that we can get it before the deadline. A simple solution (not exactly the same thing but close) would be to add a line to the table for PMAs at which cumulative %iles of prethreshold were diagnosed. We can do that for the presentation/manuscript.

[I don't think we really need to address this. It is a clinical judgement made by the ophthalmologists and we are not ophthalmologists. Let's not go there. The guidelines say that stopping examinations depends on the eye findings. Let it go. There is not a 100% safe answer, especially for a neonatologist. –DLP]

I added the information about treatment after discharge. I just want to verify (quadruple check) that it was initial treatment (not "touch-up of previous laser treatment or vitrectomy or scleral buckle). What did you do with the ones where the date was uncertain? You should have the date of the first exam after treatment because that's when they met study outcome, right? If there was a long interval between that exam and the previous one, they would have been removed before because of uncertain timing of onset, right?

[As I count up the SUPPORT data: 132 infants were treated. 5 after discharge and 9 after transfer = 14.

14/132 is 10% of infants went on to treatment after leaving the primary hospital, ~1/3 of

those after discharge to home. It is a real problem everyone needs to be aware of. –DLP]

I've attached a new version. The changes (except for moving things around) are in yellow.

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Cc: Wrage, Lisa Ann (wrage@rti.org); Phelps, Dale; Archer, Stephanie (NIH/NICHD) [E] (archerst@mail.nih.gov); Higgins, Rosemary (NIH/NICHD)
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To: Gantz, Marie; wcarlo@peds.uab.edu; Das, Abhik; Roger.Faix@hsc.utah.edu; nfiner@ucsd.edu; alaptook@WIHRI.org; nxs5@cwru.edu; wrich@ucsd.edu; kurt.schibler@cchmc.org; Michele.Walsh@UHhospitals.org; Bradley.Yoder@hsc.utah.edu
Cc: Wrage, Lisa Ann; dale_phelps@urmc.rochester.edu; Archer, Stephanie (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Revised ROP Natural History Abstract
Date: Friday, October 14, 2011 11:19:25 AM

What we're saying in that section of the Design/Methods is that the protocol said all enrolled infants were to be followed according to those criteria. That's not the same thing as saying that no babies were seen outside those limits.

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From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Friday, October 14, 2011 10:15 AM
To: Kennedy, Kathleen A; wcarlo@peds.uab.edu; Das, Abhik; Roger.Faix@hsc.utah.edu; nfiner@ucsd.edu; alaptook@WIHRI.org; nxs5@cwru.edu; wrich@ucsd.edu; kurt.schibler@cchmc.org; Michele.Walsh@UHhospitals.org; Bradley.Yoder@hsc.utah.edu
Cc: Wrage, Lisa Ann; dale_phelps@urmc.rochester.edu; archerst@mail.nih.gov; Higgins, Rosemary (NIH/NICHD)
Subject: RE: Revised ROP Natural History Abstract

I think the abstract looks good, although I have one edit. The abstract currently states that "**Results of each exam were prospectively collected for all enrolled infants until a study endpoint was reached: ROP treatment, full vascularization to the ora serrata, vascularization in zone III in 2 consecutive exams, or the infant was 55 weeks PMA.**" Per the SUPPORT protocol, in addition to treatment for ROP, the infant was considered to have reached criteria for severe ROP if they had threshold (Type 1) ROP (about 10 infants were classified as having severe ROP on the basis of threshold ROP as opposed to surgery). Also, for infants without ROP, it sometimes took longer than 55 weeks PMA for them to reach the study endpoint (and we collected the exam data beyond 55 weeks), so I would strike "or the infant was 55 weeks PMA" from the sentence. My suggested edit is:

Results of each exam were prospectively collected for all enrolled infants until a study endpoint was reached: Type 1 ROP, ROP treatment, full vascularization to the ora serrata, vascularization in zone III in 2 consecutive exams.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org

From: Kennedy, Kathleen A [mailto:Kathleen.A.Kennedy@uth.tmc.edu]
Sent: Friday, October 14, 2011 9:50 AM
To: wcarlo@peds.uab.edu; Das, Abhik; Roger.Faix@hsc.utah.edu; nfiner@ucsd.edu; Gantz, Marie; alaptook@WIHRI.org; nxs5@cwru.edu; wrich@ucsd.edu; kurt.schibler@cchmc.org; Michele.Walsh@UHhospitals.org; Bradley.Yoder@hsc.utah.edu
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Subject: Revised ROP Natural History Abstract
Date: Friday, October 14, 2011 9:49:50 AM
Attachments: ROP Natural History PAS Abstract.doc
PAS Abstract (SUPPORT Secondary - ROP Natural History) ver 3.pdf

Thanks for all your helpful suggestions. I was able to incorporate most of them and I think this (hopefully final) version is a lot better. Michele had some very good suggestions about looking at age of onset of prethreshold and when an infant without prethreshold is no longer at risk for treatable ROP. We don't have the data for that right now but it can be added to the presentation/manuscript.

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Evaluating the Retinopathy of Prematurity (ROP) Screening Guidelines for 24-27 Week Gestational Age Infants

Kathleen A. Kennedy MD MPH, Lisa Wrage, MPH, Dale L. Phelps MD, Rosemary D. Higgins on behalf of the SUPPORT Subcommittee for the NICHD Neonatal Research Network

Background:
Timely detection of treatable ROP is important to assure optimal outcomes for infants who meet the criteria for treatment. The timing of onset of ROP is related most closely to postmenstrual age (PMA = gestational age at birth + postnatal age). Current (2006) screening guidelines are based on natural history data from randomized trials that enrolled infants from 1986-1997: screening should begin by 31 weeks PMA and continue until the vessels have reached zone III at ≥ 35 weeks, or, for infants without prethreshold ROP, until a PMA of 45 weeks. Since the 1980s, survival of lower gestational age infants has increased, and earlier treatment of ROP (Type 1 ROP: stage 3 or ROP with plus disease in zone I or stage 2-3 with plus disease in zone II) is recommended.

Objective:
To validate current screening recommendations for detection of treatable ROP in 24-27 week gestational age infants.

Design/Methods:
In the NICHD Network SUPPORT trial, severe ROP (Type 1 ROP or treatment with laser, cryotherapy, or bevacizumab) or death was the primary outcome for the O_2 saturation target arm of the factorial design. Infants 24 0/7 to 27 6/7 weeks gestational age (no birth weight limits) with consent prior to delivery were eligible for this study. ROP examinations were conducted according to current screening recommendations and recorded using the international classification of ROP. Results of each exam were prospectively collected for all enrolled infants until a study endpoint was reached: ROP treatment, full vascularization to the ora serrata, vascularization in zone III in 2 consecutive exams, or the infant was 55 weeks PMA.

Results:
1316 infants were enrolled. 1091 (83%) of infants survived to the age of ROP determination. 997 (91%) of these infants had a definitive ROP outcome. 644 infants developed ROP of any severity (138 infants met criteria for severe ROP); 353 infants had no ROP. Among infants with ROP, 642/644 (99.7%) of infants with any ROP and 128/138 (93%) infants with severe ROP had sufficient exam data (no missing or delayed exams before diagnosis) to determine the age of onset of ROP. As expected, infants with severe ROP were less mature [mean(SD) 25.5(0.9) wks vs 26.8(0.9) wks, p<0.0001], lower birth weight [mean(SD) 708(148)g vs 942(173)g, p<0.0001], and more likely to be White race (44% vs 35%, p=0.07) than infants with no ROP. For the infants with ROP and known age of onset, the PMAs for selected percentiles reaching diagnosis are shown in the table:

ROP type (number of infants)	Cumulative % with Diagnosis of ROP						
	1%	5%	25%	50%	75%	95%	99%
	Postmenstrual Age (weeks)						
Diagnosis of any ROP (n=642)	30.4	31.4	32.7	33.9	35.1	37.9	41.0
Diagnosis of severe (Type 1/Treated) ROP (n=128)	32.7	33.9	35.1	36.4	38.6	43.3	45.0

The PMA at onset of severe ROP ranged from 32.1 to 53.1 weeks. In this referral center cohort of 997 infants, 0.5% were diagnosed with severe ROP after back transfer to another NICU; 1.0% of the cohort (7% of infants with severe ROP) reached severe ROP criteria after discharge to home.

Our data are consistent with the 2006 ROP screening guidelines. In this cohort of 997 infants born at 24-27 weeks, we did not observe ROP needing treatment before 32 weeks PMA; only 1 infant was diagnosed with severe ROP after 45 weeks PMA. A limitation of this study is that infants < 24 weeks gestational age were not enrolled and these data may not be generalizable to less mature infants at the highest risk for ROP.

Draft Preview of Abstract #750344
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2012 PAS Annual Meeting

Subspecialty: Neonatology - General
Theme: Neonatal - Patient-Oriented Research

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QUESTIONNAIRE INFORMATION

Eastern Society for Pediatric Research: No, Do not consider this abstract for the Eastern SPR
Pediatric Hospital Medicine: No, Do not consider this abstract for presentation at the Pediatric Hospital Medicine, July 19-22, 2012
Research Type: Clinical
Presentation Sabbath Conflict on: N/A
APA Special Interest Groups, Committees or Regions: None

AWARDS APPLIED FOR:

No awards selected

SPONSOR INFORMATION

Sponsoring Member for PAS/ASPR abstract:
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Is the Sponsor an Author? Yes
Sponsoring Societies:
American Academy of Pediatrics
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Title:

Evaluating the Retinopathy of Prematurity (ROP) Screening Guidelines for 24-27 Week Gestational Age Infants

Kathleen A Kennedy, MD, MPH[1], Lisa A Wrage, MPH[2], Dale Phelps, MD[3] and Rosemary Higgins, MD[4]. [1]Pediatrics, UT Houston Medical, Houston, TX, United States; [2]RTI International, Research Triangle Park, NC, United States; [3]University of Rochester, Rochester, NY, United States and [4]the SUPPORT Subcommittee of the NICHD Neonatal Research Network, NICHD, Rockville, MD, United States.

Background: Timely detection of treatable ROP is important to assure optimal outcomes for infants who meet the criteria for treatment. The timing of onset of ROP is related most closely to postmenstrual age (PMA = gestational age at birth + postnatal age). Current (2006) screening guidelines are based on natural history data from randomized trials that enrolled infants from 1986-1997: screening should begin by 31 weeks PMA and continue until the vessels have reached zone III at ≥ 35 weeks, or, for infants without prethreshold ROP, until a PMA of 45 weeks. Since the 1980s, survival of lower gestational age infants has increased, and earlier treatment of ROP (Type 1 ROP: stage 3 or ROP with plus disease in zone I or stage 2-3 with plus disease in zone II) is recommended.

Objective: To validate current screening recommendations for detection of treatable ROP in 24-27 week gestational age infants.

Design/Methods: In the NICHD Network SUPPORT trial, severe ROP (Type 1 ROP or treatment with laser, cryotherapy, or bevacizumab) or death was the primary outcome for the O_2 saturation target arm of the factorial design. Infants 24 0/7 to 27 6/7 weeks gestational age (no birth weight limits) with consent prior to delivery were eligible for this study. ROP examinations were conducted according to current screening recommendations and recorded using the international classification of ROP. Results of each exam were prospectively collected for all enrolled infants until a study endpoint was reached: ROP treatment, full vascularization to the ora serrata, vascularization in zone III in 2 consecutive exams, or the infant was 55 weeks PMA.

Results: 1316 infants were enrolled. 1091 (83%) of infants survived to the age of ROP determination. 997 (91%) of these infants had a definitive ROP outcome. 644 infants developed ROP of any severity (138 infants met criteria for severe ROP); 353 infants had no ROP. Among infants with ROP, 642/644 (99.7%) of infants with any ROP and 128/138 (93%) infants with severe ROP had sufficient exam data (no missing or delayed exams before diagnosis) to determine the age of onset of ROP. As expected, infants with severe ROP were less mature [mean(SD) 25.5(0.9) wks vs 26.8(0.9) wks, p<0.0001], lower birth weight [mean(SD) 708(148)g vs 942(173)g, p<0.0001], and more likely to be White race (44% vs 35%, p=0.07) than infants with no ROP. For the infants with ROP and known age of onset, the PMAs for selected percentiles reaching diagnosis are shown in the table:

	Cumulative % with Diagnosis of ROP						
	1%	5%	25%	50%	75%	95%	99%
ROP type (number of infants)	Postmenstrual Age (weeks)						
Diagnosis of any ROP (n=642)	30.4	31.4	32.7	33.9	35.1	37.9	41.0
Diagnosis of Severe (Type 1/Treated) ROP (n=128)	32.7	33.9	35.1	36.4	38.6	43.3	45.0

The PMA at onset of severe ROP ranged from 32.1 to 53.1 weeks. In this referral center cohort of 997 infants, 0.5% were diagnosed with severe ROP after back transfer to another NICU; 1.0% of the cohort (7% of infants with severe ROP) reached severe ROP criteria after discharge to home.

Conclusions: Our data are consistent with the 2006 ROP screening guidelines. In this cohort of 997 infants born at 24-27 weeks, we did not observe ROP needing treatment before 32 weeks PMA; only 1 infant was diagnosed with severe ROP after 45 weeks PMA. A limitation of this study is that infants < 24 weeks gestational age were not enrolled and these data may not be generalizable to less mature infants at the highest risk for ROP.

Other Previews:

Abstract Disclosure Info: Disclosures

Print

From: Kennedy, Kathleen A
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: "Final" version
Date: Friday, October 14, 2011 9:35:04 AM

I thought it should go to "Patient-Oriented Research". It's an observational study, even though the data were collected as part of a clinical trial. I think the competition will be much stiffer if it's submitted to "Clinical Trials". I realize that not all reviewers or program organizers follow this, but I think the Clinical Trials sessions are supposed to be for the main hypotheses addressed in clinical trials. Maybe I'm confusing it with the instructions for "Late Breakers". If there is strong dissenting opinion, I'm happy to reconsider.

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From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, October 14, 2011 8:23 AM
To: Kennedy, Kathleen A
Subject: RE: "Final" version

Kathleen
I am ok with this – are you submitting for Neonatology and then either clinical trials or patient oriented research??
I think this is an outstanding analysis and very relevant to practice (but I am probably biased)!!
Thanks
Rose

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From: Kennedy, Kathleen A [mailto:Kathleen.A.Kennedy@uth.tmc.edu]
Sent: Thursday, October 13, 2011 4:49 PM
To: dale_phelps@urmc.rochester.edu; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Wrage, Lisa Ann (wrage@rti.org)
Subject: "Final" version

I think this is looking good. Lisa and I have finished arm wrestling about the numbers. If you (Dale and Rose) are ok with it, I think we can call it final, send it back to the SUPPORT Subcommittee and onto the NICHD for clearance.

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From: Kennedy, Kathleen A
To: dale_phelps@urmc.rochester.edu; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Wrage, Lisa Ann (wrage@rti.org)
Subject: "Final" version
Date: Thursday, October 13, 2011 4:49:00 PM
Attachments: ROP Natural History PAS Abstract.doc

I think this is looking good. Lisa and I have finished arm wrestling about the numbers. If you (Dale and Rose) are ok with it, I think we can call it final, send it back to the SUPPORT Subcommittee and onto the NICHD for clearance.

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Myriam Peralta, M.D."
Cc: Wally Carlo, M.D.
Subject: SUPPORT OXIMETRY FU paper
Date: Friday, October 14, 2011 9:29:00 AM

Myriam

Can I get the next revision of the SUPPORT Oximetry paper by October 20 – I would like to send it to the co-authors and steering committee for comment

Thanks

Rose

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From: Phelps, Dale
To: Kennedy, Kathleen A
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Wrage, Lisa Ann (wrage@rti.org)
Subject: RE: "Final" version
Date: Thursday, October 13, 2011 7:53:10 PM

I see what you mean when I focus on the whole sentence alone. It is fine with me if you leave the added word out.
Thanks for your patience.
Dale

From: Kennedy, Kathleen A [mailto:Kathleen.A.Kennedy@uth.tmc.edu]
Sent: Thursday, October 13, 2011 4:25 PM
To: Phelps, Dale
Subject: RE: "Final" version

I think the "ROP" where you added "severe" refers to any ROP or severe ROP in the previous part of the sentence. I think the "ROP type (number of infants) can be put in the same row as "Postmenstrual Age (weeks)". That should work. I haven't put it into the PAS system after the last set of changes but I think it will fit.

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From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Thursday, October 13, 2011 6:24 PM
To: Kennedy, Kathleen A; Higgins, Rosemary (NIH/NICHD)
Cc: Wrage, Lisa Ann (wrage@rti.org)
Subject: RE: "Final" version

Hi Kathleen,
The numbers all sync now, and it flows well.
I had to stop and re-read my old nemesis sentence a few times, but it is ok.

I have added the word "severe" in one place to prevent ambiguity in a different sentence. (highlighted in red) I hope you have room for it. ☺

Can you make the phrase in the table:
ROP type (number of infants)
Appear a line lower? That way no one will be trying to figure out if it applies to the percents.
Nice work !

Remember, you have to put the table tag into the text to have it show up. I put it there and highlighted in red.

Dale

From: Kennedy, Kathleen A [mailto:Kathleen.A.Kennedy@uth.tmc.edu]
Sent: Thursday, October 13, 2011 1:49 PM
To: Phelps, Dale; Higgins, Rosemary (NIH/NICHD)
Cc: Wrage, Lisa Ann (wrage@rti.org)
Subject: "Final" version

I think this is looking good. Lisa and I have finished arm wrestling about the numbers. If you (Dale and Rose) are ok with it, I think we can call it final, send it back to the SUPPORT Subcommittee and onto the NICHD for clearance.

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From: Kennedy, Kathleen A
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: PAS Deadlines
Date: Thursday, October 13, 2011 2:55:58 PM

I can easily understand the confusion. I have trouble keeping my projects straight and I don't have nearly the number of Network-related ones that you do. I'll send it to the Subcommittee just so they'll have the final version. I'm still waiting for 1 more clarification from Lisa and then I'm hoping it's finished.

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From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, October 13, 2011 1:53 PM
To: Kennedy, Kathleen A
Subject: RE: PAS Deadlines

Kathleen –
Forgive me – this has gone to the SUPPORT Subcommittee, so you are correct. There are several SUPPORT secondaries in various stages and I had forgotten that this one had already gone to them. Once you have a "final" version, I can send through NICHD clearance and you can upload it at the PAS website.

Thanks
Rose

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From: Kennedy, Kathleen A [mailto:Kathleen.A.Kennedy@uth.tmc.edu]
Sent: Thursday, October 13, 2011 2:25 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: PAS Deadlines

I'd rather not ask for comments on something that's "final". I've done what everyone suggested

(except for Michelle who had some great suggestions that will require additional data). I guess I could ask for suggestions for the presentation/manuscript.

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From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, October 13, 2011 1:21 PM
To: Kennedy, Kathleen A
Subject: Re: PAS Deadlines

And provide comments - they already approved the secondary analysis, so I doubt we would have nays!

From: Kennedy, Kathleen A <Kathleen.A.Kennedy@uth.tmc.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Thu Oct 13 14:16:36 2011
Subject: RE: PAS Deadlines

So, if I send them a "final" version by Monday, are they just supposed to vote yay or nay before early Nov?

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From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, October 13, 2011 1:15 PM
To: Kennedy, Kathleen A
Subject: Re: PAS Deadlines

Support subcommittee
Thanks
Rose

From: Kennedy, Kathleen A <Kathleen.A.Kennedy@uth.tmc.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Thu Oct 13 14:11:58 2011
Subject: RE: PAS Deadlines

I think we're close to a final version of the ROP secondary abstract. It looks like I need to send it back to the SUPPORT subcommittee but I'm not sure what comes next. Approval from whom in advance of NICHD clearance?

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From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, September 27, 2011 10:27 AM
To: 'Beau Batton'; Phelps, Dale; 'Bell, Edward (Pediatrics)'; Michael Cotten; 'Myriam Peralta, M.D.'; 'Vaucher, Yvonne'; Susan Hintz; 'Navarrete, Cristina'; 'Erika Fernandez'; Shankaran, Seetha; 'James Wynn, M.D.'; William MD Oh (woh@wihri.org); Kennedy, Kathleen A; 'Natarajan, Girija'; alaptook@WIHRI.org; Pappas, Athina; 'vohr'
Cc: 'mcw3@cwru.edu'; 'D'Angio, Carl'; 'Ron, MD Goldberg (goldb008@mc.duke.edu)'; 'Wally Carlo (wacarlo@uab.edu)'; 'Finer, Neil'; 'vanmeurs@leland.stanford.edu'; Duara, Shahnaz; 'Das, Abhik'; Wallace, Dennis; Archer, Stephanie (NIH/NICHD) [E]; 'Zaterka-Baxter, Kristin'; Cunningham, Meg; Gabrio, Jenna; 'Newman, Jamie'
Subject: PAS Deadlines

Please note—I have included you on this email as you have a PAS abstract (s) listed on the spreadsheet.

September 30, 2011 – Initial abstract draft due to subcommittee. This need not contain final data analyses results.

October 17, 2011 – Final abstract due to subcommittee. Approvals for abstracts must be obtained in advance of NICHD Clearance

Let me know if there are any questions.

Thanks
Rose

From: Kennedy, Kathleen A
To: Wrage, Lisa Ann
Cc: Phelps, Dale; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik
Subject: RE: ROP Natural History Abstract
Date: Thursday, October 13, 2011 2:08:43 PM
Attachments: ROP Natural History PAS Abstract.doc

I like all your changes. I think it's looking good. I have 1 remaining question. Since the numbers in the paragraph below the table now include the whole cohort not the group with known age of onset, shouldn't the proportion diagnosed with severe ROP after discharge be 10/138 not 10/128?

See change highlighted in blue.

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From: Wrage, Lisa Ann [mailto:wrage@rti.org]
Sent: Thursday, October 13, 2011 12:00 PM
To: Kennedy, Kathleen A
Cc: Phelps, Dale; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik
Subject: RE: ROP Natural History Abstract

Hi,
I have attached Kathleen's latest version with some changes/comments. One of the reasons some of the numbers were confusing is because of the 138 infants with severe ROP we know age of onset of "Any ROP" for 137 of them (since they had less severe ROP before severe ROP) and we know age of onset of 'Severe ROP" for 128 of them. SO, overall we know age of onset of 'Any ROP' for 642 of the 644 who developed any type of ROP. You did not have this number. I think that in future versions of the flowchart I will flow the 'severe ROP' group out of the 'Any ROP' group so that these numbers will be in the flowchart. Anyway, I have fixed the associated numbers in the abstract draft. I also changed the cohort number back to 997 because that is less confusing and I changed some text that refers to the severe ROP group as the 'treated' group, I still find that confusing because 1) some are not treated and 2) the PMA given is for onset (diagnosis) of ROP rather than treatment. I made those types of changes so now the groups are referred to consistently throughout, at least for me this is less confusing. I made all changes in track changes.
I also think the table is looking better.
Lisa

From: Kennedy, Kathleen A [mailto:Kathleen.A.Kennedy@uth.tmc.edu]
Sent: Thursday, October 13, 2011 12:01 PM
To: Wrage, Lisa Ann
Subject: RE: ROP Natural History Abstract

I've rearranged the results section because it seemed to confuse people. I have enough space so I

was able to put more of the numbers in there. Please use this one if you're checking the data.

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From: Wrage, Lisa Ann [mailto:wrage@rti.org]
Sent: Thursday, October 13, 2011 10:41 AM
To: Kennedy, Kathleen A; Phelps, Dale
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: ROP Natural History Abstract

Fyi I am going through the numbers, etc. now and will send an updated version of the abstract with my comments shortly.

From: Kennedy, Kathleen A [mailto:Kathleen.A.Kennedy@uth.tmc.edu]
Sent: Wednesday, October 12, 2011 6:46 PM
To: Phelps, Dale
Cc: Wrage, Lisa Ann; 'Higgins, Rosemary (NIH/NICHD) [E]'
Subject: RE: ROP Natural History Abstract

About Lisa's response:
I think we're all saying the same thing (understanding that "severe ROP" conceptually means "should be treated" and that our operational definition was treated or Type 1 ROP. (Your previous email said threshold rather Type 1 but we don't use that term anymore so I think you meant Type 1). You're also correct that it would be very unlikely for a baby to get diagnosed with Type 1 ROP before discharge and then get treated after discharge. It sounds like there was 1 baby diagnosed with Type 1 ROP after discharge who was not treated. I've added that 1 to the abstract, but just wanted to verify.

I re-ran the numbers a little too quickly before running off to class. Now I see where there's a problem and why my last version did agree with my previous calculations.

Lisa, in the flow diagram in the document you sent in September, there are 506 infants with ROP that did not meet Type 1 criteria and regressed without treatment. Beneath that, it says that 505 had known age of onset and 3 did not. That doesn't add up. I think it's because there are 2 babies who had some missing exams and they were moved from the "regressed ROP" to the "no ROP" category, but they were left in the box for unknown age of onset. So that box should really be 1, not 3. Is that correct?

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From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Wednesday, October 12, 2011 4:18 PM
To: Kennedy, Kathleen A
Cc: Wrage, Lisa Ann (wrage@rti.org); 'Higgins, Rosemary (NIH/NICHD) [E]'
Subject: RE: ROP Natural History Abstract

Hi Kathleen,

Thank you for the good revisions: we are getting there. I am still struggling with numbers, but I'm sure you and Lisa can figure these out.

Per the abstract:
1316 enrolled and 1091 survived to ROP age.
997 had a definitive ROP outcome, and 986 of those had sufficient data to determine age of onset of ROP.

So to me your key group is those 986. In the text and conclusions subsequently, you say 984,
644 developed ROP
of those 138 met the severe ROP criteria

Your sentence says that "644 infants developed ROP (138 met severe ROP criteria); 353 did not."
138 + 353 = 491, not the 644 (or 633) that you say developed ROP.
This was my confusion. What about the other 644-491 = 153 with ROP?
But I just figured it out (I think)

Is this what you meant? (seems obvious in retrospect):
644 infants developed ROP (138 of those met severe ROP criteria); 353 did not develop ROP.
644 with ROP + 353 without ROP = 997 infants... not the 984 (or 986) you say you have.
Or reverse it for clarity in the abstract (with corrected numbers) ?
353 infants did not develop ROP; 644 did (138 of those met severe ROP criteria).

In the table you report age of onset of ROP for 633 infants. Why the discrepancy between 644 and 633 ?
In the table you report PMA for onset of severe ROP for 128 infants. Why the discrepancy between 128 and 138 ?

In the title of the table, I think you have to revise a bit to say.
Cumulative Percentile with Diagnosis of ROP or Cumulative %tile with Diagnosis of ROP
But I'm not certain of this (Lisa/Marie help), but I think "%" is different than "percentile". If RTI says "no" you can leave it.

Title of the Abstract (has to be all caps)
I would say "...SCREENING GUIDELINES...." rather than "...SCREENING INTERVAL...."
The guidelines don't really talk about an interval, so I don't think you are testing an interval.

[I have put in some specific responses to you questions below, in square brackets—DLP]

and put in some minor edits or suggestions in green highlight in the attached copy of the text.

Dale

From: Kennedy, Kathleen A [mailto:Kathleen.A.Kennedy@uth.tmc.edu]
Sent: Wednesday, October 12, 2011 10:57 AM
To: Phelps, Dale
Cc: Wrage, Lisa Ann (wrage@rti.org); Higgins, Rosemary (NIH/NICHD)
Subject: RE: ROP Natural History Abstract

Thanks for the careful review. I tried to make most of these suggested changes (along with most of the suggestion in in the 16 other emails since Mon).

I have verified twice that the demographic comparisons are for severe ROP vs no ROP. Do you see something about that data that makes you think I've quoted it incorrectly?

I'm also struggling with the sentence that says what's in the table.

I think the min ages of diagnoses would be good to include and they are still consistent with the statement that treatable ROP was not diagnosed before 32 weeks. But a 0%ile really doesn't make sense, so I'm thinking we should put that in the text rather than the table. I've also added the late onset one to the text below the table because I don't think it makes sense to replace 99%ile with the 100%ile for such an extreme value.

[I agree with keeping the 99th%tile in the table and putting the range in the text. –DLP]

I haven't addressed Michelle's comment (at what point you can say a baby without prethreshold is no longer at risk to need treatment), although I think it's important, because we need more data and I doubt that we can get it before the deadline. A simple solution (not exactly the same thing but close) would be to add a line to the table for PMAs at which cumulative %iles of prethreshold were diagnosed. We can do that for the presentation/manuscript.

[I don't think we really need to address this. It is a clinical judgement made by the ophthalmologists and we are not ophthalmologists. Let's not go there. The guidelines say that stopping examinations depends on the eye findings. Let it go. There is not a 100% safe answer, especially for a neonatologist. –DLP]

I added the information about treatment after discharge. I just want to verify (quadruple check) that it was initial treatment (not "touch-up of previous laser treatment or vitrectomy or scleral buckle). What did you do with the ones where the date was uncertain? You should have the date of the first exam after treatment because that's when they met study outcome, right? If there was a long interval between that exam and the previous one, they would have been removed before because of uncertain timing of onset, right?

[As I count up the SUPPORT data: 132 infants were treated. 5 after discharge and 9 after transfer = 14.

14/132 is 10% of infants went on to treatment after leaving the primary hospital, ~1/3 of

those after discharge to home. It is a real problem everyone needs to be aware of. –DLP]

I've attached a new version. The changes (except for moving things around) are in yellow.

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Sent: Sunday, October 09, 2011 4:56 PM
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Cc: Wrage, Lisa Ann (wrage@rti.org); Archer, Stephanie (NIH/NICHD) [E] (archerst@mail.nih.gov); Higgins, Rosemary (NIH/NICHD)
Subject: RE: ROP Natural History Abstract

Thank you for your hard work on this Kathleen,
I have been through the abstract again, and discovered some things we had missed.. probably because we're too familiar with the material already. Just some clarifications, no real substantive changes. I have edited the abstract in the attached word file. (They are not track changes because my old laptop seems to confuse others when I use them.

Thanks again!
Dale

From: Kennedy, Kathleen A [mailto:Kathleen.A.Kennedy@uth.tmc.edu]
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Cc: Wrage, Lisa Ann (wrage@rti.org); Phelps, Dale; Archer, Stephanie (NIH/NICHD) [E] (archerst@mail.nih.gov); Higgins, Rosemary (NIH/NICHD)
Subject: ROP Natural History Abstract

SUPPORT Subcommittee: I've attached a draft of the PAS abstract for the ROP Natural History Secondary Study that uses data from the SUPPORT trial. Comments and suggestions are welcome. I hope to get the missing data before the deadline. If anyone knows how to navigate the submission process (how to include the NICHD without entering the NICHD as an author and then being required to submit a bunch of CME/COI disclosures for the NICHD), I'd appreciate the help.

Stephanie, could you please check to make sure I haven't missed anyone on the SUPPORT Subcommittee?

Lisa, if we could get the data for treatment after back transfer and after discharge, that would be great. If you can tabulate the 0 and 100%iles and they look reasonable (no extreme outliers), we could replace the 1 and 99%iles in the table with 0 and 100%iles.

Kathleen A. Kennedy, MD, MPH
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Evaluating the Retinopathy of Prematurity (ROP) Screening Guidelines for 24-27 Week Gestational Age Infants

Kathleen A. Kennedy MD MPH, Lisa Wrage, MPH, Dale L. Phelps MD, Rosemary D. Higgins on behalf of the SUPPORT Subcommittee for the NICHD Neonatal Research Network

Background:
Timely detection of treatable ROP is important to assure optimal outcomes for infants who meet the criteria for treatment. Current (2006) screening guidelines are based on natural history data from randomized trials that enrolled infants between 1986-1997: screening should begin by 31 weeks postmenstrual age (PMA = gestational age at birth + postnatal age) and continue until the vessels have reached zone III at ≥ 35 weeks, or, for infants without prethreshold ROP, until a PMA of 45 weeks. Since the 1980s, survival of lower gestational age infants has increased, and earlier treatment of ROP (Type 1 ROP: stage 3 or ROP with plus disease in zone I or stage 2-3 with plus disease in zone II) is recommended. The timing of onset of ROP is related most closely to PMA.

Objective:
To validate current screening recommendations for detection of treatable ROP in 24-27 week gestational age infants.

Design/Methods:
In the NICHD Network SUPPORT trial, severe ROP (Type 1 ROP or treatment with laser, cryotherapy or bevacizumab) or death was the primary outcome for the O_2 saturation target arm of the factorial design. Infants 24 0/7 to 27 6/7 weeks gestational age (no birth weight limits) with consent prior to delivery were eligible for this study. ROP examinations were conducted according to current screening recommendations and recorded using the international classification of ROP. Results of each exam were prospectively collected for all enrolled infants until a study endpoint was reached: ROP treatment, full vascularization to the ora serrata, vascularization in zone III in 2 consecutive exams, or the infant was 55 weeks PMA.

Results:
1316 infants were enrolled. 1091 (83%) of infants survived to the age of ROP determination. 997 (91%) of these infants had a definitive ROP outcome. 644 infants developed ROP of any severity (138 infants met criteria for severe ROP); 353 infants had no ROP. Among infants with ROP, 642/644 (99.7%) of infants with any ROP and 128/138 (93%) infants with severe ROP had sufficient exam data (no missing or delayed exams before diagnosis) to determine the age of onset of ROP. As expected, infants with severe ROP were less mature [mean (SD) 25.5 (0.9) wks vs 26.8 (0.9) wks, p<0.0001], lower birth weight [mean (SD) 708 (148)g vs 942 (173)g, p<0.0001], and more likely to be White race (44% vs 35%, p=0.07) than infants with no ROP. For the infants with ROP and known age of onset, the PMAs for selected percentiles are shown in the table:

ROP type (number of infants)	Cumulative % with Diagnosis of ROP						
	1%	5%	25%	50%	75%	95%	99%
	Postmenstrual Age (weeks)						
Diagnosis of any ROP (n=642)	30.4	31.4	32.7	33.9	35.1	37.9	41.0
Diagnosis of severe (Type 1/Treated) ROP (n=128)	32.7	33.9	35.1	36.4	38.6	43.3	45.0

The PMA at onset of severe ROP ranged from 32.1 to 53.1 weeks. In this referral center cohort of 997 infants, 0.5% were diagnosed with severe ROP after back transfer to another NICU; 1.0% of the cohort ([redacted] of infants with severe ROP) reached severe ROP criteria after discharge to home.

Our data are consistent with the 2006 ROP screening guidelines. In this cohort of 997 infants born at 24-27 weeks, we did not observe ROP needing treatment before 32 weeks PMA; only 1 infant was diagnosed with severe ROP after 45 weeks PMA. A limitation of this study is that infants < 24 weeks gestational age were not enrolled and these data may not be generalizable to less mature infants at the highest risk for ROP.

From:	Roger Faix
To:	Higgins, Rosemary (NIH/NICHD) [E]; "Finer, Neil"; "Vaucher, Yvonne"; "Wally Carlo (wacarlo@uab.edu)"; Myriam Peralta, M.D.; kurt.schibler@cchmc.org; "mcw3@cwru.edu"; Bradley Yoder; "Das, Abhik"; Gantz, Marie; "Nancy Newman"; Rich, Wade
Cc:	Archer, Stephanie (NIH/NICHD) [E]
Subject:	RE: Support NDI_09-26-2011
Date:	Thursday, October 13, 2011 11:49:26 AM
Attachments:	Support NDI_09-26-2011.doc

See comments on attachment. Items are bold red are suggested for deletion. Items in bold purple are suggested for for insertion. Items in bold purple are questions/comments for your consideration. I hope these are helpful.

I concur that it is important to emphasize as much as we can that the difference in severe ROP noted in the high sat group in the original report did NOT result in any significant difference in blindness or other major ocular morbidity on follow-up.

Roger

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]
Sent: Friday, September 30, 2011 6:32 AM
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Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: Support NDI_09-26-2011

Here is the SUPPORT oximetry follow up paper. Please indicated which CONSORT diagram you would like to use.

Please send comment back to Myriam Peralta by October 13.

Thanks
Rose

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Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Support NDI_09-26-2011

Here is the last draft that I have for now, I am not sure which flow chart we would like to use as we had discussed both, so I included both. I will send you the abstract later today, thanks.

Neurodevelopmental Outcome of Extremely Preterm Infants in a Trial of Different Oxygen Saturation Targets

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Word Count

Abstract: 248

Text: 1,148

ABSTRACT

BACKGROUND

Targeting lower (vs. higher) oxygen saturations in the SUPPORT Trial decreased severe retinopathy of prematurity but increased mortality before discharge. We hypothesized that the effects of different oxygen levels on long term neurodevelopmental intact survival were not significant.

METHODS

We followed 1211 of 1316 (92%) infants born at 24 to 27 week gestation and randomized to higher (91-95%) or lower oxygen saturation targets (85-89%) from birth to 36 weeks corrected age. The outcome of this follow up study was a composite of death or neurodevelopment impairment at 18 to 22 months corrected age. Neurodevelopmental impairment was defined as a Bayley III cognitive composite score of less than 70, modified Gross Motor Function Classification System $\geq$2, presence of moderate to severe cerebral palsy, permanent hearing loss, and/or bilateral blindness.

RESULTS

Death or neurodevelopmental impairment occurred in 185 (30.2%) infants in the lower oxygen saturation group and 171 (27.5%) infants in the higher oxygen saturation group (relative risk 1.12; confidence interval 0.94, 1.32; p=0.21). Death occurred in 140 (22.1%) of the children in the lower oxygen saturation group and in 118 (18.2%) in the higher oxygen saturation group

(relative risk 1.25; confidence interval 1, 1.55, p=0.05). **Should we include findings re: blindness/visual morbidity in abstract, since the lack of apparent difference attributable to ROP on follow-up is one of the major points of this article, in my opinion.**

CONCLUSIONS

Among extremely preterm infants targeted at different levels of oxygen saturation, no significant difference in death or neurodevelopmental impairment was observed at 18 to 22 months. Mortality remained elevated in the lower oxygen target group at 18 to 22 months, though the trend was only borderline statistically significant.

Oxygen supplementation is a vital therapy for survival of many preterm infants with respiratory disorders. However, oxygen supplementation may increase the risk of retinopathy of prematurity, bronchopulmonary dysplasia,[Tin et al, 2001] periventricular leukomalacia,[Chow et al, 2003] and cerebral palsy.[Anderson et al, 2004] Restrictive oxygen therapy decreases retinopathy but has resulted in increased deaths in randomized controlled trials.[Bolton DP et al, 1997; Askie et al, 2009; Carlo et al, 2010; Stenson et al, 2011]

Comment [WC1]: These references are quoted in my NEJM paper

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development SUPPORT Trial demonstrated no significant difference in a composite outcome including retinopathy of prematurity and death between a lower oxygen saturation group (85-89%) and the higher saturation target group (91-95%). However, mortality was increased and severe retinopathy of prematurity was reduced in the lower oxygen saturation group compared to the higher saturation target group. A recent meta-analysis that included the SUPPORT Trial and two other subsequently multi-center randomized controlled trials with a total of 3631 infants showed that infants randomized to an oxygen saturation of 91-95% % had a lower mortality rate than infants randomized to oxygen saturation targets of 85-89% (17.3% versus 14.4%, P=0.015).[Stenson, NEJM 2011] There has been keen interest in determining whether oxygen supplementation can reduce neurodevelopmental impairment. However, in two non randomized studies of oxygen saturation targeting,[Tin et al, 2001; Bradley et al, 1993] neurodevelopmental outcome did not differ by oxygen targets.

Comment [WC2]: Spell out

This study evaluated the composite outcome of death or neurodevelopmental impairment at 18 to 22 months corrected age in the subjects enrolled in the SUPPORT trial and randomized to two

groups of extremely preterm infants randomized to lower (85-89%) or higher oxygen saturation targets (91-95%) from birth to 36 weeks corrected age.

METHODS

Study Design

1316 extremely preterm infants (24 weeks 0 days to 27 weeks 6 days) born between February 2005 and February 2009 at 20 centers in the United States participating in the Neonatal Research Network of the Eunice Kennedy Shriver National Institute of Child Health and Human Development were enrolled immediately following delivery in the prospective, randomized, controlled SUPPORT trial. Permuted block randomization was used, with stratification according to center and gestational age (24 weeks 0 days to 25 weeks 6 days or 26 weeks 0 days to 27 weeks 6 days). The infants were randomly assigned before birth to a target range of oxygen saturation of 85% to 89% (the lower oxygen saturation group) or 91 to 95% (the higher oxygenation group). Using a 2-by-2 factorial design, participants were also randomly assigned to receive either CPAP immediately following delivery and a limited ventilation strategy if subsequent intubation was required or intubation with surfactant administration within an hour after birth. Procedures for enrollment, intervention and data collection have been previously reported. [Carlo NEJM] . The study was approved by the institutional review board at each participating site and RTI international **(Does RTI stand for Research Triangle International? If so, the extra International after RTI is redundant.)** which is the independent data coordinating center for the Neonatal Research Network. Written informed consent was obtained from the parent(s) or guardian (s) of each child before delivery.

Assessments

All infants who survived to 36 weeks corrected age were eligible to participate in the prospective follow up cohort of the SUPPORT trial. A comprehensive neurodevelopmental assessment was performed at 18-22 months of corrected age by neurologic examiners and neurodevelopmental testers who were unaware of the treatment assignments and had been trained annually for reliability of assessments during a 2-day workshop. Developmental assessment was assessed using The Bayley Scales for Infant Development 3rd edition (BSID III) (ref). Cognitive Composite Scores are reported as a standardized score with a mean of 100 and a standard deviation of 15. The modified Gross Motor Function Classification System (GMFCS) (ref) describes the gross motor performance and has a range from 0 (normal) to 5 (most impaired). Examiners also recorded the presence of cerebral palsy defined as a nonprogressive disorder of the central nervous system and characterized by abnormal muscle tone in at least one arm or leg associated with abnormal control of movement or posture with delayed attainment of motor milestones. Cerebral palsy was classified depending on severity into mild (GMFCS $\leq$1) (**This seems to imply that a GMFCS of zero would be categorized as mild.)**, moderate (GMFCS 2 or 3) or severe (GMFCS $\geq$ 4). Hearing and visual impairment were determined based on parental history and examination.

Certified research nurses collected demographic and neonatal data using standardized definitions in the trial's manual of operations. Data collection included (but was not limited to) gestational age, birthweight, gender, multiple gestation, race/ethnicity, ROP status, BPD status, history of medical or surgical NEC, history of late onset sepsis, use of postnatal steroids, rehospitalizations, interim medical history, surgeries, insurance status, marital status, maternal education, household

income, language spoken at home, whether living with biological parents. Socioeconomic data was updated during the 18-22 month visit and if not available, data during the neonatal period was included.

Outcome

The composite of death or neurodevelopmental impairment at 18 to 22 months corrected age for prematurity was the primary neurodevelopmental outcome. This composite outcome was selected because infants who died before 18 months could not be classified as having neurodevelopmental impairment. Neurodevelopmental impairment was defined as having any of the following: BSID III cognitive composite score less than 70, GMFCS $\geq$ 2, presence of moderate or severe cerebral palsy, permanent hearing loss that does not permit the child to understand directions of the examiner and communicate despite amplification with hearing aids or cochlear implants, or bilateral visual impairment (vision < 20/200).

Analysis

Data was entered in standard forms and was transmitted to RTI International **(see previous comment)** which stored, managed and analyzed the data for this study. Details regarding sample size calculations for the SUPPORT trial have been previously reported (ref finer). All analyses were performed according to the intention to treat principle. The denominator that was used to calculate the rate of each outcome was the number of infants for whom the outcome was known. The primary analysis focused on the percentage of infants in each group for whom the primary

outcome of death or NDI at 18 to 22 months corrected age could be assigned. Analysis of this and all other categorical outcomes was performed with the used of robust Poisson regression in a generalized-estimating-equation model to obtain adjusted relative risks with 95% confidence intervals. **(Move description of factors adjusted for from next paragraph to here)** Continuous outcomes were analyzed with the use of mixed-effects linear models to obtain adjusted means and standard errors.

In the analysis of all outcomes, the results were adjusted, as pre-specified, for gestational-age strata, center and familial clustering **(Move this sentence to previous paragraph).** Two-sided p value of less than 0.05 were considered to indicate statistical significance, and no adjustments have been made for multiple comparisons. RESULTS

Characteristics of the Study Sample

The SUPPORT trial enrolled 1316 study in the study (see flowchart in Figure 1). Five hundred twenty four infants in the lower oxygen saturation group and 555 in the higher oxygen saturation group survived to discharge from the hospital. The baseline characteristics of the entire group have been reported previously.(Carlo NEJM) Ten children in the lower oxygen saturation group and 11 children in the higher oxygen saturation group died after discharge from the nursery prior to the 18 to 22 month adjusted age follow up visit. Thirty five children in the lower saturation group and 33 children in the higher saturation group were lost to follow up. However 9/35 in the lower saturation group and 11/33 in the higher saturation group were known to be alive at 18 to 22 months adjusted age. Neurodevelopmental assessment was performed in 990/1058 eligible infants (93.6%). Of those who were evaluated at the 18 to 22 months adjusted age, neurodevelopmental impairment was determined in 976 children. From the entire cohort the pre-

specified outcome of death or neurodevelopmental impairment was able to be determined in 93.8% (1234/1316). There were no significant differences in the baseline characteristics of the cohort that was followed up and then lost to follow up. The mothers **at the of those** lost to follow up were more likely to be married and more likely to have public health insurance. *(add numbers, Marie not sure if I have these ones, I could not find them)*

We looked at the baseline characteristics of the follow up cohort and the entire trial cohort which is presented in Table 1. The percentage of infants who were small for gestational age in the higher saturation target group was higher compared to the infants who were in the lower saturation target group in the follow up cohort group. In addition, as reported previously, severe retinopathy of prematurity had a higher incidence in the higher oxygen saturation group compared to the lower saturation group. No other significant differences were reported in the baseline characteristics of the eligible infants for follow up.

Primary Outcome

The mean corrected age for neurodevelopmental evaluation was similar between both groups (low SpO2 19.9 m $\pm$ 2.4 vs. High SpO2 20.2 $\pm$ 2.7 mo, p=0.076). Prevalence of the composite primary outcome of death or neurodevelopmental impairment was not significantly different between the lower and higher oxygen saturation target groups. (Table 2) Similar results were observed within both gestational age strata (Low SpO2 115/261, 44.1% vs. High SpO2 112/276, 40.6%, P= 0.4201 for the 24 0/7-25 6/7 wks ga; and Low SpO2 70/351, 19.9% vs High SpO2 59/346, 17.1%, p=0.33 for the 26 0/7 – 27 6/7 wks GA). Death prior to the 18 to 22 month adjusted age visit was higher among infants in the lower oxygen saturation target group compared to those in the higher saturation target group. (Low SpO2 140/633, 22.1% vs. high

SpO2 118/648 , 18.2%, relative risk 1.25 95% CI 1, 1.55, p=0.0462). However death at 18 to 22 months adjusted age was not significantly different within both gestational age strata (low SpO2 91/267, 34.1% vs. High SpO2 79/283, 27.9%, relative risk 1.23 95% CI 0.95, 1.59 P=0.118 for the 24 0/7-25 6/7 wks GA; and Low SpO2 49/366, 13.4% vs. High SpO2 39/365, 10.7%, relative risk 1.28 95% CI 0.86, 1.89, p=0.2195).

The rate of neurodevelopmental impairment among survivors followed at 18 to 22 month adjusted age visit was similar between the lower and the higher oxygen saturation target groups. Rates for neurodevelopmental impairment were not significantly different in either of the gestational age strata groups.

Outcomes among survivors at follow up

The percentage of children with Bayley III cognitive scores below 70 was not significantly different between the lower and higher oxygen saturation group. In addition we looked into the percentage of children with Bayley cognitive scores below 85 and these were not significantly different between the groups. Mean scores of the Bayley Scales of Cognitive Composite are presented in table 3.

The rate of retinopathy of prematurity as well as infants, who required eye surgery, was higher in the higher oxygen target group compared to the lower oxygen target group; however the rate of blindness was not significantly different at the 18 to 22 month adjusted age visit. Other visual outcomes are presented in table 3. **(Any point worth adding re: contrast/comparisons with CPAP vs Surf part of study?)**

DISCUSSION

In this multicenter, follow up study of infants randomized to a lower target range of oxygen saturation (85 to 89%) or to a higher target oxygen saturation (91 to 95%) there were no significant difference in the prespecified outcome of death or neurodevelopmental impairment. To our knowledge this is the only large comprehensive study that has included neurodevelopmental impairment as an outcome for evaluating effects on different oxygen target saturation levels. There has been a previous concern of using lower saturation target and increased mortality in extreme premature infants (ref) In addition we found that death prior to discharge in the SUPPORT trial showed increased mortality among children who were assigned to lower target saturation levels,. **however I In** this follow up study, death at 18 to 22 months of age was not significantly different between the two target groups or at the different gestational age stratification levels.

We had reported previously that our lower saturation oxygen target was associated with a large reduction in the incidence of severe retinopathy of prematurity among survivors. (ref) It has been previously reported that severe ROP may be associated with poor visual outcomes even with treatment(ref) Although our study was not powered to detect small differences in eye disorders or visual function at 18 to 22 months of age, we did find that there were no significant differences in the report of unilateral and bilateral blindness among the two groups. Eye surgery was reported higher in our group with a higher oxygen saturation target more likely related to higher incidence of severe retinopathy of prematurity, although data regarding specifics of eye surgery **was were** not collected (*Marie I think we actually did this but did not have it in the*

table). Additional analysis regarding eye findings and its association with presence of severe retinopathy of prematurity is needed.

There had been concerns that lower saturation oxygen saturation targets are associated with effects on long term neurdevelopmental impairment (ref). However NDI as we defined in this study was not found to be significant in the lower or higher oxygen saturation assigned group.

In addition Cerebral Palsy was not significant in both groups. it is **to note notable** that the incidence of CP was lower as previously reported in other outcome studies.

It has been recognized that higher oxygen levels can be associated with lung disease, however we found no difference in the use of postnatal corticosteroids, diuretics or long term use of oxygen as well as rehospitalization between the two groups.

This study has some limitations,. tThis study reports only follow up to 18 to 22 months of age, which may had not been enough time to detect the presence of other minor **however but** important disabilities. However it is **to note here notable that** when we used the cutoff of Bayley III to less than 85 we also did not find significant differences between the groups. In addition there is an ongoing follow up SUPPORT study that will be reporting in the future the follow up outcome of these children at school age. These children were enrolled in tertiary care centers therefore generalizibility is a concern, however we include 20 centers around the country. **(This last sentence is awkward.)**

In summary we found no significant differences in death or Neurodevelopmental impairment, at 18 to 22 months corrected age in extremely premature infants that were randomized to receive lower target oxygen saturation or higher target oxygen saturation. Increased death at discharge

that was found on our previous report associated with lower target oxygen saturation was still present at 18 to 22 months adjusted age. Although retinopathy of prematurity was associated with higher oxygen saturation target levels, blindness was not significantly different among survivors.

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Comment [bbj]: Check references

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Tin W, Milligan DW, Pennefather P, Hey E. Pulse oximetry, severe retinopathy, and outcome at one year in babies of less than 28 weeks gestation. Arch Dis Child Fetal Neonatal. 2001;84:F106-F110.

Table 1. Baseline characteristics of the SUPPORT group

Formatted: Width: 11", Height: 8.5"

Characteristics	Trial Cohort		Cohort with Follow-up Visit	
	Lower Oxygen Saturation	Higher Oxygen Saturation	Lower Oxygen Saturation	Higher Oxygen Saturation
	N=654	N=662	N=479	N=510
Birth weight – g	835.5± 193.4	824.8± 193	857.8 ± 186.3	843.9± 191.6
Gestational age – wk	26.2 ± 1.1	26.1 ± 1.1	26.3 ± 1.1	26.2 ± 1
Small for gestational age – no./total no. (%)	41/654 (6.3)	55/662 (8.3)	17/479 (3.5)*	38/511 (7.4)*
Male sex – no./total no. (%)	341/654 (52.1)	371/662 (56)	240/479 (50.1)	281/510 (55.1)
Race or ethnic group – no./total no. (%)				
Non Hispanic Black	257/654 (39.3)	232/662 (35)	201/479 (42)	176/510 (34.5)
Non Hispanic White	242/654 (37)	279/662 (42.1)	178/479 (37.2)	217/510 (42.5)

Hispanic	132/654 (20.2)	127/662 (19.2)	86/479 (18)	97/510 (19)
Other or unknown	23/654 (3.5)	24/662 (3.6)	14/479 (2.9)	20/510 (3.9)
Multiple births – no./total no. (%)	161/654 (24.6)	176/662 (26.6)	124/479 (25.9)	128/510 (25.1)
Maternal educational level <high school no./total no. (%)	148/594 (24.9)	165/612 (27)	115/471 (24.4)	129/504 (25.6)
Public Health Insurance only – no./total no. (%)	356/650 (54.8)	348/660 (52.7)	253/479 (52.8)	266/511 (52.1)
Mother married – no./total no. (%)	284/652 (43.6)	308/661 (46.6)	222/479 (46.3)	243/511 (47.6)
Lives with both biological parents – no./total no. (%)	354/508 (69.7)	364/547 (66.5)	332/478 (69.5)	345/511 (67.5)
Household income < $30,000/year – no./total no.(%)	247/474 (52.1)	291/528 (55.1)	239/456 (52.4)	272/498 (54.6)
English as primary language – no./total no. (%)	402/477 (84.3)	429/513 (83.6)	402/477 (84.3)	427/511 (83.6)
Cesarean section – no./total no. (%)	441/654 (67.4)	442/662 (66.8)	332/479 (69.3)	335/511 (65.6)
Antenatal steroids – no./total no. (%)	633/654 (96.8)	632/661 (95.6)	462/479 (96.5)	487/511 (95.3)
Retinopathy of prematurity – no./total no. (%)	41/475 (8.6)**	91/509 (17.9)**	38/442 (8.6)**	82/471 (17.4)**

Bronchopulmonary dysplasia – no./total no. (%)	205/540 (38)	237/568 (41.7)	177/479 (37)	203/511 (39.7)
Intraventricular hemorrhage grade 3 or 4 or Periventricular leukomalacia – no./total no. (%)	98/630 (15.6)	100/640 (15.6)	56/478 (11.7)	60/510 (11.8)
Necrotizing enterocolitis – no./total no. (%)	76/641 (11.9)	70/649 (10.8)	42/479 (8.8)	44/511 (8.6)
Late onset sepsis/meningitis – no./total no. (%)	228/624 (36.5)	226/634 (35.6)	155/479 (32.4)	166/511 (32.5)
Post natal steroids – no./total no. (%)	61/636 (9.6)	69/644 (10.7)	41/477 (8.6)	48/507 (9.5)
CPAP – no./total no. (%)	336/654 (51.4)	327/662 (49.4)	254/479(53)	257/511 (50.3)
Surfactant – no./total no. (%)	318/654 (48.6)	335/662 (50.6)	225/479 (47)	254/511 (49.7)

*p<0.05, **p<0.001

Table 2. Primary Outcomes at 18-22 Months Adjusted AGe

	Lower Oxygen Saturation N=654	Higher Oxygen Saturation N=662	Adjusted Relative Risk	p value
Death prior to discharge – no./total no. (%)	130/654 (19.9)	107/662 (16.2)		
Outcome determined by death or NDI – no./total no. (%)	612/654 (93.6)	622/662 (94)	1 (0.97, 1.03)	0.7927
Died by 18-22 months – no./total no. (%)	140/633 (22.1)	118/648 (18.2)	1.25 (1, 1.55)	0.0462
Neurodevelopmental impairment or death – no./total no. (%)	185/612 (30.2)	171/662 (27.5)	1.12 (0.94, 1.32)	0.2098
Survivors at follow-up				
Neurodevelopmental impairment – no./total no. (%)	45/472 (9.5)	53/504 (10.5)	0.87 (0.6, 1.28)	0.4920
Bayley III cognitive composite score < 70 – no./total no. (%)	34/471 (7.2)	38/503 (7.6)	0.91 (0.58, 1.43)	0.6870
Gross motor function level ≥ 2 – no./total no. (%)	26/479 (5.4)	23/511 (4.5)	1.17 (0.68, 2.01)	0.5597
Moderate/severe cerebral palsy – no./total no. (%)	20/479 (4.2)	20/511 (3.9)	1 (0.54, 1.83)	0.9971
Blindness – no./total no. (%)	5/479 (1)	8/511 (1.6)	0.67 (0.22. 2.02)	0.4789
Deafness – no./total no. (%)	12/479 (2.5)	12/511 (2.3)	1.16 (0.54, 2.49)	0.7013

Table 3. Medical Outcomes by Group

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Outcome	Low SpO2 (N=479)	High SpO2 (N=510)	Relative Risk for Low SpO2 vs. High SpO2 (95% CI)	Adjusted difference in means (95% CI)	Adjusted P-value
Bayley Scales of Infant Development III					
Cognitive composite < 70					
Cognitive composite <85	105/471 (22.3)	131/502 (26.1)	0.86 (0.69, 1.07)		0.1831
Mean Scores					0.2940
Median Scores					
					0.8121
					0.3016
Neurologic findings					0.8948
Mild cerebral palsy	23/459 (5.0)	21/490 (4.3)	1.16 (0.66, 2.02)		0.6105

Moderate cerebral palsy	11/447 (2.5)	10/479 (2.1)	1.19 (0.52, 2.71)	0.6873
Severe cerebral palsy	9/445 (2.0)	10/479 (2.1)	0.95 (0.39, 2.27)	0.9026
Any cerebral palsy	43/479 (9.0)	41/510 (8.0)	1.12 (0.76, 1.65)	0.5766
Abnormal neurologic exam	108/479 (22.5)	114/510 (22.4)	1.02 (0.82, 1.27)	0.8606
Vision findings				
Strabismus	46/478 (9.6)	41/509 (8.1)	1.2 (0.7, 1.8)	0.3845
Nystagmus	22/479 (4.6)	12/509 (2.4)	1.95 (0.94, 4.07)	0.0737
Tracks 180 degrees	462/476 (97.1)	492/506 (97.2)	1 (0.98, 1.02)	0.9330
Corrective lenses both eyes vs. normal both eyes	21/468 (4.5)	20/492 (4.1)	1.14 (0.62, 2.08)	0.6774
Blind, some function, both eyes	3/450 (0.7)	2/474 (0.4)	1.56 (0.27, 8.95)	0.6151
Blind, no useful vision, both eyes	2/449 (0.4)	4/476 (0.8)	0.54 (0.1, 2.95)	0.4789
Other abnormal vision	6/453 (1.3)	12/484 (2.5)	0.55 (0.21, 1.46)	0.2301
Eye surgery	31/477 (6.5)	67/508 (13.2)	0.52 (0.35, 0.78)	0.0014
Medicines				
Bronchodilators	159/475 (33.5)	185/505 (36.6)	0.92 (0.78, 1.09)	0.3583
Steroids	95/475 (20.0)	108/505 (21.4)	0.92 (0.72, 1.18)	0.5016

Diuretics	15/475 (3.2)	14/505 (2.8)	1.16 (0.58,2.34)	0.6717
Anticonvulsants	12/478 (2.5)	12/510 (2.4)	1.08 (0.49, 2.37)	0.8514
Readmission	210/478 (43.9)	238/510 (46.7)	0.94 (0.82, 1.08)	0.4111
Readmission for respiratory reason	110/470 (23.4)	127/503 (25.2)	0.93 (0.74, 1.16)	0.5114
No Readmission for growth/nutrition	12/470 (2.6)	13/503 (2.6)	1.05 (0.49, 2.25)	0.8953

From: Phelps, Dale
To: "Kennedy, Kathleen A"
Cc: Wrage, Lisa Ann (wrage@rti.org); Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: ROP Natural History Abstract
Date: Wednesday, October 12, 2011 7:24:21 PM

How soon we forget! :-)

You're right. I am rereading the background very carefully with this in mind, and I think you are correct. You have been very careful in your statement to say that the guidelines are based on those natural history studies.
I would not change it.
Dale

From: Kennedy, Kathleen A [mailto:Kathleen.A.Kennedy@uth.tmc.edu]
Sent: Wednesday, October 12, 2011 4:20 PM
To: Phelps, Dale
Subject: RE: ROP Natural History Abstract

There's also the paper from Sweden that you sent awhile back. Neither of these has the detail that would be needed for revising recommendations. I think I was careful not to say that "no one else has looked at it". Do you think I need to mention these two papers? It would take a couple of sentences to explain why this abstract provides new information if we do that.

Kathleen A. Kennedy, MD, MPH
Richard W. Mithoff Professor of Pediatrics
Director, MS in Clinical Research Degree Program
UT-Houston Medical School
6431 Fannin, Suite 2.106
Houston, TX 77030
713 500-6708

From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Wednesday, October 12, 2011 6:09 PM
To: Kennedy, Kathleen A
Cc: Wrage, Lisa Ann (wrage@rti.org); 'Higgins, Rosemary (NIH/NICHD) [E]'
Subject: RE: ROP Natural History Abstract

Thanks for working on this, sounds like you've about got it. (yes, I did meant Type 1 ROP, not 'threshold', thanks).

There is one more conceptual revision we need to seriously consider for the wording of the abstract.

The ETROP study enrolled infants <1251 grams from 2000-2002, and reported the incidence and various ROP 'events' by PMA in 2320 infants.
They report the PMA of prethreshold ROP, but not threshold. (also PMA for stage 1, stage 2, stage 3, and plus disease)
They report median, 5% and 95%, (but not 1%, 99% nor range).

So we can't really say no one else has looked at this since 1997, but it is also true that the manner in which the ETROP results were reported, you can't use their data to 'test' the 2006 guidelines.

I attach the reprint.

Dale

From: Kennedy, Kathleen A [mailto:Kathleen.A.Kennedy@uth.tmc.edu]
Sent: Wednesday, October 12, 2011 3:46 PM
To: Phelps, Dale
Cc: Wrage, Lisa Ann (wrage@rti.org); 'Higgins, Rosemary (NIH/NICHD) [E]'
Subject: RE: ROP Natural History Abstract

About Lisa's response:
I think we're all saying the same thing (understanding that "severe ROP" conceptually means "should be treated" and that our operational definition was treated or Type 1 ROP. (Your previous email said threshold rather Type 1 but we don't use that term anymore so I think you meant Type 1). You're also correct that it would be very unlikely for a baby to get diagnosed with Type 1 ROP before discharge and then get treated after discharge. It sounds like there was 1 baby diagnosed with Type 1 ROP after discharge who was not treated. I've added that 1 to the abstract, but just wanted to verify.

I re-ran the numbers a little too quickly before running off to class. Now I see where there's a problem and why my last version did agree with my previous calculations.

Lisa, in the flow diagram in the document you sent in September, there are 506 infants with ROP that did not meet Type 1 criteria and regressed without treatment. Beneath that, it says that 505 had known age of onset and 3 did not. That doesn't add up. I think it's because there are 2 babies who had some missing exams and they were moved from the "regressed ROP" to the "no ROP" category, but they were left in the box for unknown age of onset. So that box should really be 1, not 3. Is that correct?

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713 500-6708

From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Wednesday, October 12, 2011 4:18 PM
To: Kennedy, Kathleen A
Cc: Wrage, Lisa Ann (wrage@rti.org); 'Higgins, Rosemary (NIH/NICHD) [E]'
Subject: RE: ROP Natural History Abstract

Hi Kathleen,

Thank you for the good revisions: we are getting there. I am still struggling with numbers, but I'm sure you and Lisa can figure these out.

Per the abstract:
1316 enrolled and 1091 survived to ROP age.
997 had a definitive ROP outcome, and 986 of those had sufficient data to determine age of onset of ROP.

So to me your key group is those 986. In the text and conclusions subsequently, you say 984,
644 developed ROP
of those 138 met the severe ROP criteria

Your sentence says that "644 infants developed ROP (138 met severe ROP criteria); 353 did not."
138 + 353 = 491, not the 644 (or 633) that you say developed ROP.
This was my confusion. What about the other 644-491 = 153 with ROP?
But I just figured it out (I think)

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644 infants developed ROP (138 of those met severe ROP criteria); 353 did not develop ROP.
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Or reverse it for clarity in the abstract (with corrected numbers) ?
353 infants did not develop ROP; 644 did (138 of those met severe ROP criteria).

In the table you report age of onset of ROP for 633 infants. Why the discrepancy between 644 and 633 ?
In the table you report PMA for onset of severe ROP for 128 infants. Why the discrepancy between 128 and 138 ?

In the title of the table, I think you have to revise a bit to say.
Cumulative Percentile with Diagnosis of ROP or Cumulative %tile with Diagnosis of ROP
But I'm not certain of this (Lisa/Marie help), but I think "%" is different than "percentile". If RTI says "no" you can leave it.

Title of the Abstract (has to be all caps)
I would say "...SCREENING GUIDELINES...." rather than "...SCREENING INTERVAL...."
The guidelines don't really talk about an interval, so I don't think you are testing an interval.

[I have put in some specific responses to you questions below, in square brackets—DLP]

and put in some minor edits or suggestions in green highlight in the attached copy of the text.

Dale

From: Kennedy, Kathleen A [mailto:Kathleen.A.Kennedy@uth.tmc.edu]
Sent: Wednesday, October 12, 2011 10:57 AM
To: Phelps, Dale
Cc: Wrage, Lisa Ann (wrage@rti.org); Higgins, Rosemary (NIH/NICHD)
Subject: RE: ROP Natural History Abstract

Thanks for the careful review. I tried to make most of these suggested changes (along with most of the suggestion in in the 16 other emails since Mon).

I have verified twice that the demographic comparisons are for severe ROP vs no ROP. Do you see something about that data that makes you think I've quoted it incorrectly?

I'm also struggling with the sentence that says what's in the table.

I think the min ages of diagnoses would be good to include and they are still consistent with the statement that treatable ROP was not diagnosed before 32 weeks. But a 0%ile really doesn't make sense, so I'm thinking we should put that in the text rather than the table. I've also added the late onset one to the text below the table because I don't think it makes sense to replace 99%ile with the 100%ile for such an extreme value.

[I agree with keeping the 99th%tile in the table and putting the range in the text. –DLP]

I haven't addressed Michelle's comment (at what point you can say a baby without prethreshold is no longer at risk to need treatment), although I think it's important, because we need more data and I doubt that we can get it before the deadline. A simple solution (not exactly the same thing but close) would be to add a line to the table for PMAs at which cumulative %iles of prethreshold were diagnosed. We can do that for the presentation/manuscript.

[I don't think we really need to address this. It is a clinical judgement made by the ophthalmologists and we are not ophthalmologists. Let's not go there. The guidelines say that stopping examinations depends on the eye findings. Let it go. There is not a 100% safe answer, especially for a neonatologist. –DLP]

I added the information about treatment after discharge. I just want to verify (quadruple check) that it was initial treatment (not "touch-up of previous laser treatment or vitrectomy or scleral buckle). What did you do with the ones where the date was uncertain? You should have the date of the first exam after treatment because that's when they met study outcome, right? If there was a long interval between that exam and the previous one, they would have been removed before because of uncertain timing of onset, right?

[As I count up the SUPPORT data: 132 infants were treated. 5 after discharge and 9 after transfer = 14.

14/132 is 10% of infants went on to treatment after leaving the primary hospital, ~1/3 of those after discharge to home. It is a real problem everyone needs to be aware of. –DLP]

I've attached a new version. The changes (except for moving things around) are in yellow.

Kathleen A. Kennedy, MD, MPH
Richard W. Mithoff Professor of Pediatrics
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From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]

Sent: Sunday, October 09, 2011 4:56 PM
To: Kennedy, Kathleen A; wcarlo@peds.uab.edu; Das, Abhik; Roger.Faix@hsc.utah.edu; nfiner@ucsd.edu; Gantz, Marie; alaptook@WIHRI.org; nxs5@cwru.edu; wrich@ucsd.edu; kurt.schibler@cchmc.org; Michele.Walsh@UHhospitals.org; Bradley.Yoder@hsc.utah.edu
Cc: Wrage, Lisa Ann (wrage@rti.org); Archer, Stephanie (NIH/NICHD) [E] (archerst@mail.nih.gov); Higgins, Rosemary (NIH/NICHD)
Subject: RE: ROP Natural History Abstract

Thank you for your hard work on this Kathleen,
I have been through the abstract again, and discovered some things we had missed.. probably because we're too familiar with the material already. Just some clarifications, no real substantive changes. I have edited the abstract in the attached word file. (They are not track changes because my old laptop seems to confuse others when I use them.

Thanks again!
Dale

From: Kennedy, Kathleen A [mailto:Kathleen.A.Kennedy@uth.tmc.edu]
Sent: Saturday, October 08, 2011 9:56 AM
To: wcarlo@peds.uab.edu; Das, Abhik; Roger.Faix@hsc.utah.edu; nfiner@ucsd.edu; Gantz, Marie; alaptook@WIHRI.org; nxs5@cwru.edu; wrich@ucsd.edu; kurt.schibler@cchmc.org; Michele.Walsh@UHhospitals.org; Bradley.Yoder@hsc.utah.edu
Cc: Wrage, Lisa Ann (wrage@rti.org); Phelps, Dale; Archer, Stephanie (NIH/NICHD) [E] (archerst@mail.nih.gov); Higgins, Rosemary (NIH/NICHD)
Subject: ROP Natural History Abstract

SUPPORT Subcommittee: I've attached a draft of the PAS abstract for the ROP Natural History Secondary Study that uses data from the SUPPORT trial. Comments and suggestions are welcome. I hope to get the missing data before the deadline. If anyone knows how to navigate the submission process (how to include the NICHD without entering the NICHD as an author and then being required to submit a bunch of CME/COI disclosures for the NICHD), I'd appreciate the help.

Stephanie, could you please check to make sure I haven't missed anyone on the SUPPORT Subcommittee?

Lisa, if we could get the data for treatment after back transfer and after discharge, that would be great. If you can tabulate the 0 and 100%iles and they look reasonable (no extreme outliers), we could replace the 1 and 99%iles in the table with 0 and 100%iles.

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To: "Kennedy, Kathleen A"
Cc: Wrage, Lisa Ann (wrage@rti.org); Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: ROP Natural History Abstract
Date: Wednesday, October 12, 2011 7:09:46 PM
Attachments: Good.ETROP.Incidence.pdf

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To: Kennedy, Kathleen A
Cc: Wrage, Lisa Ann (wrage@rti.org); 'Higgins, Rosemary (NIH/NICHD) [E]'
Subject: RE: ROP Natural History Abstract

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Sent: Wednesday, October 12, 2011 10:57 AM
To: Phelps, Dale
Cc: Wrage, Lisa Ann (wrage@rti.org); Higgins, Rosemary (NIH/NICHD)
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[I don't think we really need to address this. It is a clinical judgement made by the ophthalmologists and we are not ophthalmologists. Let's not go there. The guidelines say that stopping examinations depends on the eye findings. Let it go. There is not a 100% safe answer, especially for a neonatologist. –DLP]

I added the information about treatment after discharge. I just want to verify (quadruple check) that it was initial treatment (not "touch-up of previous laser treatment or vitrectomy or scleral buckle).

What did you do with the ones where the date was uncertain? You should have the date of the first exam after treatment because that's when they met study outcome, right? If there was a long interval between that exam and the previous one, they would have been removed before because of uncertain timing of onset, right?

[As I count up the SUPPORT data: 132 infants were treated. 5 after discharge and 9 after transfer = 14.

14/132 is 10% of infants went on to treatment after leaving the primary hospital, ~1/3 of those after discharge to home. It is a real problem everyone needs to be aware of. –DLP]

I've attached a new version. The changes (except for moving things around) are in yellow.

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From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Sunday, October 09, 2011 4:56 PM
To: Kennedy, Kathleen A; wcarlo@peds.uab.edu; Das, Abhik; Roger.Faix@hsc.utah.edu; nfiner@ucsd.edu; Gantz, Marie; alaptook@WIHRI.org; nxs5@cwru.edu; wrich@ucsd.edu; kurt.schibler@cchmc.org; Michele.Walsh@UHhospitals.org; Bradley.Yoder@hsc.utah.edu
Cc: Wrage, Lisa Ann (wrage@rti.org); Archer, Stephanie (NIH/NICHD) [E] (archerst@mail.nih.gov); Higgins, Rosemary (NIH/NICHD)
Subject: RE: ROP Natural History Abstract

Thank you for your hard work on this Kathleen,
I have been through the abstract again, and discovered some things we had missed.. probably because we're too familiar with the material already. Just some clarifications, no real substantive changes. I have edited the abstract in the attached word file. (They are not track changes because my old laptop seems to confuse others when I use them.

Thanks again!
Dale

From: Kennedy, Kathleen A [mailto:Kathleen.A.Kennedy@uth.tmc.edu]
Sent: Saturday, October 08, 2011 9:56 AM
To: wcarlo@peds.uab.edu; Das, Abhik; Roger.Faix@hsc.utah.edu; nfiner@ucsd.edu; Gantz, Marie; alaptook@WIHRI.org; nxs5@cwru.edu; wrich@ucsd.edu; kurt.schibler@cchmc.org; Michele.Walsh@UHhospitals.org; Bradley.Yoder@hsc.utah.edu
Cc: Wrage, Lisa Ann (wrage@rti.org); Phelps, Dale; Archer, Stephanie (NIH/NICHD) [E] (archerst@mail.nih.gov); Higgins, Rosemary (NIH/NICHD)
Subject: ROP Natural History Abstract

SUPPORT Subcommittee: I've attached a draft of the PAS abstract for the ROP Natural History Secondary Study that uses data from the SUPPORT trial. Comments and suggestions are welcome. I hope to get the missing data before the deadline. If anyone knows how to navigate the submission process (how to include the NICHD without entering the NICHD as an author and then being required to submit a bunch of CME/COI disclosures for the NICHD), I'd appreciate the help.

Stephanie, could you please check to make sure I haven't missed anyone on the SUPPORT Subcommittee?

Lisa, if we could get the data for treatment after back transfer and after discharge, that would be great. If you can tabulate the 0 and 100%iles and they look reasonable (no extreme outliers), we could replace the 1 and 99%iles in the table with 0 and 100%iles.

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The Incidence and Course of Retinopathy of Prematurity: Findings From the Early Treatment for Retinopathy of Prematurity Study

Pediatrics 2005;116;15
DOI: 10.1542/peds.2004-1413

The Incidence and Course of Retinopathy of Prematurity: Findings From the Early Treatment for Retinopathy of Prematurity Study

Early Treatment for Retinopathy of Prematurity Cooperative Group

ABSTRACT. *Objectives.* **To estimate the incidence of retinopathy of prematurity (ROP) in the Early Treatment for Retinopathy of Prematurity (ETROP) Study and compare these results with those reported in the Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) Study.**

Methods. **The ETROP Study, as part of its protocol, screened 6998 infants at 26 centers throughout the United States. Serial eye examinations were conducted for infants born weighing <1251 g, making it possible to estimate the frequency of ROP in different birth weight and gestational age categories. ROP was categorized according to the International Classification for ROP.**

Results. **The incidence of any ROP was 68% among infants of <1251 g. The findings were compared with those for infants born in 1986 and 1987 in the CRYO-ROP Study. The overall incidences of ROP were similar in the 2 studies, but there was more zone I ROP in the ETROP Study. Among infants with ROP, more-severe ROP (prethreshold) occurred for 36.9% of infants in the ETROP Study and 27.1% of infants in the CRYO-ROP Study. The gestational age of onset of ROP of different severities has changed very little since the CRYO-ROP Study was conducted.**

Conclusions. **ROP remains a common important problem among infants with birth weights of <1251 g. The incidence of ROP, time of onset, rate of progression, and time of onset of prethreshold disease have changed little since the CRYO-ROP natural-history study.** ***Pediatrics* 2005;116:15–23;** ***retinopathy of prematurity, incidence.***

ABBREVIATIONS. ROP, retinopathy of prematurity; CRYO-ROP, Cryotherapy for Retinopathy of Prematurity; ICROP, International Classification for Retinopathy of Prematurity; ETROP, Early Treatment for Retinopathy of Prematurity.

Retinopathy of prematurity (ROP) is a disease in which retinal blood vessels of premature infants fail to grow and develop normally, sometimes resulting in visual impairment and blindness. In the largest previous study of a natural-history cohort that reported the incidence of ROP, the Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) Study reported an incidence of ROP of 65.8% among infants of <1251 g, all of whom were born between January 1, 1986, and November 30, 1987.[1] Since the time of enrollment of infants in that study, advances in neonatal care, with accompanying decreases in mortality rates, have occurred, and it is reasonable to consider that such changes in care could have affected the incidence and severity of ROP. This assumption is supported, in part, by the knowledge that ROP is a disorder associated with, and affected by, survival and systemic disease.[2–5] However, studies conducted during the past 15 years on the incidence of ROP have shown differing results, some indicating a decrease in the incidence of ROP and others suggesting no change.[4,6–8]

The Early Treatment for Retinopathy of Prematurity (ETROP) Study, as part of its protocol, screened 6998 infants at 26 centers throughout the United States. The study design included serial eye examinations of infants born weighing <1251 g, for the purposes of identifying infants with high-risk prethreshold ROP for randomization to early versus conventional treatment and of estimating the frequency of ROP in different birth weight and gestational age categories. ROP was categorized according to the International Classification for Retinopathy of Prematurity (ICROP).[9]

The purpose of this report was to estimate the incidence of ROP in the ETROP Study and to compare these results with those reported in the CRYO-ROP Study. The tracking of infants in the ETROP Study provided the opportunity to estimate the incidence of ROP in a 21st century cohort and, where possible, to compare this with the results of previous studies, particularly the CRYO-ROP natural-history study, conducted 15 years earlier.

METHODS

Study Group

The institutional review boards for each participating hospital approved the study protocol. From October 1, 2000, to September 30, 2002, investigators logged all infants weighing <1251 g at each of the 26 participating centers. Each nursery was checked at least weekly for the admission of such infants, with identifying information being recorded in a logbook. These census reports were transmitted every 2 weeks to the coordinating center, where a central log of potential participating infants was maintained.

Infants were included in this study if they were born in one of the study center hospitals, remained in the hospital, and were monitored by a study-certified ophthalmologist or they were transferred to a study center hospital before 42 days of age, remained in the hospital, and were monitored by a study-certified ophthalmologist. Infants were monitored until a diagnosis of ROP was established or an eye examination showed vascularization into zone III. If ROP developed, then parents were asked to sign a consent form to allow the more frequent examinations necessary to track the course and severity of ROP in the ETROP Study.

Birth weight, gestational age, and race were recorded when the infant was logged. Gestational age was assigned by the neonatol-

From the Smith-Kettlewell Eye Research Institute, San Francisco, California.
Accepted for publication Oct 22, 2004.
doi:10.1542/peds.2004-1413
No conflict of interest declared.
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ogist caring for the patient and was based on obstetric data such as early ultrasound findings and menstrual history when available or physical examination findings at the time of birth. The race of the infants was based on the race of the mother.

Exclusion criteria included severe systemic anomalies or ocular anomalies in 1 or both eyes that would prevent entry into the randomization phase of the study. Additional details of this procedure and study protocol have been published.[10,11]

Standardization of Examination Techniques

All ophthalmologists involved in the diagnosis and monitoring of ROP in this study were required to be certified by the American Board of Ophthalmology and experienced in managing ROP. They were certified for the study by attending a 2-day course at the beginning of the study. Alternatively, watching a videotape describing the study and its procedures and reading the manual of procedures[12] could be used to obtain certification, as long as the ophthalmologist was board certified, with experience in the diagnosis of ROP. Experience criteria included either participation in ≥1 of the prior multicenter ROP clinical trials (the CRYO-ROP Study, the Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity Study, or the Effects of Light Reduction on Retinopathy of Prematurity Study) or participation in 3 masked paired examinations of infants with ROP with a study-certified ophthalmologist. Results of these examinations were evaluated for concordance at the study headquarters in San Francisco. When agreement between examiners was unsatisfactory, additional examinations were required until good agreement was achieved. Principal investigators from each center met at 6-month intervals to review ROP findings, cases of ROP with photographs, and diagnostic criteria for zones, stages, and plus disease.

For eye examinations, infants' pupils were dilated with cyclomydril (Alcon Laboratories, Inc [Fort Worth, TX]; 0.2% cyclopentolate and 1.0% phenylephrine). If necessary because of poor dilation, 0.5% cyclopentolate and/or 2.5% phenylephrine was used. The examination procedure involved the use of sterile eyelid specula and scleral depressors as necessary, to see the peripheral retina. A binocular indirect ophthalmoscope was used with a hand-held lens. Ophthalmologists also followed any other local criteria for maintaining sterility.

The use of topical anesthetic agents for examinations was optional, because of concern that their use might cloud the cornea and obscure visibility of the retina. Infants were examined while being carefully monitored for signs of any distress caused by the examination. Infants who could not tolerate the examination were reevaluated later or on another day.

Diagnosis of ROP and Examination Schedule

All infants of <1251 g underwent eye examinations, whether or not they developed any ROP. When no ROP was present, the location where blood vessels terminated was recorded. For infants with blood vessels ending in zone 1 (an imaginary circle whose radius is twice the distance from the optic disc to the macula) in 1 or both eyes, follow-up examinations were conducted on a weekly basis. All other infants for whom no ROP was present were examined every 2 weeks. Infants with no ROP were monitored until retinal vessels had developed to within 1 disc diameter of the ora serrata on the nasal side in ≥2 contiguous clock hours (sectors). If a second examination conducted 2 weeks later confirmed this maturation of vessels, then additional follow-up monitoring occurred at the discretion of the physician caring for the child.

In eyes in which ROP was observed, the location and severity were recorded according to the ICROP.[9] Zone 1 ROP was diagnosed when ≥1 clock hour (sector) of ROP was seen within zone I (defined above). Zone II ROP was diagnosed when retinal vessel maturation had not occurred to within 1 disk diameter of the nasal ora serrata in those 2 contiguous clock hours and ≥1 clock hour of ROP was present, with no ROP in zone I. Zone III ROP was diagnosed when retinal vessel maturation had occurred to within 1 disk diameter of the nasal ora serrata in those 2 contiguous clock hours and ≥1 clock hour of ROP was present elsewhere in the eye (Table 1). After diagnosis of zone III ROP, infants were examined 1 more time, not more than 2 weeks later, and then at the discretion of the physician caring for the infant.

The stage of ROP was also diagnosed according to the ICROP.[9] Flat neovascularization in zone I was considered stage 3, even when an actual ridge did not exist. Plus disease required ≥2 quadrants of dilation and tortuosity of posterior pole retinal blood vessels, equal to or exceeding that of a standard published photograph (Fig 1).[13]

Examinations were conducted at least every 2 weeks after ROP was first seen. When "near-prethreshold" (zone II, stage 2) ROP was diagnosed, examinations were conducted at least weekly. Prethreshold ROP was defined as (1) any ROP in zone I, (2) ROP in zone II with plus disease, (3) zone II with stage 3 ROP and no plus disease, or (4) zone II with plus disease and stage 3 ROP but with less than the 5 contiguous or 8 cumulative clock hours of stage 3 ROP required for diagnosis of threshold ROP (Table 1).

When prethreshold ROP was observed, in the absence of threshold ROP in either eye, a multivariate logistic risk model based on infant and eye characteristics (RM-ROP2) was used to calculate whether the infant was at high or low risk for retinal detachment. An earlier publication gives a detailed description of the RM-ROP2 model,[14] and access to the risk model is available online (at www.sph.uth.tmc.edu/rmrop/Riskcalc/disclaimer.aspx). If high-risk prethreshold ROP was observed in 1 or both eyes and was confirmed by a second examiner, then the infant was eligible for entry into the randomized trial. Infants with bilateral, high-risk, prethreshold disease had 1 eye randomized to treatment within 48 hours, whereas the fellow eye received conventional management, with examinations occurring at intervals of ≤1 week and with treatment if threshold ROP was diagnosed. Infants with high-risk prethreshold ROP in only 1 eye had that eye randomized to treatment within 48 hours or to conventional management. The fellow eye was not included in the study and was treated conventionally (eg, treated at the conventional threshold, if ROP progressed to this point). Infants with low-risk prethreshold ROP were examined at least every 4 days for at least 2 weeks (total of 5 examinations). If ROP did not progress to high-risk prethreshold or threshold ROP, then infants were monitored at the physician's discretion but at least once per week as long as prethreshold ROP persisted.

Statistical Methods

In some cases, infants were logged into the study and screened but were transferred to nonparticipating hospitals, were discharged from the hospital, or died before all ROP screening examinations that might have revealed ROP had been completed

TABLE 1. Definitions of ROP Used in the ETROP Study

Category	Retinal Findings
Zone III	ROP is present and retinal vessel maturation is to within 1 disc diameter of the ora serrata on the nasal side, in ≥2 clock hours (sectors)
Mild	Zone II, stage 1 ROP
Near prethreshold	Zone II, ≥1 clock hour of stage 2 ROP and no plus disease or stage 3 ROP
Prethreshold	(1) Zone I any ROP, (2) zone II, stage 2 ROP with plus disease, (3) zone II, any amount of stage 3 ROP and no plus disease, or (4) zone II, stage 3 ROP with plus disease but less than required threshold clock hours
Threshold	Zone I or II, 5 contiguous or 8 composite hours of stage 3 ROP, with plus disease

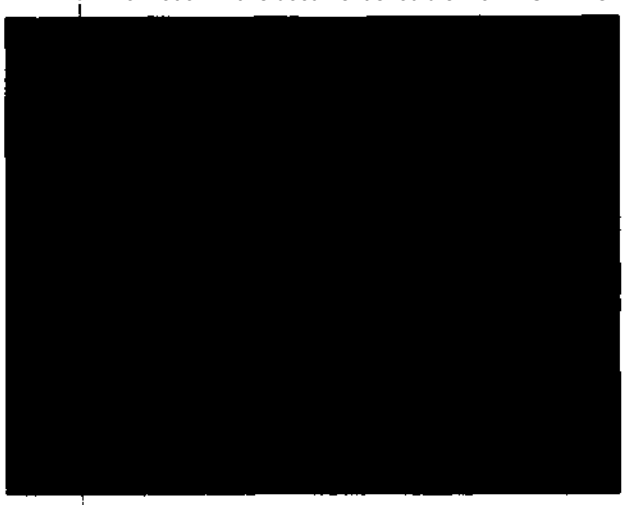

Fig 1. Photograph of retinal vessel dilation and tortuosity used as the minimal standard for plus disease in the ETROP Study. At least 2 quadrants of plus disease were necessary to qualify as plus disease.

("ROP not observed, follow-up incomplete") (Fig 2). Their actual ROP status is consequently unknown. If ROP was observed in one of the early screening examinations, then the infants were included in the study cohort; therefore, dropping those infants with no ROP would produce a bias. To estimate the incidence of ROP, we used the data for infants who were monitored and whose ROP status was known ("ROP observed, or mature") (Fig 2) to provide an equation that was then applied to all 6998 infants in the study, to establish the rate of ROP.

A logistic risk equation based on infant characteristics (birth weight, gestational age, race, inborn/outborn status, single/multiple status, and gender) was obtained from the analysis of data for infants who were actually observed and whose ROP status was known. A risk value was then computed from the logistic equation for each of these infants. With the same logistic equation and data on birth weight, gestational age, race, inborn/outborn status, single/multiple status, and gender, a risk value for ROP was imputed only for children who received ≥1 screening examination but were not observed in additional follow-up examinations to have developed ROP or to have mature retinal vascularizaton. This provided risk values for infants who were actually monitored and risk values for infants who were not monitored. All calculations used the same equation with the characteristics for each infant to calculate the 6998 risk values. The incidence of ROP was obtained for all infants by taking the average of the 6998 risk values. The incidence of ROP for subgroups was obtained by using the average risk for infants within the subgroup.

RESULTS

Data for 9721 infants were entered into nursery accession logs. The natural-history cohort for the ETROP Study is composed of 6998 of these patients. Data were not obtained for 2723 infants who died before the first examination, were transferred to another hospital before the first examination, were discharged from the hospital without an eye examination, or were ineligible for the study because of systemic and ocular anomalies (Fig 2). The remaining 6998 infants received their first eye examination by a certified examiner and, of those, 5541 are known to have developed ROP or to have proceeded to zone III vascularization without ROP. After the diagnosis of ROP in 1 or both eyes, consent for inclusion of follow-up eye examination results and for examinations that were more frequent than usual, as part of the ETROP Study, was obtained from the parents or guardians of 2320 infants.

Table 2 shows the demographic characteristics of the 6998 infants screened in the natural-history cohort, the 2320 infants with ROP whose parents consented to participation in the prospective study, and the 856 infants in the prospective study who developed prethreshold or worse ROP in 1 or both eyes. The incidence of ROP among the 6998 infants in the natural-history cohort is presented in Table 3, along with data on the incidence of ROP among the 4099 infants who were born between January 1, 1986, and November 30, 1987, and participated in the natural-history portion of the CRYO-ROP Study. The incidences of ROP were similar in these 2 cohorts of infants with birth weights of <1251 g. In both cohorts, the incidences were similar for black and nonblack patients and for male and female patients. The incidence decreased with increasing birth weight and gestational age and was lower for infants born in a study hospital, compared with outborn infants.

Table 4 shows the highest severity of ROP that occurred in either eye of infants who developed ROP and whose parents consented to participation in the prospective evaluation of progression of ROP. Data in Table 4 indicate that the rates of progression and the location of ROP depended markedly on birth weight and gestational age.

The median postmenstrual age at which stage 1 ROP, stage 2 ROP, stage 3 ROP, and plus disease were diagnosed among infants with ROP whose parents consented to the prospective study is shown in Table 5, with similar data for the infants in the CRYO-ROP Study. The median postmenstrual ages for the first diagnosis of stage 1 to 3 ROP and for diagnosis of plus disease were very similar in the 2 studies. The median postmenstrual ages at the first diagnosis of prethreshold ROP (Table 6) in the 2 studies were also remarkably similar, although the median chronologic age at the diagnosis of prethreshold ROP was 1 week less in the CRYO-ROP Study than in the ETROP Study.

DISCUSSION

The ETROP Study is the largest multicenter study on the incidence of ROP to take place in >15 years. Nearly 10 000 infants at 26 centers were logged, resulting in 6998 infants who could be examined at least once and 5541 who were monitored for the development and progression of ROP. Examinations were standardized carefully and were performed by board-certified and study-certified examiners, with a protocol very similar to that used in the CRYO-ROP Study. The results of this collaborative effort showed that the incidence of ROP was 68% among infants of <1251 g. Although the overall incidence of ROP was similar to that found in the CRYO-ROP Study (Table 3),[1] more zone I ROP was observed. The overall incidence of more-severe ROP (prethreshold) was 36.9% among infants with ROP in the ETROP Study, whereas the incidence was 27.1% for patients in the CRYO-ROP Study who developed ROP (recomputed for patients with ROP).[1]

In comparing the rates between the ETROP Study

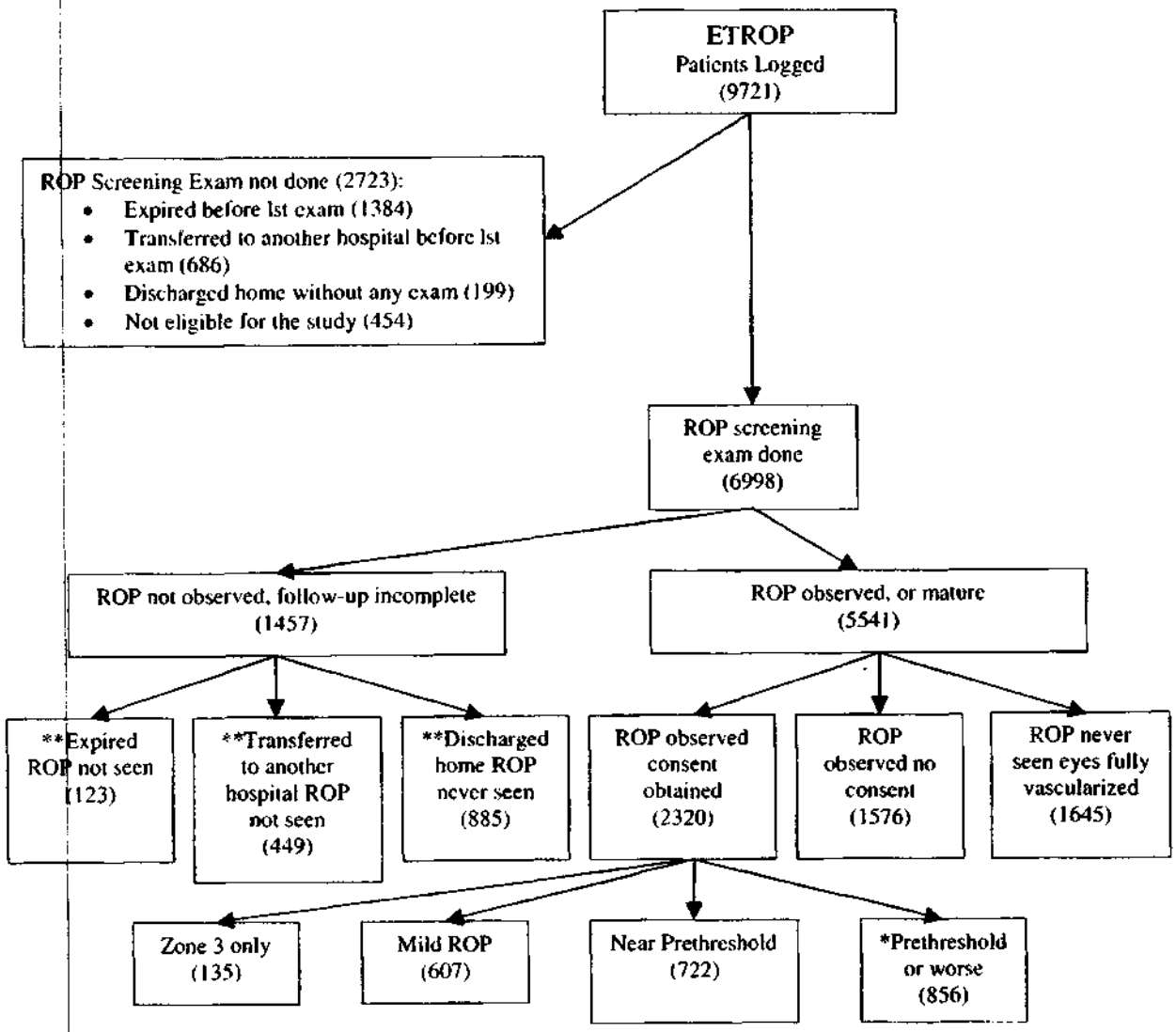

Fig 2. Flowchart showing what happened to infants after they were logged in the ETROP Study. * Includes 28 patients not previously reported, who reached threshold but were never documented to have prethreshold. ** Data on risk of ROP was imputed for these groups. (See Statistical Methods.)

and the CRYO-ROP Study, the differences between protocols should be noted. In the ETROP Study, once zone II stage 2 or zone I immature vessels developed, infants were examined on a weekly basis, ie, more frequently than in the CRYO-ROP Study. In the CRYO-ROP Study, infants could be examined at up to 2-week intervals until prethreshold ROP was seen. This would not affect the comparison of the overall incidences of ROP, but prethreshold and threshold ROP might have been diagnosed at a slightly earlier age in the ETROP Study, because infants with signs of possible future development of prethreshold disease were monitored more closely, to ensure prompt diagnosis of prethreshold disease.

Another difference between these 2 studies concerns the timing of consent for study. In the ETROP Study, consent was obtained for possibly more frequent examinations only after ROP was diagnosed. In the CRYO-ROP Study, consent was obtained before the first eye examination and therefore before ROP was diagnosed. It is unlikely that these different approaches would affect a comparison of the overall incidences of ROP, as calculated in this report. In both studies, there were some infants who escaped surveillance (and possibly consent) by being transferred out of a study center or discharged from the hospital before the first eye examination.

Comparisons with other incidence studies are limited in value, because the studies often have different entry criteria and methods or are based on small sample sizes.[6,15,16] In 1 large retrospective study covering the years 1989–1997, the incidence of ROP was 34% for infants of <1251 g,[6] approximately one half the rate in the ETROP Study. The Vermont Oxford Network Database reported an incidence of ROP of 57.2% in 1997,[7] still less than the incidences in the ETROP Study and the CRYO-ROP Study. One single-center study reported an incidence of 36.1%[8] and rates of prethreshold and threshold disease that were lower than those in the ETROP Study. Although these studies reported low incidence rates for ROP, relative to those in the CRYO-ROP Study, the ETROP

TABLE 2. Baseline Characteristics of Patients Screened, Patients With ROP With Consent, and Patients With Consent Who Developed Prethreshold or Worse ROP in 1 or Both Eyes

Characteristics	Screened (N = 6998)	ROP With Consent (N = 2320)	Prethreshold or Worse (N = 856)
Born in study hospital, %	84.1	85.6	83.6
Male, %	51.2	50.6	54.2
Race, %			
White	52.0	55.2	56.5
Black	30.2	27.6	23.1
Hispanic	12.6	12.3	14.5
Other	5.2	4.9	5.8
Birth weight			
Mean, g	907	812	740
SD, g	205	188	163
<750 g, %	24.9	40.4	56.9
750–999 g, %	37.7	41.3	35.5
1000–1250 g, %	37.3	18.2	7.6
Gestational age			
Mean, wk	27.4	26.4	25.6
SD, wk	2.2	1.8	1.5
≤27 wk, %	47.2	69.0	84.9
>27–31 wk, %	49.4	30.5	14.8
≥32 wk, %	3.4	0.5	0.2
Multiple birth, %			
Single	73.8	70.1	69.6
Twins	20.7	22.9	23.3
Triplets	4.6	5.8	5.8
Other	1.0	1.2	1.3

TABLE 3. Proportions of Patients With ROP According to Baseline Characteristics

Baseline Characteristics	ETROP Study		CRYO-ROP Study, Published % ROP (N = 4099)
	No. Screened	Estimated % ROP*	
Black	2114	67.6	63.2
Non-black	4884	68.2	67.5
Male	3585	67.8	66.4
Female	3411	68.3	65.3
<750 g	1745	92.7	90.0
750–999 g	2640	75.8	78.2
1000–1250 g	2613	43.7	46.9
≤27 wk	3305	89.0	83.4
>27–31 wk	3454	51.7	55.3
≥32 wk	239	14.2	29.5
Inborn	5887	67.0	64.3
Outborn	1111	73.4	72.9
Single	5162	68.0	66.0
Multiple	1836	68.0	65.1
Total	6998	68.0	65.8

* Estimated with a multivariate logistic-regression equation to include all patients screened for ROP in the ETROP Study (see Methods).

Study did not, which suggests that the low incidence values resulted partly from the use of small nonrepresentative samples of infants. Other factors that could affect incidence figures in smaller studies include high rates of back-transfers, lack of collection of ROP data after discharge home, and relatively small proportions of infants with birth weights of <750 g.

In the ETROP Study, some infants who had been screened were transferred out of study hospitals before investigators had the chance to observe whether ROP would develop. This led to the formulation of an incidence figure based on a multivariate logistic-regression analysis of data for infants who were actually observed for their possible development of ROP coupled with an imputed value for infants who left the hospital or died before completing follow-up evaluations for ROP (see "Methods"). This calculation was made for infants who underwent ≥1 screening examination.

Imputing reduces the bias in estimating rates of ROP. Another approach to deal with the infants who were transferred out before completing examinations for ROP at one of our participating hospitals is to report 2 figures for the incidence. First, all infants who were transferred with no ROP are deleted from the denominator. This gives an incidence of 70.3%, which is an overestimate. Second, these infants are included in the denominator and it is assumed that none of them ever developed ROP. The resulting figure for the incidence is 55.7%, which is an underestimate of the true incidence. Our estimate obtained with the imputing method is 68.0%, which is between these 2 values.

TABLE 4. Patients With ROP Observed and Consent Obtained, With Various Categories of ROP, in Selected Subgroups

Subgroup	Total Population (*N*)	Highest Stage*						Ever Zone I*		Plus Disease*		Prethreshold or Worse*	
		Stage 1		Stage 2		Stage 3							
		n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Total	2320	672	29.0	821	35.4	826	35.6	210	9.1	556	24.0	856	36.9
Birth weight													
<750 g	938	167	17.8	320	34.1	451	48.1	155	16.5	313	33.4	487	51.9
750–999 g	959	291	30.3	368	38.4	300	31.3	47	4.9	205	21.4	304	31.7
1000–1250 g	423	214	50.6	133	31.4	75	17.7	8	1.9	38	9.0	65	15.4
Gestational age													
≤27 wk	1601	327	20.4	580	36.2	694	43.3	187	11.7	478	29.9	727	45.4
>27–31 wk	707	337	47.7	238	33.7	131	18.5	22	3.1	78	11.0	127	18.0
≥32 wk	12	8	66.7	3	25.0	1	8.3	1	8.3	0	0.0	2	16.7
Race													
White	1281	381	29.7	416	32.5	484	37.8	105	8.2	351	27.4	484	37.8
Black	640	203	31.7	262	40.9	174	27.2	64	10.0	93	14.5	198	30.9
Other	399	88	22.1	143	35.8	168	42.1	41	10.3	112	28.1	174	43.6
Gender													
Male	1175	309	26.3	417	35.5	448	38.1	112	9.5	300	25.5	464	39.5
Female	1145	363	31.7	404	35.3	378	33.0	98	8.6	256	22.4	392	34.2
Born in hospital													
Inborn	1987	595	29.9	696	35.0	695	35.0	173	8.7	461	23.2	716	36.0
Outborn	333	77	23.1	125	37.5	131	39.3	37	11.1	95	28.5	140	42.0
Multiple birth													
Single	1627	458	28.1	597	36.7	571	35.1	158	9.7	384	23.6	596	36.6
Other	693	214	30.9	224	32.3	255	36.8	52	7.5	172	24.8	260	37.5

* In either eye.

TABLE 5. Onset of Different Events With Respect to Postmenstrual Age

	Onset (Postconceptional Age), wk, Median (5%, 95%)	
	ETROP Study (2002)	CRYO-ROP Study* (1987)
Stage 1	34.1 (ND, 38.9)	34.3 (ND, 39.1)
Stage 2	35.1 (32.4, 40.1)	35.4 (32.0, 40.7)
Stage 3	36.6 (33.4, 41.6)	36.6 (32.9, 42.4)
Plus	36.0 (33.0, 41.4)	36.3 (32.6, 42.9)

ND indicates not determined.
* Published CRYO-ROP Study data.[1]

TABLE 6. Onset of Prethreshold ROP

	Onset, wk, Median (5%, 95%)	
	ETROP Study (2002)	CRYO-ROP Study (1987)
Chronologic age	10.6 (7.0, 16.0)	9.6* (6.2, 14.8)
Postconceptional age	36.1 (32.1, 42.1)	36.1 (32.4, 41.5)

* The average gestational age of the infants at birth in the CRYO-ROP study was 1 week older.

The average birth weight and gestational age for infants with prethreshold ROP in the ETROP Study were less than those in the CRYO-ROP Study (740 vs 831 g and 25.6 vs 26.5 weeks),[14] indicating that prethreshold ROP occurred among smaller and younger infants in the ETROP Study cohort than in the CRYO-ROP Study cohort. With postmenstrual age as the time factor, the average age of onset of each ICROP category of disease in the ETROP Study is remarkably similar to that found in the CRYO-ROP Study (Tables 5 and 6). The development of ROP might have changed slightly in 15 years; therefore, factors responsible for its occurrence might have changed. However, factors responsible for the timing of onset of ROP and its ultimate progression probably have not changed or have changed in a manner in which the net effect on onset and progression of ROP is negligible.

In the ETROP Study, the incidences of ROP were the same among white and black infants, but severe (prethreshold) ROP occurred more commonly among white children. This finding confirms similar findings in many other studies.[1,17,18] Outborn infants continued to bear a greater risk of developing ROP than did infants born in study-affiliated hospitals.

More infants with zone I ROP were observed in this study than previously. The incidence of zone I ROP was 9.1% for infants with ROP and parental consent in the ETROP Study, compared with 2.0% in the CRYO-ROP Study.[14] ROP is fundamentally a developmental disease of retinal blood vessel

growth; therefore, the earlier in gestation that an infant is born, and thus presumably the earlier the onset of retinal vessel injury, the more likely it is that the vessels will be in zone I at birth/injury, resulting in ROP in zone I. More infants with low birth weights and low gestational ages were observed in this study than in the CRYO-ROP Study. Other factors could also have contributed to the increase in cases of zone I ROP in the ETROP Study. In the ETROP Study, any ROP in zone I was considered prethreshold and triggered a potential randomization process. Observers might have viewed zone I ROP with the perspective that its diagnosis would potentially lead to a known effective treatment and therefore might have diagnosed as zone I ROP some cases that were marginal between zones I and II. Also, immature vessels in zone I in the ETROP Study triggered more frequent examinations. In the CRYO-ROP Study, infants with immature vessels in zone I were examined every 2 weeks. Some of the infants in the CRYO-ROP Study might have had ROP that passed undiagnosed through zone I ROP before becoming zone II ROP.

Without doubt, many factors are involved in the development and progression of ROP and cause it to proceed regularly to an end point defined by postmenstrual age. This inexorable progression of ROP suggests that factors that are inherent in the infant, or even maternally transmitted across the placenta before or around the time of premature delivery, could play a role in the genesis and progression of ROP. A partially inherent causation for ROP is also suggested by the incidence and severity data for different ethnic groupings in this study. White infants were much more likely to have severe ROP than were black infants.

Oxygenation of infants in the hours and days after birth is once again under investigation as a possible etiologic factor for ROP.[19,20] The mechanism that would impugn early oxygenation as causative invokes oxygen-induced retinal vascular ischemia and subsequent upregulated angiogenesis in the immediate days after birth. This perinatal oxygenation/disease theory does not account entirely for the onset of prethreshold disease being so tightly linked to gestational age. The predictable timing of the onset of prethreshold ROP based on the postmenstrual age of the infant suggests that factors that are present from the time of conception may play a significant role in ROP progression.

Clearly, ROP remains an important and common disease.[21] Potentially more-severe ROP (prethreshold ROP and zone I ROP) is probably more common now than in the CRYO-ROP Study. Future research is needed to learn ways to prevent ROP from developing and to prevent it from progressing.

ACKNOWLEDGMENTS

This work was supported by cooperative agreements (5U10 EY12471 and 5U10 EY12472) with the National Eye Institute of the National Institutes of Health, US Department of Health and Human Services (Bethesda, MD).

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The Incidence and Course of Retinopathy of Prematurity: Findings From the Early Treatment for Retinopathy of Prematurity Study

Pediatrics 2005;116;15
DOI: 10.1542/peds.2004-1413

From: Phelps, Dale
To: "Kennedy, Kathleen A"
Cc: Wrage, Lisa Ann (wrage@rti.org); Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: ROP Natural History Abstract
Date: Wednesday, October 12, 2011 5:18:24 PM
Attachments: ROP Natural History PAS Abstract.dlp.10.12.doc

Hi Kathleen,

Thank you for the good revisions: we are getting there. I am still struggling with numbers, but I'm sure you and Lisa can figure these out.

Per the abstract:
1316 enrolled and 1091 survived to ROP age.
997 had a definitive ROP outcome, and 986 of those had sufficient data to determine age of onset of ROP.

So to me your key group is those 986. In the text and conclusions subsequently, you say 984,
644 developed ROP
of those 138 met the severe ROP criteria

Your sentence says that "644 infants developed ROP (138 met severe ROP criteria); 353 did not."
138 + 353 = 491, not the 644 (or 633) that you say developed ROP.
This was my confusion. What about the other 644-491 = 153 with ROP?
But I just figured it out (I think)

Is this what you meant? (seems obvious in retrospect):
644 infants developed ROP (138 of those met severe ROP criteria); 353 did not develop ROP.
644 with ROP + 353 without ROP = 997 infants... not the 984 (or 986) you say you have.
Or reverse it for clarity in the abstract (with corrected numbers) ?
353 infants did not develop ROP; 644 did (138 of those met severe ROP criteria).

In the table you report age of onset of ROP for 633 infants. Why the discrepancy between 644 and 633 ?
In the table you report PMA for onset of severe ROP for 128 infants. Why the discrepancy between 128 and 138 ?

In the title of the table, I think you have to revise a bit to say.
Cumulative Percentile with Diagnosis of ROP or Cumulative %tile with Diagnosis of ROP
But I'm not certain of this (Lisa/Marie help), but I think "%" is different than "percentile". If RTI says "no" you can leave it.

Title of the Abstract (has to be all caps)
I would say "...SCREENING GUIDELINES...." rather than "...SCREENING INTERVAL...."
The guidelines don't really talk about an interval, so I don't think you are testing an interval.

[I have put in some specific responses to you questions below, in square brackets—DLP]

and put in some minor edits or suggestions in green highlight in the attached copy of the text.

Dale

From: Kennedy, Kathleen A [mailto:Kathleen.A.Kennedy@uth.tmc.edu]
Sent: Wednesday, October 12, 2011 10:57 AM
To: Phelps, Dale
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Subject: RE: ROP Natural History Abstract

Thanks for the careful review. I tried to make most of these suggested changes (along with most of the suggestion in in the 16 other emails since Mon).

I have verified twice that the demographic comparisons are for severe ROP vs no ROP. Do you see something about that data that makes you think I've quoted it incorrectly?

I'm also struggling with the sentence that says what's in the table.

I think the min ages of diagnoses would be good to include and they are still consistent with the statement that treatable ROP was not diagnosed before 32 weeks. But a 0%ile really doesn't make sense, so I'm thinking we should put that in the text rather than the table. I've also added the late onset one to the text below the table because I don't think it makes sense to replace 99%ile with the 100%ile for such an extreme value.

[I agree with keeping the 99th%tile in the table and putting the range in the text. –DLP]

I haven't addressed Michelle's comment (at what point you can say a baby without prethreshold is no longer at risk to need treatment), although I think it's important, because we need more data and I doubt that we can get it before the deadline. A simple solution (not exactly the same thing but close) would be to add a line to the table for PMAs at which cumulative %iles of prethreshold were diagnosed. We can do that for the presentation/manuscript.

[I don't think we really need to address this. It is a clinical judgement made by the ophthalmologists and we are not ophthalmologists. Let's not go there. The guidelines say that stopping examinations depends on the eye findings. Let it go. There is not a 100% safe answer, especially for a neonatologist. –DLP]

I added the information about treatment after discharge. I just want to verify (quadruple check) that it was initial treatment (not "touch-up of previous laser treatment or vitrectomy or scleral buckle). What did you do with the ones where the date was uncertain? You should have the date of the first exam after treatment because that's when they met study outcome, right? If there was a long interval between that exam and the previous one, they would have been removed before because of uncertain timing of onset, right?

[As I count up the SUPPORT data: 132 infants were treated. 5 after discharge and 9 after transfer = 14.

14/132 is 10% of infants went on to treatment after leaving the primary hospital, ~1/3 of those after discharge to home. It is a real problem everyone needs to be aware of. –DLP]

I've attached a new version. The changes (except for moving things around) are in yellow.

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From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Sunday, October 09, 2011 4:56 PM
To: Kennedy, Kathleen A; wcarlo@peds.uab.edu; Das, Abhik; Roger.Faix@hsc.utah.edu; nfiner@ucsd.edu; Gantz, Marie; alaptook@WIHRI.org; nxs5@cwru.edu; wrich@ucsd.edu; kurt.schibler@cchmc.org; Michele.Walsh@UHhospitals.org; Bradley.Yoder@hsc.utah.edu
Cc: Wrage, Lisa Ann (wrage@rti.org); Archer, Stephanie (NIH/NICHD) [E] (archerst@mail.nih.gov); Higgins, Rosemary (NIH/NICHD)
Subject: RE: ROP Natural History Abstract

Thank you for your hard work on this Kathleen,
I have been through the abstract again, and discovered some things we had missed.. probably because we're too familiar with the material already. Just some clarifications, no real substantive changes. I have edited the abstract in the attached word file. (They are not track changes because my old laptop seems to confuse others when I use them.

Thanks again!
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Stephanie, could you please check to make sure I haven't missed anyone on the SUPPORT Subcommittee?

Lisa, if we could get the data for treatment after back transfer and after discharge, that would be great. If you can tabulate the 0 and 100%iles and they look reasonable (no extreme outliers), we could replace the 1 and 99%iles in the table with 0 and 100%iles.

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6431 Fannin, Suite 2.106
Houston, TX 77030
713 500-6708

Evaluating the Retinopathy of Prematurity (ROP) Screening GUIDELINES ~~Interval~~ for 24-27 Week Gestation Infants

Kathleen A. Kennedy MD MPH, Lisa Wrage, MPH, Dale L. Phelps MD, Rosemary D. Higgins on behalf of the SUPPORT Subcommittee for the NICHD Neonatal Research Network

Background:
Timely detection of treatable ROP is important to assure optimal outcomes for infants who meet the criteria for treatment. Current screening guidelines are based on natural history data from randomized trials that enrolled infants between 1986-1997: screening should begin by 31 weeks postmenstrual age(PMA) and continue until the vessels have reached zone III at ≥ 35 weeks, or, for infants without prethreshold ROP, until a PMA~~postmenstrual age~~ of 45 weeks. Since the 1980s, survival of lower gestational age(GA) infants has increased, and earlier treatment of ROP (Type 1 ROP: stage 3 or ROP with plus disease in zone ~~1~~ I or stage 2-3 with plus disease in zone II ~~2~~) is recommended. The timing of onset of ROP is related most closely to postmenstrual age (PMA = gestational age at birth + postnatal age).

Objective:
To validate current screening recommendations for detection of treatable ROP in 24-27 week gestational age infants.

Design/Methods:
In the NICHD Network SUPPORT trial, severe ROP (Type 1 ROP or treatment with laser, cryotherapy or bevacizumab) or death was the primary outcome for the O_2 saturation target arm of the factorial design. Infants 24 0/7 to 27 6/7 weeks gestation (no birth weight limits) and consented prior to delivery were eligible for this study. ROP examinations were conducted according to current screening recommendations and recorded using the international classification of ROP. Results of each exam were prospectively collected for all enrolled infants~~. Study eye exam data were recorded~~ until a study endpoint was reached: ROP treatment, full vascularization to the ora serrata, vascularization in zone III in 2 consecutive exams, or the infant was 55 weeks PMA.

Results:
1316 infants were enrolled. 1091 (83%) of infants survived to the age of ROP determination. 997 (91%) of these infants had a definitive ROP outcome and 986 (90%) had sufficient exam data (no missing or delayed exams before diagnosis) to determine the diagnosis and age of onset of ROP. 644 infants developed ROP (138 met severe ROP criteria); 353 infants did not. As expected, infants with severe ROP were less mature [mean (SD) 25.5 (0.9) wks vs 26.8 (0.9) wks, p<0.0001], lower birth weight [mean (SD) 708 (148)g vs 942 (173)g, p<0.0001], and more likely to be White race (44% vs 35%, p=0.07) than infants with no ROP. For the 633 infants with ROP and known age of onset, the PMA for selected cumulative %iles is shown in the table:
see e-mail about discrepant numbers all highlighted--dlp

ROP type (number of infants)	Cumulative %tile with Diagnosis of ROP						
	1%	5%	25%	50%	75%	95%	99%
	Postmenstrual Age (weeks)						
Diagnosis of any ROP (n=633)	30.4	31.4	32.7	33.9	35.1	37.9	41.0
Diagnosis of severe (Type 1/Treated) ROP (n=128)	32.7	33.9	35.1	36.4	38.6	43.3	45.0

The PMA for initial treatment ranged from 32.1 to 53.1 weeks. In this referral center cohort of 984 infants, 0.5% required ROP treatment after back transfer to another NICU; 0.9% (7% of treated infants) required their initial treatment after discharge to home.

Our data are consistent with ~~these~~ the 2006 guidelines. In this cohort of 984 infants born at 24-27 weeks, we did not observe ROP needing treatment before 32 weeks PMA; only 1 infant received initial ROP treatment ~~was treated~~ after 45 weeks PMA. A limitation of this study is that infants < 24 weeks gestation were not enrolled and these data may not be generalizable to less mature infants at the highest risk for ROP.

From: Kennedy, Kathleen A
To: Phelps, Dale
Cc: Wrage, Lisa Ann (wrage@rti.org); Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: ROP Natural History Abstract
Date: Wednesday, October 12, 2011 1:57:26 PM
Attachments: ROP Natural History PAS Abstract.doc

Thanks for the careful review. I tried to make most of these suggested changes (along with most of the suggestion in in the 16 other emails since Mon).

I have verified twice that the demographic comparisons are for severe ROP vs no ROP. Do you see something about that data that makes you think I've quoted it incorrectly?

I'm also struggling with the sentence that says what's in the table.

I think the min ages of diagnoses would be good to include and they are still consistent with the statement that treatable ROP was not diagnosed before 32 weeks. But a 0%ile really doesn't make sense, so I'm thinking we should put that in the text rather than the table. I've also added the late onset one to the text below the table because I don't think it makes sense to replace 99%ile with the 100%ile for such an extreme value.

I haven't addressed Michelle's comment (at what point you can say a baby without prethreshold is no longer at risk to need treatment), although I think it's important, because we need more data and I doubt that we can get it before the deadline. A simple solution (not exactly the same thing but close) would be to add a line to the table for PMAs at which cumulative %iles of prethreshold were diagnosed. We can do that for the presentation/manuscript.

I added the information about treatment after discharge. I just want to verify (quadruple check) that it was initial treatment (not "touch-up of previous laser treatment or vitrectomy or scleral buckle). What did you do with the ones where the date was uncertain? You should have the date of the first exam after treatment because that's when they met study outcome, right? If there was a long interval between that exam and the previous one, they would have been removed before because of uncertain timing of onset, right?

I've attached a new version. The changes (except for moving things around) are in yellow.

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Evaluating the Retinopathy of Prematurity (ROP) Screening Interval for 24-27 Week Gestation Infants

Kathleen A. Kennedy MD MPH, Lisa Wrage, MPH, Dale L. Phelps MD, Rosemary D. Higgins on behalf of the SUPPORT Subcommittee for the NICHD Neonatal Research Network

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Gabrio, Jenna"
Subject: SUPPORT Subcommittee Call 10 11 2011
Date: Wednesday, October 12, 2011 12:21:00 PM
Attachments: SUPPORT Subcommittee Call 10 11 2011.doc

Here you go

Thanks
Rose

SUPPORT Subcommittee Call
October 11, 2011

Participants: Wally Carlo, Wade Rich, Neil Finer, Kurt Schibler, Marie Gantz, Yvonne Vaucher, Abbot Laptook, Abhik Das, Michele Walsh, Roger Faix
NICHD: Rose Higgins
Data Coordinating Center: Jenna Gabrio, Kris Zaterka-Baxter

- Dr. Finer provided an overview of the primary analysis in CPAP versus surfactant arms.
  - There doesn't appear to be a difference in death or NDI
  - We are dealing with processes dependent on level of maturity at birth.
  - Major concern has to do with analysis published in letter form and presented at PAS by other trials that included SUPPORT data.
- They may be trying to publish this paper now and there is a possibility that we may not have anything definitive until 2014. ~~There is a concern about a potential a benefit to immature babies to be managed with CPAP with low SpO2~~The infants randomized to CPAP and low saturation had less death/ROP in the 24-25 week strata; that being said, death/NDI at 18-22 months was not different.
- Dr. Finer asked the subcommittee if they felt we should we say anything about this, and if so, how should we say this.
- Comments:
  - Dr. Schibler said that when looking at the low overall blindness rate of whole trial he thinks the conclusion from hospital outcome is strengthened by no difference in NDI and a low blindness rate despite ROP. This still comes down to the finality of death and that ROP is not as severe as it used to be as the rate of blindness in the trial is about 1 %.
  - Dr. Carlo said that death goes in the other direction as expected from the trial. High saturation group had lower mortality. He noted that this is fairly consistent and happened for both groups.
  - ~~Dr. Finer asked if we should we send a measure as to how this disclosure should be interpreted.~~
  - Dr. Walsh said that this is a lot of complex data and she is not sure that it lends itself to an abstract. Perhaps this may be better in a manuscript. We could be criticized for breaking down the cohort into 8 subcategories for which we were not powered. Dr. Walsh was concerned about changing ~~main~~ the conclusion from main trial.
  - Drs. Carlo and Finer agreed that it would be best to have full disclosure at least within the group.
  - Dr. Faix said that he may agree with Dr. Walsh and feels it may be more effective to write this in a manuscript rather than an abstract. He does feel that it is worth pursuing.
  - Dr. Schibler also feels that it would also be better laid out in a manuscript.
  - Dr. Das said that since there is some indication of interaction statistically we can justify looking at the subgroups for that outcome. The subcommittee needs to decide whether it is an important enough outcome to evaluate.
  - It was noted that in a manuscript we could explore severest form of interaction.
  - There was concern about causing more confusion for the public, and Dr. Finer is not sure that this will lead to clarity.
  - Action: Dr. Finer feels that we should just put this on hold for now and not rush into it.
- Barbara Schmidt raised a question—Was there some selection bias in low SPO2 babies. Where they sicker? Since the question has been raised, we should answer this.

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- Michele Walsh – this sub cohort differs from the SUPPORT cohort. In the main cohort the low sat arm got off the oximeter quicker. The high sat group had more time in room air. In this sub cohort they were on the oximeter the same amount of time between groups. So you could infer they are sicker. Julie tried to separate out the infants by the mode of support they were on, but this was not doable. How do we address the severity of illness issue? Should we before submitting the manuscript? We can submit the manuscript and make changes later if this question comes up. The manuscript is in internal review and we will wait for comments to come back.

- The growth abstract has been circulated. Susan Hintz's abstract is pending additional analyses and will be sent shortly.
- ROP Natural History secondary from Drs. Phelps and Kennedy has been sent for comment. ~~??? – Rose was talking about a third abstract. Both Abhik and I have no idea what she said, so ask her when you send the draft.~~
- The two follow-up papers have been circulated. Please send comments to Yvonne and Myriam by the end of this week.
- SUPPORT will be presented at Hot Topics.
- Prior to the SC meetingit was suggested to ~~, we should~~ survey all centers to see if they adopted a higher sat in their NICU's. We will bring this up at the steering committee meeting in October.

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From: Kennedy, Kathleen A
To: Wrage, Lisa Ann; Phelps, Dale
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Gantz, Marie
Subject: RE: ROP Natural History Abstract
Date: Wednesday, October 12, 2011 12:16:39 PM

What was the date of birth?

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From: Wrage, Lisa Ann [mailto:wrage@rti.org]
Sent: Wednesday, October 12, 2011 10:43 AM
To: Kennedy, Kathleen A; Phelps, Dale
Cc: higgins Higgins; Das, Abhik; Gantz, Marie
Subject: RE: ROP Natural History Abstract

This infant was born (b)(6) at 24 6/7 weeks GA, had 14 exams between (b)(6) (b)(6) Most exams show stage 2 ROP (starting in Sept), a few exams show stage 3, and then the last exam on (b)(6) indicates laser surgery on that day. This patient was discharged on (b)(6) so is one of the infants treated after discharge. The only problem I see with the data is that the (b)(6) (b)(6) If you like I can have this form reviewed and/or can send you the data for this infant so you can look at it directly.

Thanks.

Lisa

From: Kennedy, Kathleen A [mailto:Kathleen.A.Kennedy@uth.tmc.edu]
Sent: Tuesday, October 11, 2011 6:17 PM
To: Phelps, Dale; Wrage, Lisa Ann
Cc: higgins Higgins; Das, Abhik; Gantz, Marie
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I also think we need to check whether there wasn't some other error (mistake in gestational age, mistake in date of treatment, lost for awhile between exams, etc) before reporting this.

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From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Tuesday, October 11, 2011 5:15 PM

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Subject: RE: ROP Natural History Abstract

Wow... we're a little surprised.

The oldest kid to get surgery for his/her ROP was 53.1 weeks PMA.
Can you confirm this was either laser surgery, or Avastin, or cryotherapy? (not scleral buckle or vitrectomy)

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Sent: Tuesday, October 11, 2011 2:34 PM
To: Kennedy, Kathleen A; Phelps, Dale
Cc: higgins Higgins; Das, Abhik; Gantz, Marie
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Hello,
Here are the numbers that you wanted:

For the "Any ROP" group, min PMA of onset=29.3, max=46.7, mean=34.1
For the "Severe ROP" group, min PMA of onset=32.1, max=53.1, mean=37.1

There were 9 (0.9% of total cohort) infants who were treated after discharge and 5 (0.5% of total cohort) infants who were treated after transfer. (total cohort n=984).

As to Dale's comment regarding the table:
We are showing the cumulative distribution of PMA at onset of 'Any ROP' and 'Severe ROP'. I think that "Postmenstrual Age at Onset of ROP (weeks)" is ok for the title with 'Cumulative % with diagnosis of ROP' or something like that is ok for the subtitle (basically a mix of what Kathleen already had and your suggested changes). I will think about it some more though if you are still not satisfied.

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Subject: RE: ROP Natural History Abstract
Date: Tuesday, October 11, 2011 6:28:16 PM

I agree..
However, it's not out of line with other large series where outliers of 42 weeks or 52 weeks or 48 weeks PMA have been reported for ROP that has been indolent... just won't go away (regress) but final gets bad enough to force treatment.
It is not common, but it happens on occasion.

It is my understanding that this is why the guidelines say "conclusion of acute retinal screening examinations should be based on age and retinal ophthalmoscopic findings."
and "Findings that suggest that examinations can be curtailed.... and there are 4 situations listed
1. zone III without previous zone I or zone II ROP and past 35 weeks PMA
2. full retinal vascularization (presumably has the same qualifier about 35 weeks PMA and being sure)
3. PMA 45 weeks and no prethreshold ROP or worse present
4. regression of ROP, taking care to be sure that there is no abnormal vascular tissue present that is capable of reactivation and progression.

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To: wcarlo@peds.uab.edu; Das, Abhik; Roger.Faix@hsc.utah.edu; nfiner@ucsd.edu; Gantz, Marie; alaptook@WIHRI.org; nxs5@cwru.edu; wrich@ucsd.edu; kurt.schibler@cchmc.org; Michele.Walsh@UHhospitals.org; Bradley.Yoder@hsc.utah.edu
Cc: Wrage, Lisa Ann; dale_phelps@urmc.rochester.edu; Archer, Stephanie (NIH/NICHD) [E] (archerst@mail.nih.gov); Higgins, Rosemary (NIH/NICHD)
Subject: ROP Natural History Abstract

SUPPORT Subcommittee: I've attached a draft of the PAS abstract for the ROP Natural History Secondary Study that uses data from the SUPPORT trial. Comments and suggestions are welcome. I hope to get the missing data before the deadline. If anyone knows how to navigate the submission process (how to include the NICHD without entering the NICHD as an author and then being required to submit a bunch of CME/COI disclosures for the NICHD), I'd appreciate the help.

Stephanie, could you please check to make sure I haven't missed anyone on the SUPPORT Subcommittee?

Lisa, if we could get the data for treatment after back transfer and after discharge, that would be great. If you can tabulate the 0 and 100%iles and they look reasonable (no extreme outliers), we could replace the 1 and 99%iles in the table with 0 and 100%iles.

Kathleen A. Kennedy, MD, MPH

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Laptook, Abbot"
Subject: FW: Support NDI_09-26-2011
Date: Tuesday, October 11, 2011 1:04:00 PM
Attachments: follow up chart.doc
Oxygen trial chart_Peralta.doc
Support NDI_09-26-2011.doc

Abbot
I had not included you on the email – SORRY!
ROSE

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To: 'Finer, Neil'; 'Vaucher, Yvonne'; 'Wally Carlo (wacarlo@uab.edu)'; Myriam Peralta, M.D.; kurt.schibler@cchmc.org; 'mcw3@cwru.edu'; Roger Faix; Bradley Yoder; 'Das, Abhik'; Gantz, Marie; 'Nancy Newman'; Rich, Wade
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: Support NDI_09-26-2011

Here is the SUPPORT oximetry follow up paper. Please indicated which CONSORT diagram you would like to use.

Please send comment back to Myriam Peralta by October 13.

Thanks
Rose

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To: Wally Carlo, M.D.
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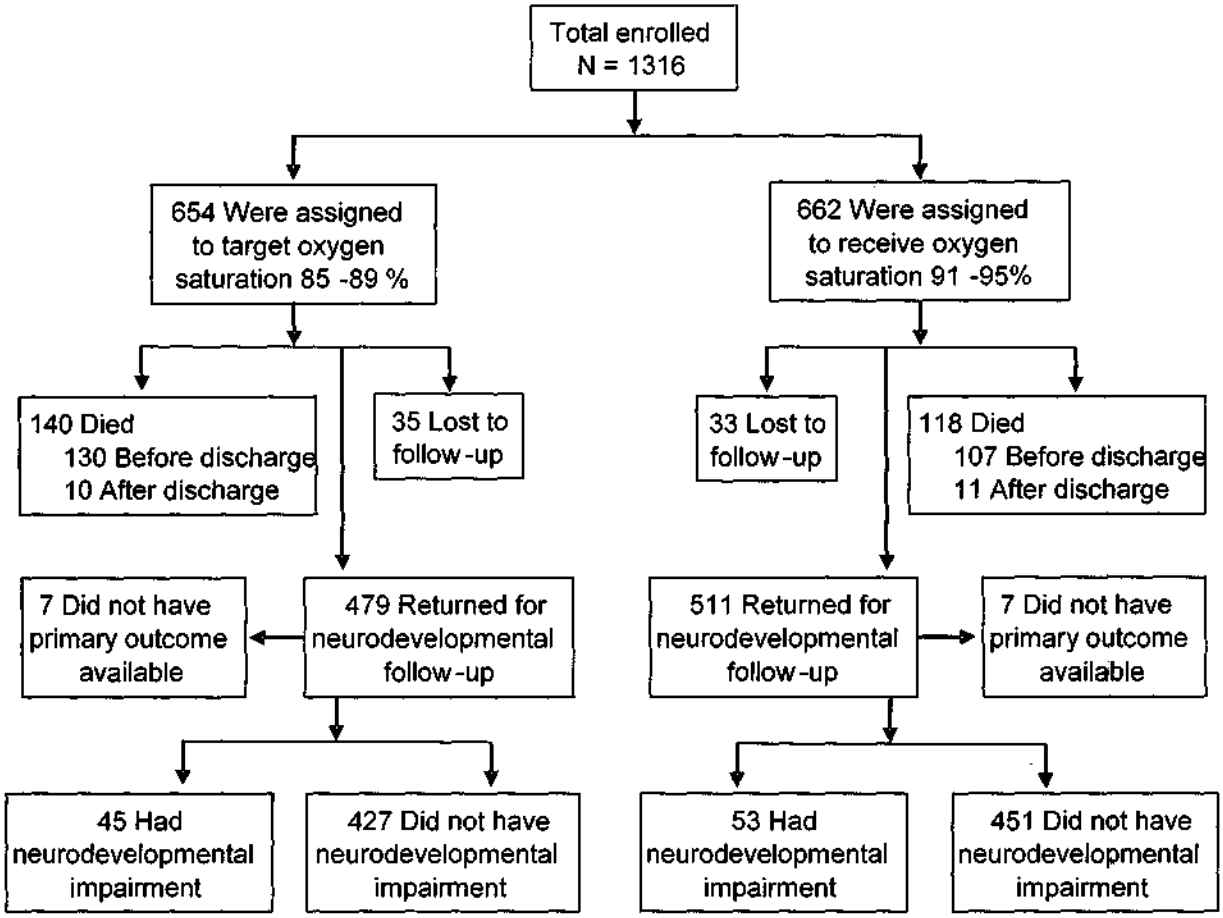
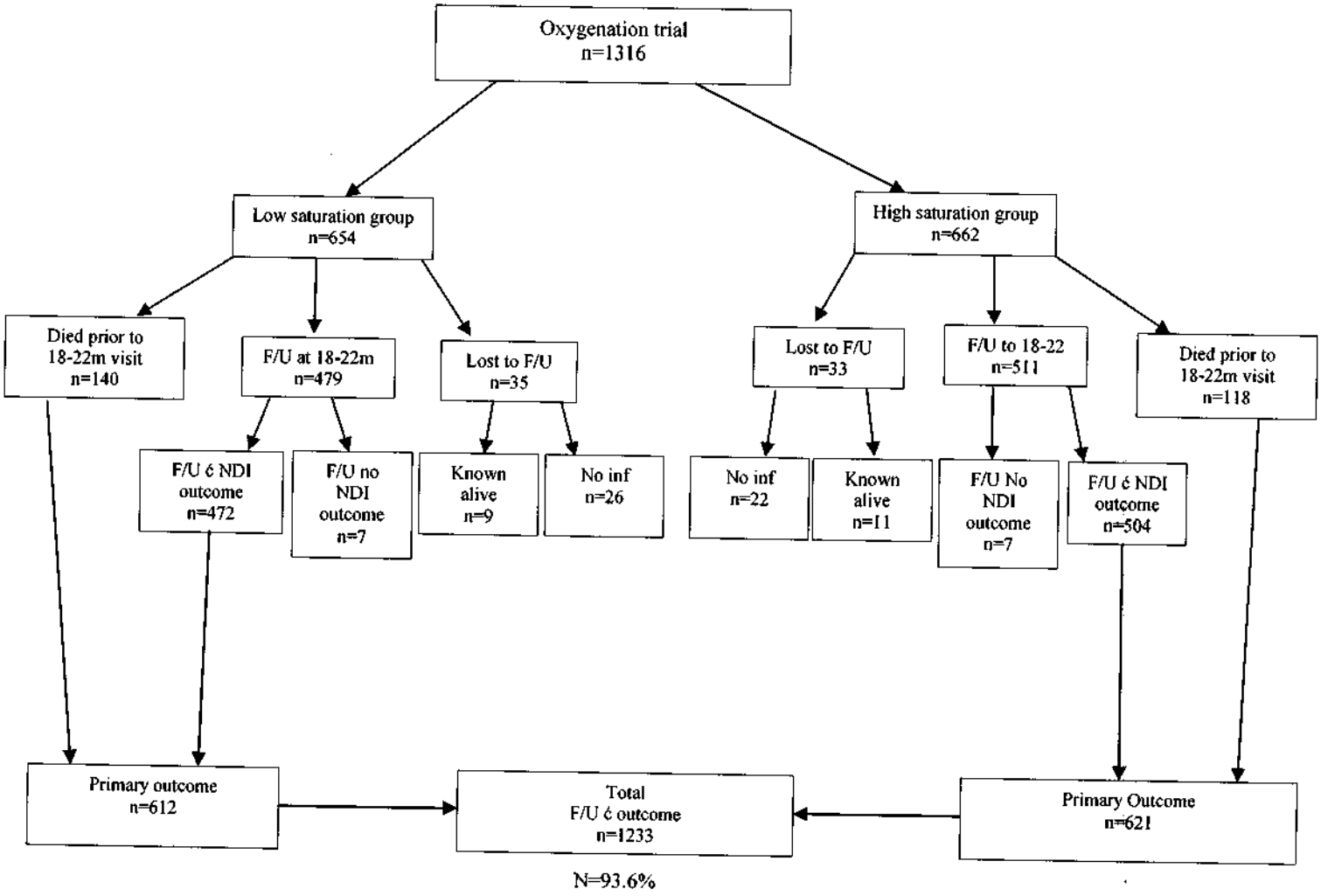
Subject: Support NDI_09-26-2011

Here is the last draft that I have for now, I am not sure which flow chart we would like to use as we had discussed both, so I included both. I will send you the abstract later today, thanks.





Neurodevelopmental Outcome of Extremely Preterm Infants in a Trial of Different Oxygen Saturation Targets

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Word Count

Abstract: 248

Text: 1,148

ABSTRACT

BACKGROUND

Targeting lower (vs. higher) oxygen saturations in the SUPPORT Trial decreased severe retinopathy of prematurity but increased mortality before discharge. We hypothesized that the effects of different oxygen levels on long term neurodevelopmental intact survival were not significant.

METHODS

We followed 1211 of 1316 (92%) infants born at 24 to 27 week gestation and randomized to higher (91-95%) or lower oxygen saturation targets (85-89%) from birth to 36 weeks corrected age. The outcome of this follow up study was a composite of death or neurodevelopment impairment at 18 to 22 months corrected age. Neurodevelopmental impairment was defined as a Bayley III cognitive composite score of less than 70, modified Gross Motor Function Classification System ≥2, presence of moderate to severe cerebral palsy, permanent hearing loss, and/or bilateral blindness.

RESULTS

Death or neurodevelopmental impairment occurred in 185 (30.2%) infants in the lower oxygen saturation group and 171 (27.5%) infants in the higher oxygen saturation group (relative risk 1.12; confidence interval 0.94, 1.32; p=0.21). Death occurred in 140 (22.1%) of the children in

the lower oxygen saturation group and in 118 (18.2%) in the higher oxygen saturation group (relative risk 1.25; confidence interval 1, 1.55, p=0.05).

CONCLUSIONS

Among extremely preterm infants targeted at different levels of oxygen saturation, no significant difference in death or neurodevelopmental impairment was observed at 18 to 22 months. Mortality remained elevated in the lower oxygen target group at 18 to 22 months, though the trend was only borderline statistically significant.

Oxygen supplementation is a vital therapy for survival of many preterm infants with respiratory disorders. However, oxygen supplementation may increase the risk of retinopathy of prematurity, bronchopulmonary dysplasia,[Tin et al, 2001] periventricular leukomalacia,[Chow et al, 2003] and cerebral palsy.[Anderson et al, 2004] Restrictive oxygen therapy decreases retinopathy but has resulted in increased deaths in randomized controlled trials.[Bolton DP et al, 1997; Askie et al, 2009; Carlo et al, 2010; Stenson et al, 2011]

Comment [WC1]: These references are quoted in my NEJM paper

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development SUPPORT Trial demonstrated no significant difference in a composite outcome including retinopathy of prematurity and death between a lower oxygen saturation group (85-89%) and the higher saturation target group (91-95%). However, mortality was increased and severe retinopathy of prematurity was reduced in the lower oxygen saturation group compared to the higher saturation target group. A recent meta-analysis that included the SUPPORT Trial and two other subsequently multi-center randomized controlled trials with a total of 3631 infants showed that infants randomized to an oxygen saturation of 91-95% % had a lower mortality rate than infants randomized to oxygen saturation targets of 85-89% (17.3% versus 14.4%, P=0.015).[Stenson, NEJM 2011] There has been keen interest in determining whether oxygen supplementation can reduce neurodevelopmental impairment. However, in two non randomized studies of oxygen saturation targeting,[Tin et al, 2001; Bradley et al, 1993] neurodevelopmental outcome did not differ by oxygen targets.

Comment [WC2]: Spell out

This study evaluated the composite outcome of death or neurodevelopmental impairment at 18 to 22 months corrected age in the subjects enrolled in the SUPPORT trial and randomized to two

groups of extremely preterm infants randomized to lower (85-89%) or higher oxygen saturation targets (91-95%) from birth to 36 weeks corrected age.

METHODS

Study Design

1316 extremely preterm infants (24 weeks 0 days to 27 weeks 6 days) born between February 2005 and February 2009 at 20 centers in the United States participating in the Neonatal Research Network of the Eunice Kennedy Shriver National Institute of Child Health and Human Development were enrolled immediately following delivery in the prospective, randomized, controlled SUPPORT trial. Permuted block randomization was used, with stratification according to center and gestational age (24 weeks 0 days to 25 weeks 6 days or 26 weeks 0 days to 27 weeks 6 days). The infants were randomly assigned before birth to a target range of oxygen saturation of 85% to 89% (the lower oxygen saturation group) or 91 to 95% (the higher oxygenation group). Using a 2-by-2 factorial design, participants were also randomly assigned to receive either CPAP immediately following delivery and a limited ventilation strategy if subsequent intubation was required or intubation with surfactant administration within an hour after birth. Procedures for enrollment, intervention and data collection have been previously reported. [Carlo NEJM]. The study was approved by the institutional review board at each participating site and RTI international which is the independent data coordinating center for the Neonatal Research Network. Written informed consent was obtained from the parent or guardian of each child before delivery.

Assessments

All infants who survived to 36 weeks corrected age were eligible to participate in the prospective follow up cohort of the SUPPORT trial. A comprehensive neurodevelopmental assessment was performed at 18-22 months of corrected age by neurologic examiners and neurodevelopmental testers who were unaware of the treatment assignments and had been trained annually for reliability of assessments during a 2-day workshop. Developmental assessment was assessed using The Bayley Scales for Infant Development 3rd edition (BSID III) (ref). Cognitive Composite Scores are reported as a standardized score with a mean of 100 and a standard deviation of 15. The modified Gross Motor Function Classification System (GMFCS) (ref) describes the gross motor performance and has a range from 0 (normal) to 5 (most impaired). Examiners also recorded the presence of cerebral palsy defined as a nonprogressive disorder of the central nervous system and characterized by abnormal muscle tone in at least one arm or leg associated with abnormal control of movement or posture with delayed attainment of motor milestones. Cerebral palsy was classified depending on severity into mild (GMFCS $\leq$1), moderate (GMFCS 2 or 3) or severe (GMFCS $\geq$ 4). Hearing and visual impairment were determined based on parental history and examination.

Certified research nurses collected demographic and neonatal using standardized definitions in the trial's manual of operations. Data collection included gestational age, birthweight, gender, multiple gestation, race/ethnicity, ROP status, BPD status, history of medical or surgical NEC, history of late onset sepsis, use of postnatal steroids, rehospitalizations, interim medical history, surgeries, insurance status, marital status, maternal education, household income, language spoken at home, whether living with biological parents. Socioeconomic data was updated during the 18-22 month visit and if not available, data during the neonatal period was included.

Outcome

The composite of death or neurodevelopmental impairment at 18 to 22 months corrected age for prematurity was the primary neurodevelopmental outcome. This composite outcome was selected because infants who died before 18 months could not be classified as having neurodevelopmental impairment. Neurodevelopmental impairment was defined as having any of the following: BSID III cognitive composite score less than 70, GMFCS $\geq$ 2, presence of moderate or severe cerebral palsy, permanent hearing loss that does not permit the child to understand directions of the examiner and communicate despite amplification with hearing aids or cochlear implants, or bilateral visual impairment (vision < 20/200).

Analysis

Data was entered in standard forms and was transmitted to RTI International which stored, managed and analyzed the data for this study. Details regarding sample size calculations for the SUPPORT trial have been previously reported (ref finer). All analyses were performed according to the intention to treat principle. The denominator that was used to calculate the rate of each outcome was the number of infants for whom the outcome was known. The primary analysis focused on the percentage of infants in each group for whom the primary outcome of death or NDI at 18 to 22 months corrected age could be assigned. Analysis of this and all other categorical outcomes was performed with the used of robust Poisson regression in a generalized-estimating-equation model to obtain adjusted relative risks with 95% confidence intervals.

Continuous outcomes were analyzed with the use of mixed-effects linear models to obtain adjusted means and standard errors.

In the analysis of all outcomes, the results were adjusted, as pre-specified, for gestational-age strata, center and familial clustering. Two-sided p value of less than 0.05 were considered to indicate statistical significance, and no adjustments have been made for multiple comparisons.

RESULTS

Characteristics of the Study Sample

The SUPPORT trial enrolled 1316 study in the study (see flowchart in Figure 1). Five hundred twenty four infants in the lower oxygen saturation group and 555 in the higher oxygen saturation group survived to discharge from the hospital. The baseline characteristics of the entire group have been reported previously(Carlo NEJM) Ten children in the lower oxygen saturation group and 11 children in the higher oxygen saturation group died after discharge from the nursery prior to the 18 to 22 month adjusted age follow up visit. Thirty five children in the lower saturation group and 33 children in the higher saturation group were lost to follow up. However 9/35 in the lower saturation group and 11/33 in the higher saturation group were known to be alive at 18 to 22 months adjusted age. Neurodevelopmental assessment was performed in 990/1058 eligible infants (93.6%). Of those who were evaluated at the 18 to 22 months adjusted age, neurodevelopmental impairment was determined in 976 children. From the entire cohort the pre-specified outcome of death or neurodevelopmental impairment was able to be determined in 93.8% (1234/1316). There were no significant differences in the baseline characteristics of the cohort that was followed up and the lost to follow up. The mothers at the lost to follow up were

more likely to be married and more likely to have public health insurance. (*add numbers, Marie not sure if I have these ones, I could not find them)*

We looked at the baseline characteristics of the follow up cohort and the entire trial cohort which is presented in Table 1. The percentage of infants who were small for gestational age in the higher saturation target group was higher compared to the infants who were in the lower saturation target group in the follow up cohort group. In addition as reported previously severe retinopathy of prematurity had a higher incidence in the higher oxygen saturation group compared to the lower saturation group. No other significant differences were reported in the baseline characteristics of the eligible infants for follow up.

Primary Outcome

The mean corrected age for neurodevelopmental evaluation was similar between both groups (low SpO2 19.9 m $\pm$ 2.4 vs. High SpO2 20.2 $\pm$ 2.7 mo, p=0.076). Prevalence of the composite primary outcome of death or neurodevelopmental impairment was not significantly different between the lower and higher oxygen saturation target groups. (Table 2) Similar results were observed within both gestational age strata (Low SpO2 115/261, 44.1% vs. High SpO2 112/276, 40.6%, P= 0.4201 for the 24 0/7-25 6/7 wks ga; and Low SpO2 70/351, 19.9% vs High SpO2 59/346, 17.1%, p=0.33 for the 26 0/7 – 27 6/7 wks GA). Death prior to the 18 to 22 month adjusted age visit was higher among infants in the lower oxygen saturation target group compared to those in the higher saturation target group. (Low SpO2 140/633, 22.1% vs. high SpO2 118/648 , 18.2%, relative risk 1.25 95% CI 1, 1.55, p=0.0462). However death at 18 to 22 months adjusted age was not significantly different within both gestational age strata (low SpO2 91/267, 34.1% vs. High SpO2 79/283, 27.9%, relative risk 1.23 95% CI 0.95, 1.59 P=0.118 for

the 24 0/7-25 6/7 wks GA; and Low SpO2 49/366, 13.4% vs. High SpO2 39/365, 10.7%, relative risk 1.28 95% CI 0.86, 1.89, p=0.2195).

The rate of neurodevelopmental impairment among survivors followed at 18 to 22 month adjusted age visit was similar between the lower and the higher oxygen saturation target groups. Rates for neurodevelopmental impairment were not significantly different in either of the gestational age strata groups.

Outcomes among survivors at follow up

The percentage of children with Bayley III cognitive scores below 70 was not significantly different between the lower and higher oxygen saturation group. In addition we looked into the percentage of children with Bayley cognitive scores below 85 and these were not significantly different between the groups. Mean scores of the Bayley Scales of Cognitive Composite are presented in table 3.

The rate of retinopathy of prematurity as well as infants, who required eye surgery, was higher in the higher oxygen target group compared to the lower oxygen target group; however the rate of blindness was not significantly different at the 18 to 22 month adjusted age visit. Other visual outcomes are presented in table 3.

DISCUSSION

In this multicenter, follow up study of infants randomized to a lower target range of oxygen saturation (85 to 89%) or to a higher target oxygen saturation (91 to 95%) there were no

significant difference in the prespecified outcome of death or neurodevelopmental impairment. To our knowledge this is the only large comprehensive study that has included neurodevelopmental impairment as an outcome for evaluating effects on different oxygen target saturation levels. There has been a previous concern of using lower saturation target and increased mortality in extreme premature infants (ref) In addition we found that death prior to discharge in the SUPPORT trial showed increase mortality among children who were assigned to lower target saturation levels, however in this follow up study death at 18 to 22 months of age was not significantly different between the two target groups or at the different gestational age stratification levels.

We had reported previously that our lower saturation oxygen target was associated with a large reduction in the incidence of severe retinopathy of prematurity among survivors. (ref) It has been previous reported that severe ROP may be associated with poor visual outcomes even with treatment(ref) Although our study was not powered to detect small differences in eye disorders or visual function at 18 to 22 months of age we did find that there were no significant differences in the report of unilateral and bilateral blindness among the two groups. Eye surgery was reported higher in our group with a higher oxygen saturation target more likely related to higher incidence of severe retinopathy of prematurity although data regarding specifics of eye surgery was not collected (*Marie I think we actually did this but did not have it in the table)*. Additional analysis regarding eye findings and its association with presence of severe retinopathy of prematurity is needed.

There had been concerns that lower saturation oxygen saturation targets are associated with effects on long term neurdevelopmental impairment (ref). However NDI as we defined in this study was not found to be significant in the lower or higher oxygen saturation assigned group.

In addition Cerebral Palsy was not significant in both groups it is to note that the incidence of CP was lower as previously reported in other outcome studies.

It has been recognized that higher oxygen levels can be associated with lung disease, however we found no difference in the use of postnatal corticosteroids, diuretics or long term use of oxygen as well as rehospitalization between the two groups.

This study has some limitations, this study reports only follow up to 18 to 22 months of age, which may had not been enough time to detect the presence of other minor however important disabilities. However it is to note here when we used the cutoff of Bayley III to less than 85 we also did not find significant differences between the groups. In addition there is an ongoing follow up SUPPORT study that will be reporting in the future the follow up outcome of these children at school age. These children were enrolled in tertiary care centers therefore generalizibility is a concern, however we include 20 centers around the country.

In summary we found no significant differences in death or Neurodevelopmental impairment, at 18 to 22 months corrected age in extremely premature infants that were randomized to receive lower target oxygen saturation or higher target oxygen saturation. Increased death at discharge that was found on our previous report associated with lower target oxygen saturation was still present at 18 to 22 months adjusted age. Although retinopathy of prematurity was associated

with higher oxygen saturation target levels, blindness was not significant different among survivors.

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Comment [bb3]: Check references

Morris BH, Laroia N, Phelps DL, Poindexter BB, Cotten CM, Van Meurs KP, Duara S, Narendran V, Sood BG, O'Shea TM, Bell EF, Ehrenkranz RA, Watterberg KL, Higgins RD. Target Ranges of Oxygen Saturation in Extremely Preterm Infants. N Engl J Med 2010; 362:1959-1969.

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Table 1. Baseline characteristics of the SUPPORT group

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Characteristics	Trial Cohort		Cohort with Follow-up Visit	
	Lower Oxygen Saturation	Higher Oxygen Saturation	Lower Oxygen Saturation	Higher Oxygen Saturation
	N=654	N=662	N=479	N=510
Birth weight – g	835.5± 193.4	824.8± 193	857.8 ± 186.3	843.9± 191.6
Gestational age – wk	26.2 ± 1.1	26.1 ± 1.1	26.3 ± 1.1	26.2 ± 1
Small for gestational age – no./total no. (%)	41/654 (6.3)	55/662 (8.3)	17/479 (3.5)*	38/511 (7.4)*
Male sex – no./total no. (%)	341/654 (52.1)	371/662 (56)	240/479 (50.1)	281/510 (55.1)
Race or ethnic group – no./total no. (%)				
Non Hispanic Black	257/654 (39.3)	232/662 (35)	201/479 (42)	176/510 (34.5)
Non Hispanic White	242/654 (37)	279/662 (42.1)	178/479 (37.2)	217/510 (42.5)

Hispanic	132/654 (20.2)	127/662 (19.2)	86/479 (18)	97/510 (19)
Other or unknown	23/654 (3.5)	24/662 (3.6)	14/479 (2.9)	20/510 (3.9)
Multiple births – no./total no. (%)	161/654 (24.6)	176/662 (26.6)	124/479 (25.9)	128/510 (25.1)
Maternal educational level <high school no./total no. (%)	148/594 (24.9)	165/612 (27)	115/471 (24.4)	129/504 (25.6)
Public Health Insurance only – no./total no. (%)	356/650 (54.8)	348/660 (52.7)	253/479 (52.8)	266/511 (52.1)
Mother married – no./total no. (%)	284/652 (43.6)	308/661 (46.6)	222/479 (46.3)	243/511 (47.6)
Lives with both biological parents – no./total no. (%)	354/508 (69.7)	364/547 (66.5)	332/478 (69.5)	345/511 (67.5)
Household income < $30,000/year – no./total no.(%)	247/474 (52.1)	291/528 (55.1)	239/456 (52.4)	272/498 (54.6)
English as primary language – no./total no. (%)	402/477 (84.3)	429/513 (83.6)	402/477 (84.3)	427/511 (83.6)
Cesarean section – no./total no. (%)	441/654 (67.4)	442/662 (66.8)	332/479 (69.3)	335/511 (65.6)
Antenatal steroids – no./total no. (%)	633/654 (96.8)	632/661 (95.6)	462/479 (96.5)	487/511 (95.3)
Retinopathy of prematurity – no./total no. (%)	41/475 (8.6)**	91/509 (17.9)**	38/442 (8.6)**	82/471 (17.4)**

Bronchopulmonary dysplasia – no./total no. (%)	205/540 (38)	237/568 (41.7)	177/479 (37)	203/511 (39.7)
Intraventricular hemorrhage grade 3 or 4 or Periventricular leukomalacia – no./total no. (%)	98/630 (15.6)	100/640 (15.6)	56/478 (11.7)	60/510 (11.8)
Necrotizing enterocolitis – no./total no. (%)	76/641 (11.9)	70/649 (10.8)	42/479 (8.8)	44/511 (8.6)
Late onset sepsis/meningitis – no./total no. (%)	228/624 (36.5)	226/634 (35.6)	155/479 (32.4)	166/511 (32.5)
Post natal steroids – no./total no. (%)	61/636 (9.6)	69/644 (10.7)	41/477 (8.6)	48/507 (9.5)
CPAP – no./total no. (%)	336/654 (51.4)	327/662 (49.4)	254/479(53)	257/511 (50.3)
Surfactant – no./total no. (%)	318/654 (48.6)	335/662 (50.6)	225/479 (47)	254/511 (49.7)

*p<0.05, **p<0.001

Table 2. Primary Outcomes at 18-22 Months Adjusted AGe

	Lower Oxygen Saturation N=654	Higher Oxygen Saturation N=662	Adjusted Relative Risk	p value
Death prior to discharge – no./total no. (%)	130/654 (19.9)	107/662 (16.2)		
Outcome determined by death or NDI – no./total no. (%)	612/654 (93.6)	622/662 (94)	1 (0.97, 1.03)	0.7927
Died by 18-22 months – no./total no. (%)	140/633 (22.1)	118/648 (18.2)	1.25 (1, 1.55)	0.0462
Neurodevelopmental impairment or death – no./total no. (%)	185/612 (30.2)	171/662 (27.5)	1.12 (0.94, 1.32)	0.2098
Survivors at follow-up				
Neurodevelopmental impairment – no./total no. (%)	45/472 (9.5)	53/504 (10.5)	0.87 (0.6, 1.28)	0.4920
Bayley III cognitive composite score < 70 – no./total no. (%)	34/471 (7.2)	38/503 (7.6)	0.91 (0.58, 1.43)	0.6870
Gross motor function level ≥ 2 – no./total no. (%)	26/479 (5.4)	23/511 (4.5)	1.17 (0.68, 2.01)	0.5597
Moderate/severe cerebral palsy – no./total no. (%)	20/479 (4.2)	20/511 (3.9)	1 (0.54, 1.83)	0.9971
Blindness – no./total no. (%)	5/479 (1)	8/511 (1.6)	0.67 (0.22. 2.02)	0.4789
Deafness – no./total no. (%)	12/479 (2.5)	12/511 (2.3)	1.16 (0.54, 2.49)	0.7013

Table 3. Medical Outcomes by Group

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Outcome	Low SpO2 (N=479)	High SpO2 (N=510)	Relative Risk for Low SpO2 vs. High SpO2 (95% CI)	Adjusted difference in means (95% CI)	Adjusted P-value
Bayley Scales of Infant Development III					
Cognitive composite < 70					
Cognitive composite <85	105/471 (22.3)	131/502 (26.1)	0.86 (0.69, 1.07)		0.1831
Mean Scores					0.2940
Median Scores					0.8121
					0.3016
Neurologic findings					0.8948
Mild cerebral palsy	23/459 (5.0)	21/490 (4.3)	1.16 (0.66, 2.02)		0.6105

Moderate cerebral palsy	11/447 (2.5)	10/479 (2.1)	1.19 (0.52, 2.71)	0.6873
Severe cerebral palsy	9/445 (2.0)	10/479 (2.1)	0.95 (0.39, 2.27)	0.9026
Any cerebral palsy	43/479 (9.0)	41/510 (8.0)	1.12 (0.76, 1.65)	0.5766
Abnormal neurologic exam	108/479 (22.5)	114/510 (22.4)	1.02 (0.82, 1.27)	0.8606
Vision findings				
Strabismus	46/478 (9.6)	41/509 (8.1)	1.2 (0.7, 1.8)	0.3845
Nystagmus	22/479 (4.6)	12/509 (2.4)	1.95 (0.94, 4.07)	0.0737
Tracks 180 degrees	462/476 (97.1)	492/506 (97.2)	1 (0.98, 1.02)	0.9330
Corrective lenses both eyes vs. normal both eyes	21/468 (4.5)	20/492 (4.1)	1.14 (0.62, 2.08)	0.6774
Blind, some function, both eyes	3/450 (0.7)	2/474 (0.4)	1.56 (0.27, 8.95)	0.6151
Blind, no useful vision, both eyes	2/449 (0.4)	4/476 (0.8)	0.54 (0.1, 2.95)	0.4789
Other abnormal vision	6/453 (1.3)	12/484 (2.5)	0.55 (0.21, 1.46)	0.2301
Eye surgery	31/477 (6.5)	67/508 (13.2)	0.52 (0.35, 0.78)	0.0014
Medicines				
Bronchodilators	159/475 (33.5)	185/505 (36.6)	0.92 (0.78, 1.09)	0.3583
Steroids	95/475 (20.0)	108/505 (21.4)	0.92 (0.72, 1.18)	0.5016

Diuretics	15/475 (3.2)	14/505 (2.8)	1.16 (0.58,2.34)	0.6717
Anticonvulsants	12/478 (2.5)	12/510 (2.4)	1.08 (0.49, 2.37)	0.8514
Readmission	210/478 (43.9)	238/510 (46.7)	0.94 (0.82, 1.08)	0.4111
Readmission for respiratory reason	110/470 (23.4)	127/503 (25.2)	0.93 (0.74, 1.16)	0.5114
No Readmission for growth/nutrition	12/470 (2.6)	13/503 (2.6)	1.05 (0.49, 2.25)	0.8953

From: [redacted]
To: [redacted]
Cc: [redacted]
Subject: RE: SUPPORT Subcommittee Call - [redacted]
Date: Tuesday, October 11, 2011 11:36:16 AM

Hi Everyone

Here is a final version of the CPAP/SpO2 abstract

First Author: Neil N Finer, MD **Filename:** 750127

Responsible Author: Neil N Finer, MD
Presenting Author: Neil N Finer, MD
Contact Person: Neil N Finer, MD

2012 PAS Annual Meeting

Subspecialty: Neonatology - General
Theme: Neonatal - Patient-Oriented Research

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Responsible Author Declaration: As the responsible author, I confirm that the individual listed as the sponsor has been contacted and given the opportunity to review the abstract and has subsequently agreed to sponsor this abstract.

Presenting Author: Neil N Finer, MD
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The presenting author is member of these Alliance Societies:
Is Presenting Author a Trainee? No, Not a Trainee
Presenter Copyright Declaration:
I certify that any material I will use, display, distribute, reproduce or have reproduced or distributed in connection with my above noted presentation for which I do not have permission to use, is my original work and/or is public information or another type of material which does not require securing permission from another party to use, display, distribute, reproduce or have reproduced or distributed

QUESTIONNAIRE INFORMATION
Eastern Society for Pediatric Research: No, Do not consider this abstract for the Eastern SPR
Pediatric Hospital Medicine: No, Do not consider this abstract for presentation at the Pediatric Hospital Medicine, July 19-22, 2012
Research Type: Clinical
Presentation Sabbath Conflict on: N/A
APA Special Interest Groups, Committees or Regions: None

AWARDS APPLIED FOR:
No awards selected

SPONSOR INFORMATION
Sponsoring Member for PAS/ASPR abstract:
Sponsor Name: Neil Norman Finer
Email: nfiner@ucsd.edu
Is the Sponsor an Author? Yes
Sponsoring Societies:
Society for Pediatric Research

Title: Early CPAP Versus Surfactant: The Effect Of A Lower SpO2 Range Secondary Outcomes Of The SUPPORT Trial

Neil N Finer, MD[UCSD], Waldemar Carlo, MD[University of A] and Support Group[NICHD] [1]Neonatology, Pediatrics, University California San Diego, San Diego, Ca, 92103, United States

Background: The SUPPORT Trial prospectively compared early CPAP and a limited ventilator strategy to early surfactant and also randomized all infants to a lower (85-89%) versus a higher (91-95%) SpO2 range from 2 hours of birth (NEJM 2010) The results demonstrated a significant reduction in death for infants who were randomized to CPAP in the extremely premature strata (24 to 25 wk, 23.9% vs 32.1%, p=0.028) Infants randomized to the lower SpO2 range had less ROP (8.6% vs 17.9%, p=0.001 and increased death (19.9% vs 16.2%, p=0.04). A prespecified secondary outcome for the SUPPORT Trial was that infants randomized to CPAP and a low SpO2 strategy would have a lower rate of death/ROP. There was no overall interaction between the respiratory arms and the SpO2 ranges. We did not initially evaluate the gestational age strata for such an interaction

Objective: This study evaluated the effect of the SpO2 range on the outcomes for infants in the 2 gestational age strata, 24-25 wks, and 26-27 weeks

Design/Methods: The surviving infants were assessed at 18 to 22 months for full neurodevelopmental evaluation, which included hearing, vision, and mental and motor outcomes using the Bayley 3. Tests for interaction were adjusted for GA center and family clustering.

Results: There were 1316 infants randomized in the SUPPORT Trial and deaths prior to discharge, (16.4% vs 19.6%), and deaths prior to follow-up (18.4% vs 21.9%) and the overall ROP rates among survivors (13.1% vs 13.7%) were not different between CPAP and Surf infants. ROP was less frequent in the 24-25wk strata, (22.2% vs 31.6%, p=0.04)whereas ROP was greater in CPAP infants in the 26-27 wk strata (7.3% vs 3.6% p=0.04). Death at follow-up for the 24-25 wk infants remained significantly lower for the CPAP infants (26.4% vs 35.5%, p=0.019). For the overall study and for the 26-27 wk strata there were no significant interactions between SpO2 group and the intervention groups for death/ROP or death/NDI. There was a significant interaction between SpO2 low vs high and CPAP vs Surf in the EPS, the p value for the interaction between CPAP/surfactant and SpO2 was .05. ROP was significantly lower for those randomized to CPAP vs. surf in the Low SpO2 target group (p=.01) but not those in the High SpO2 group (p= .71). For the outcome of death or ROP, while no interaction was seen in the overall study, the 24-25wk infants in the Low SpO2 strata had a lower rate of ROP/death (p=.001), such differences were not seen in the High SpO2 group (p= 2)

Death/ROP for 24-25 wk Strata and 26-27 wk Strata - Low vs High SpO2

SpO2 Range	CPAP/Surf	Death - (24-25)	ROP - (24-25)	Death/ROP - (24-25)	Death - (26-27)	ROP - (26-27)	Death/ROP (26-27)
Low	CPAP	37/142 (26%)	11/95 (12%)**	48/132 (36%)*	25/194(13%)	8/153(5%)	33/178(19%)
	Surf	48/134 (36%)	21/76 (28%)**	69/124 (56%)*	20/184(11%)	1/151(1%)	21/171(12%)
High	CPAP	31/143 (22%)	33/103 (32%)	64/134 (48%)	15/185(9%)	15/160(9%)	31/176(18%)
	Surf	42/146 (29%)	33/95 (35%)	75/137 (55%)	18/189(10%)	10/141(7%)	28/169(17%)

* p = 0.001, ** p=0.01

There was no differences in death/NDI comparing SPO2 strategy overall or for either strata.

Conclusions: The lowest death rate was seen in the CPAP infants treated with a high SpO2 approach, supporting the use of a higher SpO2 approach. However death and ROP were significantly lower in the low SpO2 arm of the 24-25 wk infants. In addition the other large randomized trials comparing SpO2 ranges did not randomize infants to a respiratory support strategy and their preliminary results support a higher mortality in the Low SpO2 range infamnts. For extremely immature infants a strategy of early CPAP with a limited ventilator approach combined with a lower SpO2 target may be optimal. Such an approach in this immature population requires further confirmation in future prospective trials.

Neil

From: Gabno, Jenna [mailto:jgabno@rti.org]
Sent: Tuesday, October 11, 2011 6:30 AM
To: abbptook@WIHRI.org; Bradley Yoder; adas@rto.org; mgalvez@rti.org; Higgins, Rosemary (NIH/NICHD) [E]; kurt.schibler@cchmc.org; mcw3@cwru.edu; MPerelta@PEDS.UAB.EDU; nancy newman; Finer, Neil; Roger.Fair@hsc.utah.edu; Wallace, Dennis; Wally Carlo, M.D.; Rich, Wade; Vaucher, Yvonne
Cc: sharon.gough@hsc.utah.edu; Archer, Stephanie (NIH/NICHD) [E]; Brenda Vecchio; Cunningham, Meg; Martinez, Fernando; Hulema, Carolyn Petne; Zaterka-Baxter, Kristin
Subject: RE: SUPPORT Subcommittee Call--10/11, Tu, 12:00 PM ET

Reminder for today's call

From: Gabno, Jenna
Sent: Thursday, September 22, 2011 4:29 PM
To: Abbot Laptook (alaptook@WIHRI.org); Bradley Yoder; Das, Abhik (adas3@rti.org); Galvez, Marie (mgalvez@rti.org); Higgins, Rosemary (NIH/NICHD) [E]; kurt.schibler@cchmc.org; mcw3@cwru.edu; MPerelta@PEDS.UAB.EDU; nancy newman; 'nfiner@ucsd.edu'; Roger Fair@hsc.utah.edu; Wallace, Dennis; Wally Carlo, M.D.; vvnch@ucsd.edu; 'Yvonne Vaucher'
Cc: (sharon.gough@hsc.utah.edu); 'Archer, Stephanie (NIH/NICHD) [E]'; Brenda Vecchio; Cunningham, Meg; mamnez@ucsd.edu; Gabno, Jenna; Hulema, Carolyn Petne; Zaterka-Baxter, Kristin
Subject: SUPPORT Subcommittee Call--10/11, Tu, 12:00 PM ET

Dear all,

The SUPPORT subcommittee call has been scheduled for

Tuesday, 10/11
12:00pm ET

Dial
Within the USA
(b)(6)
or
Outside the USA
(b)(6)
Then, enter Participant Passcode
(b)(6)

Thanks,
Jenna

Jenna Gabno
RTI International
Public Health Analyst

701 13th St. NW, Suite 750
Washington, DC 20005
Phone: 202 728-1946
Fax: 202-974 7851

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Kennedy, Kathleen A"; Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: ROP Natural History Abstract
Date: Tuesday, October 11, 2011 10:18:00 AM

Not sure that it was really brilliant, but as long as it works!!
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Kennedy, Kathleen A [mailto:Kathleen.A.Kennedy@uth.tmc.edu]
Sent: Tuesday, October 11, 2011 9:54 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: ROP Natural History Abstract

Brilliant! I haven't made the other suggested changes but I think this will work well enough for the author problem. It's listing the SUPPORT Subcommittee as your institution but it gets the right message across.

Kathleen A. Kennedy, MD, MPH
Richard W. Mithoff Professor of Pediatrics
Director, MS in Clinical Research Degree Program
UT-Houston Medical School
6431 Fannin, Suite 2.106
Houston, TX 77030
713 500-6708

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, October 11, 2011 8:40 AM
To: Kennedy, Kathleen A; Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: ROP Natural History Abstract

If you include me, can you give my affiliation as the NICHD NRN??

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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CDBPM, NIH
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higginsr@mail.nih.gov

From: Kennedy, Kathleen A [mailto:Kathleen.A.Kennedy@uth.tmc.edu]
Sent: Tuesday, October 11, 2011 9:38 AM
To: Archer, Stephanie (NIH/NICHD) [E]
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: ROP Natural History Abstract

One more clarification. Space isn't a problem with 4-5 authors. It probably would be a problem with 12-13 authors and removing 1 wouldn't make that much difference. It still seems like it would be desirable to cite the NICHD Network but that's what's causing the problem. Apparently no one else has gotten this far in the electronic process.

Kathleen A. Kennedy, MD, MPH
Richard W. Mithoff Professor of Pediatrics
Director, MS in Clinical Research Degree Program
UT-Houston Medical School
6431 Fannin, Suite 2.106
Houston, TX 77030
713 500-6708

From: Archer, Stephanie (NIH/NICHD) [E] [mailto:archerst@mail.nih.gov]
Sent: Tuesday, October 11, 2011 8:11 AM
To: Kennedy, Kathleen A
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: ROP Natural History Abstract

Hi Kathleen,

For the abstract authors, I think your list is fine the way it is (with "and the SUPPORT Subcommittee"). I would not list the NRN as an author - just Rose. That may get around the submission issues you mentioned?

If you decide to list everyone on the subcommittee, it should include (the order is up to you):

Kathleen A Kennedy, MD, MPH[1], Lisa A Wrage, MPH[2], Dale Phelps, MD[3], Rosemary Higgins, MD[4] Waldemar A. Carlo, MD[5]; Neil N. Finer, MD[6]; Michele C. Walsh, MD MS[7]; Wade Rich, RRT[6]; Marie G. Gantz, PhD[2]; Abbot R. Laptook, MD[8]; Bradley A. Yoder, MD[9]; Roger G. Faix, MD[9]; Abhik Das, PhD[10]; W. Kenneth Poole, PhD[2]; Kurt Schibler, MD[11]; Nancy S. Newman, RN[7]; for the NICHD Neonatal Research Network

[1]Pediatrics, UT Houston Medical, Houston, TX, United States;
[2]RTI International, Research Triangle Park, NC, United States;
[3]University of Rochester School of Medicine and Dentistry, Rochester, NY, United States;
[4]NICHD, Rockville, MD, United States;
[5]University of Alabama at Birmingham, Birmingham, AL, United States;

[6]University of California at San Diego, San Diego, CA, United States;
[7]Rainbow Babies & Children's Hospital, Case Western Reserve University, Cleveland, OH, United States;
[8]Women & Infants' Hospital, Brown University, Providence, RI, United States;
[9]University of Utah School of Medicine, Salt Lake City, UT, United States;
[10]RTI International, Rockville, MD, United States;
[11]Cincinnati Children's Hospital Medical Center and University of Cincinnati College of Medicine, Cincinnati, OH, United States;

Stephanie

Stephanie Wilson Archer
The Eunice Kennedy Shriver
National Institute of Child Health and Human Development
Pregnancy & Perinatology Branch
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archerst@mail.nih.gov

From: Kennedy, Kathleen A [mailto:Kathleen.A.Kennedy@uth.tmc.edu]
Sent: Saturday, October 08, 2011 12:56 PM
To: wcarlo@peds.uab.edu; Das, Abhik; Roger.Faix@hsc.utah.edu; nfiner@ucsd.edu; Gantz, Marie; alaptook@WIHRI.org; nxs5@cwru.edu; wrich@ucsd.edu; kurt.schibler@cchmc.org; Michele.Walsh@UHhospitals.org; Bradley.Yoder@hsc.utah.edu
Cc: Wrage, Lisa Ann (wrage@rti.org); dale_phelps@urmc.rochester.edu; Archer, Stephanie (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Subject: ROP Natural History Abstract

SUPPORT Subcommittee: I've attached a draft of the PAS abstract for the ROP Natural History Secondary Study that uses data from the SUPPORT trial. Comments and suggestions are welcome. I hope to get the missing data before the deadline. If anyone knows how to navigate the submission process (how to include the NICHD without entering the NICHD as an author and then being required to submit a bunch of CME/COI disclosures for the NICHD), I'd appreciate the help.

Stephanie, could you please check to make sure I haven't missed anyone on the SUPPORT Subcommittee?

Lisa, if we could get the data for treatment after back transfer and after discharge, that would be great. If you can tabulate the 0 and 100%iles and they look reasonable (no extreme outliers), we could replace the 1 and 99%iles in the table with 0 and 100%iles.

Kathleen A. Kennedy, MD, MPH
Richard W. Mithoff Professor of Pediatrics
Director, MS in Clinical Research Degree Program
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Houston, TX 77030
713 500-6708

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Duara, Shahnaz"; "Navarrete, Cristina"
Cc: "Roger Faix"
Subject: FW: Abstract_Growth_Outcomes_SUPPORT1
Date: Tuesday, October 11, 2011 9:36:00 AM

Suggestions from Roger--

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Roger Faix [mailto:Roger.Faix@hsc.utah.edu]
Sent: Monday, October 10, 2011 9:12 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Abstract_Growth_Outcomes_SUPPORT1

Hi Rose!

Could you please forward my comments below to Shahnaz and Cristina, since I do not have their e-mail addresses? Many thanks!

Roger

An important issue that needs to be addressed. Nice work so far!

1) Poor growth is defined only as weight <10%ile. Were other measures analyzed (length, head circumference) for <10%ile?
2) It would be useful to provide outcomes separately for death and poor growth, as well as the included outcome of death or poor growth.
3) Any chance of presenting the actual summary anthropometric measures at birth, 36 weeks post-menstrual and 18--22 months corrected age?
4) Any data re: the CPAP vs surf groups?
5) Any data or differences between the 2 saturation groups re: caloric intake, maternal smoking, maternal breast milk vs formula, NEC?

I hope these comments are useful.

Roger

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]
Sent: Wednesday, October 05, 2011 12:13 PM
To: nfiner@ucsd.edu; WCarlo@peds.uab.edu; 'Navarrete, Cristina'; Duara, Shahnaz; 'Rich, Wade'; 'Richard, MD Ehrenkranz (richard.ehrenkranz@yale.edu)'; Brenda Poindexter [bpoindex@iupui.edu]; 'kurt.schibler@cchmc.org'; mcw3@cwru.edu; Roger Faix; Bradley Yoder; Das, Abhik; 'Gantz, Marie'; 'Nancy Newman'; Wrage, Lisa Ann
Subject: Abstract_Growth_Outcomes_SUPPORT1

HI,

Here is the SUPPORT GROWTH OUTCOMES draft abstract. Please send comments back to Shahnaz and Tina.

Thanks

Rose

From: Roger Faix
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: ROP Natural History Abstract
Date: Monday, October 10, 2011 8:56:37 PM

FYI

From: Roger Faix
Sent: Monday, October 10, 2011 6:27 PM
To: Kennedy, Kathleen A
Subject: RE: ROP Natural History Abstract

Hi Kathleen!

As stated by others, strong work re: addressing an important question.

A few suggestions/comments for your consideration:

984 infants apparently had no missing or delayed exams before ROP diagnosis (per line 2 of results), but only 642 are included in the Table (per line 5 of results). Does the difference represent death, transfer or some other factors?

In the Table, it is unclear to me if the bottom row indicates postmenstrual age at which infants who eventually had severe ROP were diagnosed with any ROP, or is it the age at which the severe ROP was diagnosed? It may be helpful to make this more clear.

I hope this is helpful.

Roger

From: Kennedy, Kathleen A [Kathleen.A.Kennedy@uth.tmc.edu]
Sent: Saturday, October 08, 2011 10:55 AM
To: wcarlo@peds.uab.edu; Das, Abhik; Roger Faix; nfiner@ucsd.edu; Gantz, Marie; alaptook@WIHRI.org; nxs5@cwru.edu; wrich@ucsd.edu; kurt.schibler@cchmc.org; Michele.Walsh@UHhospitals.org; Bradley Yoder
Cc: Wrage, Lisa Ann (wrage@rti.org); dale_phelps@urmc.rochester.edu; Archer, Stephanie (NIH/NICHD) [E] (archerst@mail.nih.gov); Higgins, Rosemary (NIH/NICHD)
Subject: ROP Natural History Abstract

SUPPORT Subcommittee: I've attached a draft of the PAS abstract for the ROP Natural History Secondary Study that uses data from the SUPPORT trial. Comments and suggestions are welcome. I hope to get the missing data before the deadline. If anyone knows how to navigate the submission process (how to include the NICHD without entering the NICHD as an author and then being required to submit a bunch of CME/COI disclosures for the NICHD), I'd appreciate the help.

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Kathleen A. Kennedy, MD, MPH
Richard W. Mithoff Professor of Pediatrics
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713 500-6708

From: Roger Faix
To: nfiner@ucsd.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW:
Date: Monday, October 10, 2011 8:55:57 PM

Hi Neil!

I 'm sorry that my comments may be a bit late, but hope that they are still useful to you.

I agree with comments by several others that the abstract as written takes very careful reading. Nonetheless, the issue is important and should be reported (given that it was a pre-specified secondary outcome).

In results, line 2 does ROP include any ROP or only severe ROP (meeting criteria for intervention)?

As I am certain you are aware and have probably already addressed, there are a number of spelling and grammatical issues.

Although apparently not statistically different, it is interesting that in the 26-27 wk GA group death/ROP was lower in the surf group than the CPAP group.

'While unlikely' adds little except confusion to the final sentence in Conclusions, in my opinion.

Roger

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]
Sent: Friday, September 30, 2011 8:21 AM
To: Wally Carlo; 'Finer, Neil'; kurt.schibler@cchmc.org; 'mcw3@cwru.edu'; Roger Faix; Bradley Yoder; Laptook, Abbot; 'Das, Abhik'; Gantz, Marie; 'Nancy Newman'; Rich, Wade; 'Vaucher, Yvonne'; Myriam Peralta, M.D.
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW:

HI,

Here is a secondary SUPPORT analysis. Please send Neil comments by the end of next week. We have a SUPPORT call set up on 10/11 at noon and will discuss.

Thanks

Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
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higginsr@mail.nih.gov

From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Friday, September 30, 2011 9:58 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Wally Carlo
Subject:

HI Rose

Can you circulate this to the SUPPORT Subcommittee for their review and then can we have a call to

discuss
Ita about 95% full
Thanks
Neil

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Draft Preview of Abstract #750127
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First Author: Neil N Finer, MD **Filename:** 750127
Responsible Author: Neil N Finer, MD
Presenting Author: Neil N Finer, MD
Contact Person: Neil N Finer, MD

2012 PAS Annual Meeting

Subspecialty: Neonatology - General
Theme: Neonatal - Patient-Oriented Research

Contact Author: Neil N Finer, MD
Department/Institution/Address: Neonatology, Dept Pediatrics, UCSD, 200 W Arbor Dr, San Diego, Ca, 92103, United States
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Reponsible Author: Neil N Finer, MD
Department/Institution/Address: 200 W Arbor Dr, San Diego, United States
Phone: 1 619 543 3285 begin_of_the_skype_highlighting 1 619 543 3285 end_of_the_skype_highlighting **Fax:** 1 619 543 3812
Responsible Author E-mail: nfiner@ucsd.edu
Responsible Author Declaration: As the responsible author, I confirm that the individual listed as the sponsor has been contacted and given the opportunity to review the abstract and has subsequently agreed to sponsor this abstract.

Presenting Author: Neil N Finer, MD
Department/Institution/Address: Neonatology Pediatrics, UCSD, 200 W Arbor Dr, San Diego, United States
Phone: 1 619 543 3285 begin_of_the_skype_highlighting 1 619 543 3285 end_of_the_skype_highlighting **Fax:** 1 619 543 3812
Presenting Author E-mail: nfiner@ucsd.edu
The presenting author is member of these Alliance Societies:
Is Presenting Author a Trainee? No, Not a Trainee
Presenter Copyright Declaration:
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QUESTIONNAIRE INFORMATION
Eastern Society for Pediatric Research: No, Do not consider this abstract for the Eastern SPR
Pediatric Hospital Medicine: No, Do not consider this abstract for presentation at the Pediatric Hospital Medicine, July 19-21, 2012
Research Type: Clinical
Presentation Sabbath Conflict on: N/A
APA Special Interest Groups, Committees or Regions: None

AWARDS APPLIED FOR:
No awards selected

SPONSOR INFORMATION
Sponsoring Member for PAS/ASPR abstract:
Sponsor Name: Neil Norman Finer
Email: nfiner@ucsd.edu
Is the Sponsor an Author? Yes
Sponsoring Societies:
Society for Pediatric Research

Title: Early CPAP Versus Surfactant: The Effect Of A Lower SpO2 Range: Secondary Outcomes Of The SUPPORT Trial.

Neil N Finer, MD UCSD, Waldemar Carlo, MD University of A and Support Group NICHD 1 Neonatology, Pediatrics, University California San Diego, San Diego, Ca, 92103, United States.

Background: The SUPPORT Trial prospectively compared early CPAP and a limited ventilator strategy to early surfactant and also

randomized all infants to a lower (85-89%) versus a higher (91-95%) SpO2 range from 2 hours of birth (NEJM 2010) The results demonstrated a significant reduction in death for infants who were randomized to CPAP in the extremely premature strata (EPS) (24 to 25 wk, 23.9% vs 32.1%, p=0.028).Infants randomized to the lower SpO2 range had less ROP (8.6% vs 17.9%, p=0.001 and increased death (19.9% vs 16.2%, p=0.04).A prespecified secondary outcome for the SUPPORT Trial was that infants randomized to CPAP and a low SpO2 strategy would have a lower rate of death/ROP. There was no overall interaction between the respiratory arms and the SpO2 ranges. We did not initially evaluate the gestational age strata for such an interaction

Objective: This study evaluated the effect of the SpO2 range on the outcomes for infants in the 2 gestational age strata, 24-25 wks, and 26-27 weeks

Design/Methods: The surviving infants were assessed at 18 to 22 months for full neurodevelopmental evaluation, which included hearing, vision, and mental and motor outcomes using the Bayley 3. Tests for interaction were adjusted for GA center and family clustering.

Results: There were 1316 infants randomized in the SUPPORT Trial and deaths prior to discharge, (16.4% vs 19.6%), and follow-up (18.4% vs 21.9%) and the overall ROP rates among survivors (13.1% vs 13.7%) were not different between CPAP and Surf infants. ROP was less frequent in the EPS, (22.2% vs 31.6%, p=0.04)whereas ROP was greater in CPAP infants in the 26-27 wk strata (7.3% vs 3.6% p=0.04). Death at follow-up for the EPS infants remained significantly lower for the CPAP infants (26.4% vs 35.5%, p=0.019). For the overall study and for the 26-27 wk strata there were no significant intercations between SpO2 group and the intervention groups for death/ROP or death/NDI. There was a significant interaction between SpO2 low vs high and CPAP vs Surf in the EPS, the p value for the interaction between CPAP/surfactant and SpO2 was .05. ROP was significantly lower for those randomized to CPAP vs. surf in the Low SpO2 target group (p=.01) but not those in the High SpO2 group (p=.71). For the outcome of death or ROP, while no interaction was seen in the overall study, the EPS infants in the Low SpO2 strata had a lower rate of ROP/death (p=.001), such differences were not seen in the High SpO2 group (p=.2)

Death/ROP for 24-25 wk Strata and 26-27 wk Strata - Low vs High SpO2

SpO2 Range	CPAP/Surf	Death - (24-25)	ROP - (24-25)	Death/ROP - (24-25)	Death - (26-27)	ROP - (26-27)	Death/ROP (26-27)
Low	CPAP	37/142 (26%)	11/95 (12%)	48/132 (36%)*	25/194(13%)	8/153(5%)	33/178(19%)
	Surf	48/134 (36%)	21/76 (28%)	69/124 (56%)*	20/184(11%)	1/151(1%)	21/171(12%)
High	CPAP	31/143 (22%)	33/103 (32%)	64/134 (48%)	15/185(9%)	15/160(9%)	31/176(18%)
	Surf	42/146 (29%)	33/95 (35%)	75/137 (55%)	18/189(10%)	10/141(7%)	28/169(17%)

* p = 0.001

There was no differences in death/NDI comparing SPO2 strategy overall or for either strata.

Conclusions: The lowest death rate was seen in the CPAP infants treated with a high SpO2 approach, supporting the use of a higher SpO2 approach. However death and ROP were significantly lower in the low SpO2 arm in the EPS. In addition the other large randomized trials comparing SpO2 ranges did not randomize infants to a respiratory support strategy and their preliminary results support a higher mortality in the Low SpO2 range infamnts. For extremely immature infants a strategy of early CPAP with a limited ventilator approach combined with a lower SpO2 target may be optimal. While unlikely, further trials should evaluate this approach

Other Previews:
Abstract Disclosure Info:

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From: Walsh, Michele
To: jmd3@case.edu; Gantz, Marie
Cc: Finer, Neil; Schmidt, Barbara (Neonatology); Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; Richard Martin
Subject: RE: SUPPORT trial publication
Date: Monday, October 10, 2011 4:53:19 PM

Will need to look into this further when the PAS rush subsides.
Our quick look at the subcohort suggests that groups are equal in the time on
Oximeters but each group is obviously biased to the sickest in the cohort staying on longer.

Michele Walsh, MD
Chief, Division of Neonatology
216.844.3759

It's not what you look at that matters, it's what you see. Thoreau

---

From: Juliann Di Fiore [mailto:jmd3@case.edu]
Sent: Monday, October 10, 2011 2:29 PM
To: Gantz, Marie
Cc: Finer, Neil; Schmidt, Barbara (Neonatology); Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; Walsh, Michele; Richard Martin
Subject: Re: SUPPORT trial publication

As can be seen from the emails below this is complicated as infants can be on the monitor due to respiratory support with or without O2. Therefore, making conclusions on illness severity between groups based on these variables is not a simple task.

Julie

On 10/10/2011 1:29 PM, Gantz, Marie wrote:
We had found in prior analyses that infants assigned to the Low SpO2 group spent less time on the oximeters. I had actually mentioned that to Julie previously, in addition to the fact that infants in the High SpO2 group might have more time in room air represented in the pulse oximetry data based on what I had seen in other analyses (so I suggested looking only at time spent on supplemental O2).

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Thursday, October 06, 2011 5:03 AM
To: Schmidt, Barbara (Neonatology); Wally Carlo, M.D.; jmd3@case.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie
Subject: RE: SUPPORT trial publication

Hi Barb and Julie
I think Barbara raises a valid concern.
We need to ask Julie about this
Julie – can you analyze the data to determine if the infants in the low sat group where on the study oximeter longer than the hi group (should be so) and whether the late desats where seen more in Low sat infants who were on the study oximeter for a longer time or till a later PCA than the hi St group??
Thanks
Neil

From: Schmidt, Barbara (Neonatology) [mailto:barbara.schmidt@uphs.upenn.edu]
Sent: Tuesday, October 04, 2011 3:12 PM
To: Wally Carlo, M.D.; Finer, Neil
Cc: Higgins, Rosemary (NIH/NICHD) [E]; mgantz@rti.org
Subject: RE: SUPPORT trial publication

Dear Wally,
I would not consider "time on study oximeter" as an outcome.

Actually, I have been thinking about this question after looking at the paper we were all sent yesterday, led by the Cleveland group. The conclusion is that the babies in the low saturation target range had more frequent desaturations, especially late in their neonatal course.

If my hypothesis is correct, namely that babies in the low target range came off the study oximeter sooner than the babies in the high target range, the results may at least in part be due to selection bias? Only the worst babies in the low target range would stay long enough on the study oximeter to be included in the analysis?

Barbara

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Tuesday, October 04, 2011 5:58 PM
To: Schmidt, Barbara (Neonatology); nfiner@ucsd.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]; mgantz@rti.org
Subject: RE: SUPPORT trial publication

Barbara:

You are correct but the data you have asked were not pre-specified outcome measures and we generally cannot add such requests to the data center. We expected O2 supplementation and monitoring durations would be different.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
1700 6th Avenue South

176F Suite 9380R
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 (b)(6)

From: Schmidt, Barbara (Neonatology) [mailto:barbara.schmidt@uphs.upenn.edu]
Sent: Tuesday, October 04, 2011 3:46 PM
To: Wally Carlo, M.D.; nfiner@ucsd.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]; mgantz@rti.org
Subject: RE: SUPPORT trial publication

Dear Rose and Wally,
Thanks for your responses.

Wally, I did read the methods section from which you quote below and I understand the SUPPORT rules for stopping the study oximetry.

What I would like to know is this: Was there a difference in the duration of time the two groups spent on the study oximeters?

I would suspect that – on average – kids in the low saturation target group should have spent less time on the study oximeters because they had a lower threshold for getting into air. Is this correct?
Barbara

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Tuesday, October 04, 2011 1:08 PM
To: Schmidt, Barbara (Neonatology); nfiner@ucsd.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT trial publication

Hi Barbara:

Here is a quote from the Methods in the paper.

"Altered pulse oximetry was initiated within the first 2 hours after birth and was continued until 36 weeks of postmenstrual age or until the infant was breathing ambient air and did not require ventilator support or CPAP for more than 72 hours, whichever occurred first. Infants who were weaned to room air but who subsequently received oxygen supplementation before 36 weeks of postmenstrual age were placed back on the assigned study pulse oximeter. The target ranges were kept unchanged from birth until 36 weeks of postmenstrual age."

We did not report duration of O2 supplementation.
Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology

Director, Newborn Nurseries
1700 6th Avenue South
176F Suite 9380R
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
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From: Schmidt, Barbara (Neonatology) [mailto:barbara.schmidt@uphs.upenn.edu]
Sent: Tuesday, October 04, 2011 9:49 AM
To: Wally Carlo, M.D.; nfiner@ucsd.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: SUPPORT trial publication

Dear Wally and Neil,

In your protocol, study oximetry stopped when the babies were breathing room air. Have you reported the average duration of the study oximetry in each of the two saturation target groups? I cannot find this information in the NEJM paper?

Barbara

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--
Juliann Di Fiore
Research Engineer
Case Western Reserve University
Rainbow Babies & Children's Hospital

Division of Neonatology, room 3100
11100 Euclid Ave
Cleveland, OH 44106
(216) 844-1478

From: Finer, Neil
To: Phelps, Dale; Kennedy, Kathleen A
Cc: wcarlo@peds.uab.edu; Das, Abhik; Roger.Faix@hsc.utah.edu; Gantz, Marie; alaptook@WIHRI.org; nxs5@cwru.edu; Rich, Wade; kurt.schibler@cchmc.org; Michele.Walsh@UHhospitals.org; Bradley.Yoder@hsc.utah.edu; Wrage, Lisa Ann (wrage@rti.org); Archer, Stephanie (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: ROP Natural History Abstract
Date: Monday, October 10, 2011 4:50:39 PM

HI Dale and Kathleen
I was looking for the dates and PCA at surgery
I think you are saying they are the same as the data for the time of severe ROP
If that is true then it would be redundant
Thanks
Neil

-----Original Message-----
From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Monday, October 10, 2011 1:38 PM
To: Finer, Neil; Kennedy, Kathleen A
Cc: wcarlo@peds.uab.edu; Das, Abhik; Roger.Faix@hsc.utah.edu; Gantz, Marie; alaptook@WIHRI.org; nxs5@cwru.edu; Rich, Wade; kurt.schibler@cchmc.org; Michele.Walsh@UHhospitals.org; Bradley.Yoder@hsc.utah.edu; Wrage, Lisa Ann (wrage@rti.org); Archer, Stephanie (NIH/NICHD) [E] (archerst@mail.nih.gov); Higgins, Rosemary (NIH/NICHD)
Subject: RE: ROP Natural History Abstract

Hi Neil,
Since standard of care is surgery within 48 hours of diagnosis of severe ROP, why would date of actual surgery be of interest? Just curious.
Recall severe ROP is defined here as meeting criteria for surgery, or receiving surgical intervention (first surgery if there are multiple ones).

Dale

-----Original Message-----
From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Monday, October 10, 2011 1:21 PM
To: Kennedy, Kathleen A
Cc: wcarlo@peds.uab.edu; Das, Abhik; Roger.Faix@hsc.utah.edu; Gantz, Marie; alaptook@WIHRI.org; nxs5@cwru.edu; Rich, Wade; kurt.schibler@cchmc.org; Michele.Walsh@UHhospitals.org; Bradley.Yoder@hsc.utah.edu; Wrage, Lisa Ann (wrage@rti.org); Phelps, Dale; Archer, Stephanie (NIH/NICHD) [E] (archerst@mail.nih.gov); Higgins, Rosemary (NIH/NICHD)
Subject: Re: ROP Natural History Abstract

Very nice work Kathleen
Can you add an additional row to your table to show the cumulative percent at the gestational ages for surgery?.
Thanks
Neil

On Oct 8, 2011, at 12:55 PM, "Kennedy, Kathleen A"
<Kathleen.A.Kennedy@uth.tmc.edu<mailto:Kathleen.A.Kennedy@uth.tmc.edu>> wrote:

SUPPORT Subcommittee: I've attached a draft of the PAS abstract for the ROP Natural History Secondary Study that uses data from the SUPPORT trial. Comments and suggestions are welcome. I hope to get the missing data before the deadline. If anyone knows how to navigate the submission process (how to include the NICHD without entering the NICHD as an author and then being required to submit a bunch of CME/COI disclosures for the

NICHD), I'd appreciate the help.

Stephanie, could you please check to make sure I haven't missed anyone on the SUPPORT Subcommittee?

Lisa, if we could get the data for treatment after back transfer and after discharge, that would be great. If you can tabulate the 0 and 100%iles and they look reasonable (no extreme outliers), we could replace the 1 and 99%iles in the table with 0 and 100%iles.

Kathleen A. Kennedy, MD, MPH
Richard W. Mithoff Professor of Pediatrics
Director, MS in Clinical Research Degree Program
UT-Houston Medical School
6431 Fannin, Suite 2.106
Houston, TX 77030
713 500-6708

<PAS Abstract (SUPPORT Secondary - ROP Natural History).pdf>

From: Finer, Neil
To: jmd3@case.edu; Gantz, Marie
Cc: Schmidt, Barbara (Neonatology); Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; Michele Walsh; Richard Martin
Subject: RE: SUPPORT trial publication
Date: Monday, October 10, 2011 4:48:09 PM

Julie
Can we answer whether the late desats where seen more in Low sat infants who were on the study oximeter for a longer time or till a later PCA than the hi St group?
Neil

From: Juliann Di Fiore [mailto:jmd3@case.edu]
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Cc: Finer, Neil; Schmidt, Barbara (Neonatology); Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; Michele Walsh; Richard Martin
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Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

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We did not report duration of O2 supplementation.
Wally

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Edwin M. Dixon Professor of Pediatrics
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Phone: 205 934 4680
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Cell: 205 (b)(6)

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Sent: Tuesday, October 04, 2011 9:49 AM
To: Wally Carlo, M.D.; nfiner@ucsd.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]
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In your protocol, study oximetry stopped when the babies were breathing room air. Have you reported the average duration of the study oximetry in each of the two saturation target groups? I cannot find this information in the NEJM paper?

Barbara

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--
Juliann Di Fiore
Research Engineer
Case Western Reserve University
Rainbow Babies & Children's Hospital
Division of Neonatology, room 3100
11100 Euclid Ave
Cleveland, OH 44106
(216) 844-1478

Federal and Ohio law protect patient medical information, including psychiatric disorders, (H.I.V) test results, A.I.Ds-related conditions, alcohol, and/or drug dependence or abuse disclosed in this email. Federal regulation (42 CFR Part 2) and Ohio Revised Code section 5122.31 and 3701.243 prohibit disclosure of this information without the specific written consent of the person to whom it pertains, or as otherwise permitted by law.

From: Kennedy, Kathleen A
To: Finer, Neil
Cc: wcarlo@peds.uab.edu; Das, Abhik; Roger.Faix@hsc.utah.edu; Gantz, Marie; alaptook@WIHRI.org; nxs5@cwru.edu; Rich, Wade; kurt.schibler@cchmc.org; Michele.Walsh@UHhospitals.org; Bradley.Yoder@hsc.utah.edu; Wrage, Lisa Ann (wrage@rti.org); dale_phelps@urmc.rochester.edu; Archer, Stephanie (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: ROP Natural History Abstract
Date: Monday, October 10, 2011 4:45:23 PM

Similar comments to what Dale just sent:

I'm not sure what you mean. To meet the criteria for severe ROP, they either had a procedure (laser or bevacizumab) or met Type 1 criteria. If they met Type 1 criteria, they should have had a procedure within a few days. Unless there was a problem with availability of the surgeon, the two rows should look pretty much the same. Is that what you want to see (delay between diagnosis of Type 1 and treatment)? I also think, based on previous emails from Lisa, that we don't have date of treatment clearly coded that way.

Kathleen A. Kennedy, MD, MPH
Richard W. Mithoff Professor of Pediatrics
Director, MS in Clinical Research Degree Program
UT-Houston Medical School
6431 Fannin, Suite 2.106
Houston, TX 77030
713 500-6708

-----Original Message-----
From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Monday, October 10, 2011 3:21 PM
To: Kennedy, Kathleen A
Cc: wcarlo@peds.uab.edu; Das, Abhik; Roger.Faix@hsc.utah.edu; Gantz, Marie; alaptook@WIHRI.org; nxs5@cwru.edu; Rich, Wade; kurt.schibler@cchmc.org; Michele.Walsh@UHhospitals.org; Bradley.Yoder@hsc.utah.edu; Wrage, Lisa Ann (wrage@rti.org); dale_phelps@urmc.rochester.edu; Archer, Stephanie (NIH/NICHD) [E] (archerst@mail.nih.gov); Higgins, Rosemary (NIH/NICHD)
Subject: Re: ROP Natural History Abstract

Very nice work Kathleen
Can you add an additional row to your table to show the cumulative percent at the gestational ages for surgery?.
Thanks
Neil

On Oct 8, 2011, at 12:55 PM, "Kennedy, Kathleen A" <Kathleen.A.Kennedy@uth.tmc.edu<mailto:Kathleen.A.Kennedy@uth.tmc.edu>> wrote:

SUPPORT Subcommittee: I've attached a draft of the PAS abstract for the ROP Natural History Secondary Study that uses data from the SUPPORT trial. Comments and suggestions are welcome. I hope to get the missing data before the deadline. If anyone knows how to navigate the submission process (how to include the NICHD without entering the NICHD as an author and then being required to submit a bunch of CME/COI disclosures for the NICHD), I'd appreciate the help.

Stephanie, could you please check to make sure I haven't missed anyone on the SUPPORT Subcommittee?

Lisa, if we could get the data for treatment after back transfer and after discharge, that would be great. If you can tabulate the 0 and 100%iles and they look reasonable (no extreme outliers), we could replace the 1 and 99%iles in the table with 0 and 100%iles.

Kathleen A. Kennedy, MD, MPH

Richard W. Mithoff Professor of Pediatrics Director, MS in Clinical Research Degree Program UT-Houston Medical School
6431 Fannin, Suite 2.106
Houston, TX 77030
713 500-6708

<PAS Abstract (SUPPORT Secondary - ROP Natural History).pdf>

From: Phelps, Dale
To: Gantz, Marie; Kennedy, Kathleen A; wcarlo@peds.uab.edu; Das, Abhik; Roger.Faix@hsc.utah.edu; nfiner@ucsd.edu; alaptook@WIHRI.org; nxs5@cwru.edu; wrich@ucsd.edu; kurt.schibler@cchmc.org; Michele.Walsh@UHhospitals.org; Bradley.Yoder@hsc.utah.edu
Cc: Wrage, Lisa Ann; Archer, Stephanie (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: ROP Natural History Abstract
Date: Monday, October 10, 2011 2:27:14 PM

Marie and Lisa,

Can you please give us for the PMA of when primary surgery for ROP was done? (not repeat surgery or later retinal detachment surgery or scleral buckle surgery: only laser or cryo or Avastin).

Mean

Range

I guess we already have the percentiles from 1-99.

Dale

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Monday, October 10, 2011 11:16 AM
To: Phelps, Dale; Kennedy, Kathleen A; wcarlo@peds.uab.edu; Das, Abhik; Roger.Faix@hsc.utah.edu; nfiner@ucsd.edu; alaptook@WIHRI.org; nxs5@cwru.edu; wrich@ucsd.edu; kurt.schibler@cchmc.org; Michele.Walsh@UHhospitals.org; Bradley.Yoder@hsc.utah.edu
Cc: Wrage, Lisa Ann; archerst@mail.nih.gov; Higgins, Rosemary (NIH/NICHD)
Subject: RE: ROP Natural History Abstract

I think the abstract is looking good. I have a couple of comments.

1) The methods state that exams were done until 55 weeks PMA, but they were not actually stopped at that point – we have ROP exam data from beyond 55 weeks.
2) In my previous analysis of the ROP data, there were infants who reached criteria for severe ROP after 45 weeks PMA. The table presents 45 weeks as the 99th percentile, but I believe the statement in the conclusion that no infants met criteria for severe ROP after 45 weeks is incorrect.

Marie

Marie Gantz, Ph.D.
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RTI International
mgantz@rti.org
828-954-6255

From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Sunday, October 09, 2011 5:56 PM
To: 'Kennedy, Kathleen A'; wcarlo@peds.uab.edu; Das, Abhik; Roger.Faix@hsc.utah.edu; nfiner@ucsd.edu; Gantz, Marie; alaptook@WIHRI.org; nxs5@cwru.edu; wrich@ucsd.edu; kurt.schibler@cchmc.org; Michele.Walsh@UHhospitals.org; Bradley.Yoder@hsc.utah.edu
Cc: Wrage, Lisa Ann; Archer, Stephanie (NIH/NICHD) [E] (archerst@mail.nih.gov); Higgins, Rosemary (NIH/NICHD)
Subject: RE: ROP Natural History Abstract

Thank you for your hard work on this Kathleen,
I have been through the abstract again, and discovered some things we had missed.. probably because

we're too familiar with the material already. Just some clarifications, no real substantive changes. I have edited the abstract in the attached word file. (They are not track changes because my old laptop seems to confuse others when I use them.

Thanks again!
Dale

From: Kennedy, Kathleen A [mailto:Kathleen.A.Kennedy@uth.tmc.edu]
Sent: Saturday, October 08, 2011 9:56 AM
To: wcarlo@peds.uab.edu; Das, Abhik; Roger.Faix@hsc.utah.edu; nfiner@ucsd.edu; Gantz, Marie; alaptook@WIHRI.org; nxs5@cwru.edu; wrich@ucsd.edu; kurt.schibler@cchmc.org; Michele.Walsh@UHhospitals.org; Bradley.Yoder@hsc.utah.edu
Cc: Wrage, Lisa Ann (wrage@rti.org); Phelps, Dale; Archer, Stephanie (NIH/NICHD) [E] (archerst@mail.nih.gov); Higgins, Rosemary (NIH/NICHD)
Subject: ROP Natural History Abstract

SUPPORT Subcommittee: I've attached a draft of the PAS abstract for the ROP Natural History Secondary Study that uses data from the SUPPORT trial. Comments and suggestions are welcome. I hope to get the missing data before the deadline. If anyone knows how to navigate the submission process (how to include the NICHD without entering the NICHD as an author and then being required to submit a bunch of CME/COI disclosures for the NICHD), I'd appreciate the help.

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Lisa, if we could get the data for treatment after back transfer and after discharge, that would be great. If you can tabulate the 0 and 100%iles and they look reasonable (no extreme outliers), we could replace the 1 and 99%iles in the table with 0 and 100%iles.

Kathleen A. Kennedy, MD, MPH
Richard W. Mithoff Professor of Pediatrics
Director, MS in Clinical Research Degree Program
UT-Houston Medical School
6431 Fannin, Suite 2.106
Houston, TX 77030
713 500-6708

From: Kennedy, Kathleen A
To: wcarlo@peds.uab.edu; Das, Abhik; Roger.Faix@hsc.utah.edu; nfiner@ucsd.edu; Gantz, Marie; alaptook@WIHRI.org; nxs5@cwru.edu; wrich@ucsd.edu; kurt.schibler@cchmc.org; Michele.Walsh@UHhospitals.org; Bradley.Yoder@hsc.utah.edu
Cc: Wrage, Lisa Ann (wrage@rti.org); dale_phelps@urmc.rochester.edu; Archer, Stephanie (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]
Subject: ROP Natural History Abstract
Date: Saturday, October 08, 2011 12:55:48 PM
Attachments: PAS Abstract (SUPPORT Secondary - ROP Natural History).pdf

SUPPORT Subcommittee: I've attached a draft of the PAS abstract for the ROP Natural History Secondary Study that uses data from the SUPPORT trial. Comments and suggestions are welcome. I hope to get the missing data before the deadline. If anyone knows how to navigate the submission process (how to include the NICHD without entering the NICHD as an author and then being required to submit a bunch of CME/COI disclosures for the NICHD), I'd appreciate the help.

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Lisa, if we could get the data for treatment after back transfer and after discharge, that would be great. If you can tabulate the 0 and 100%iles and they look reasonable (no extreme outliers), we could replace the 1 and 99%iles in the table with 0 and 100%iles.

Kathleen A. Kennedy, MD, MPH
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Draft Preview of Abstract #750344
THIS COPY IS A DRAFT ONLY. YOUR FINAL PRINTOUT WILL BE AVAILABLE AT TIME OF SUBMISSION

First Author: Kathleen A Kennedy, MD, MPH **Filename:** 750344
Responsible Author: Kathleen A Kennedy, MD, MPH
Presenting Author: Kathleen A Kennedy, MD, MPH
Contact Person: Kathleen A Kennedy, MD, MPH

2012 PAS Annual Meeting

Subspecialty: Neonatology - General
Theme: Neonatal - Patient-Oriented Research

Contact Author: Kathleen A Kennedy, MD, MPH
Department/Institution/Address: Pediatrics, UT Houston Medical School, 6431 Fannin, MSB 2.106, Houston, TX, 77030, United States
Phone: 01 713 500-6708 **Fax:** **E-mail:** kathleen.a.kennedy@uth.tmc.edu

Reponsible Author: Kathleen A Kennedy, MD, MPH
Department/Institution/Address: Pediatrics, UT Houston Medical School, 6431 Fannin, Houston, 77030, United States
Phone: 01 713 500-6708 **Fax:**
Responsible Author E-mail: Kathleen.A.Kennedy@uth.tmc.edu
Responsible Author Declaration: As the responsible author, I confirm that the individual listed as the sponsor has been contacted and given the opportunity to review the abstract and has subsequently agreed to sponsor this abstract.

Presenting Author: Kathleen A Kennedy, MD, MPH
Department/Institution/Address: Pediatrics, 6431 Fannin, Houston, TX, 77030, United States
Phone: 01 500-6708 **Fax:**
Presenting Author E-mail: Kathleen.A.Kennedy@uth.tmc.edu
The presenting author is member of these Alliance Societies:
Is Presenting Author a Trainee? No, Not a Trainee
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QUESTIONNAIRE INFORMATION

Eastern Society for Pediatric Research: No, Do not consider this abstract for the Eastern SPR
Pediatric Hospital Medicine: No, Do not consider this abstract for presentation at the Pediatric Hospital Medicine, July 19-22, 2012
Research Type: Clinical
Presentation Sabbath Conflict on: N/A
APA Special Interest Groups, Committees or Regions: None

AWARDS APPLIED FOR:

No awards selected

SPONSOR INFORMATION

Sponsoring Member for PAS/ASPR abstract:
Sponsor Name: Kathleen A Kennedy
Email: Kathleen.A.Kennedy@uth.tmc.edu
Is the Sponsor an Author? Yes
Sponsoring Societies:
American Academy of Pediatrics
Society for Pediatric Research

Title: Optimal Retinopathy of Prematurity (ROP) Screening Interval for 24-27 Week Infants

Kathleen A Kennedy, MD, MPH[1], Lisa A Wrage, MPH[2], Dale Phelps, MD[3], Rosemary Higgins, MD[4] and the SUPPORT Subcommittee for the NICHD Neonatal Research Network[4]. [1]Pediatrics, UT Houston Medical, Houston, TX, United States; [2]RTI International, Research Triangle Park, NC, United States; [3]University of Rochester, Rochester, NY, United States and [4]NICHD, Rockville, MD, United States.

Background:

Timely detection of treatable ROP is important to assure optimal outcomes for infants who meet the criteria for treatment. Current screening guidelines are based on natural history data from randomized trials that enrolled infants between 1986-1997. Since that time, survival of lower gestational age infants has increased, and earlier treatment of ROP (Type 1 ROP: stage 3 or plus disease in zone 1 or stage 2-3 with plus disease in zone 2) is recommended. The timing of onset of ROP is related most closely to postmenstrual age (PMA = gestational age at birth + postnatal age).

Objective: To validate current screening recommendations for detection of treatable ROP in 24-27 week gestational age infants.

Design/Methods:

In the NICHD Network SUPPORT trial, severe ROP (Type 1 ROP or treatment with laser, cryotherapy or bevacizumab) or death was the primary outcome for the O_2 saturation target arm of the factorial design. Extensive ROP outcome data were prospectively collected for all enrolled infants. Infants 24 0/7 – 27 6/7 weeks gestation (no birth weight limits) were eligible for this study. Examinations were conducted according to current screening recommendations. Study eye exam data were recorded until study endpoint: ROP treatment, full vascularization to the ora serrata, vascularization in zone 3 in 2 consecutive exams, or the infant was 55 weeks postmenstrual age.

Results: 1316 infants were enrolled. 1091 (83%) of infants survived to age of ROP determination. 997 (91%) of these infants had a definitive ROP outcome and 984 (90%) had sufficient exam data (no missing or delayed exams before diagnosis) to determine the presence and age of onset of ROP. As expected, infants with severe ROP were less mature [mean (SD) 25.5 (0.9) wks vs 26.8 (0.9) wks, p<0.0001], lower birth weight [mean (SD) 708 (148)g vs 942 (173)g, p<0.0001], and more likely to be White race (44% vs 35%, p=0.07) than infants with no ROP. For the 642 infants with known age of onset of ROP, the cumulative postmenstrual age at onset is shown in the table:

	Postmenstrual Age (weeks)						
	Cumulative % with Diagnosis of ROP						
ROP type	1%	5%	25%	50%	75%	95%	99%
Any ROP (n=642)	30.4	31.4	32.7	33.9	35.1	37.9	41.0
Severe (Type 1/Treated) ROP (n=128)	32.7	33.9	35.1	36.4	38.6	43.3	45.0

Conclusions: Current ROP screening guidelines recommend that screening begins by 31 weeks postmenstrual age and is continued until the vessels have reached zone 3, or, for infants without prethreshold ROP, until postmenstrual age of 45 weeks. Our data are consistent with these guidelines. In this large SUPPORT Trial cohort, we did not observe ROP needing treatment before 32 weeks PMA nor after 45 weeks PMA among infants born at 24-27 weeks. In this referral center cohort, ___% of infants required ROP treatment after back transfer to another NICU; ___% required treatment after discharge to home. A limitation of this study is that infants < 24 weeks gestation were not enrolled and these data may not be generalizable to less mature infants at highest risk for ROP.

Other Previews:

Abstract Disclosure Info: Disclosures

Print

From: Schmidt, Barbara (Neonatology)
To: nfiner@ucsd.edu; WCarlo@peds.uab.edu; jmd3@case.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]; mgantz@rti.org
Subject: Re: SUPPORT trial publication
Date: Friday, October 07, 2011 8:49:48 AM

Thanks, Neil.

I am not a statistician, but I believe one can see the problem in many of the figures: the confidence intervals increase with increasing postnatal age much more in the low than in the high target group?

Barbara

From: Finer, Neil
To: Schmidt, Barbara (Neonatology); Wally Carlo, M.D. ; jmd3@case.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E] ; mgantz@rti.org
Sent: Thu Oct 06 05:03:18 2011
Subject: RE: SUPPORT trial publication

Hi Barb and Julie
I think Barbara raises a valid concern.
We need to ask Julie about this
Julie – can you analyze the data to determine if the infants in the low sat group where on the study oximeter longer than the hi group (should be so) and whether the late desats where seen more in Low sat infants who were on the study oximeter for a longer time or till a later PCA than the hi St group??
Thanks
Neil

From: Schmidt, Barbara (Neonatology) [mailto:barbara.schmidt@uphs.upenn.edu]
Sent: Tuesday, October 04, 2011 3:12 PM
To: Wally Carlo, M.D.; Finer, Neil
Cc: Higgins, Rosemary (NIH/NICHD) [E]; mgantz@rti.org
Subject: RE: SUPPORT trial publication

Dear Wally,
I would not consider "time on study oximeter" as an outcome.

Actually, I have been thinking about this question after looking at the paper we were all sent yesterday, led by the Cleveland group. The conclusion is that the babies in the low saturation target range had more frequent desaturations, especially late in their neonatal course.

If my hypothesis is correct, namely that babies in the low target range came off the study oximeter sooner than the babies in the high target range, the results may at least in part be due to selection bias? Only the worst babies in the low target range would stay long enough on the study oximeter to be included in the analysis?

Barbara

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Tuesday, October 04, 2011 5:58 PM

To: Schmidt, Barbara (Neonatology); nfiner@ucsd.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]; mgantz@rti.org
Subject: RE: SUPPORT trial publication

Barbara:

You are correct but the data you have asked were not pre-specified outcome measures and we generally cannot add such requests to the data center. We expected O2 supplementation and monitoring durations would be different.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
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Director, Newborn Nurseries
1700 6th Avenue South
176F Suite 9380R
Birmingham, AL 35233-7335
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From: Schmidt, Barbara (Neonatology) [mailto:barbara.schmidt@uphs.upenn.edu]
Sent: Tuesday, October 04, 2011 3:46 PM
To: Wally Carlo, M.D.; nfiner@ucsd.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]; mgantz@rti.org
Subject: RE: SUPPORT trial publication

Dear Rose and Wally,
Thanks for your responses.

Wally, I did read the methods section from which you quote below and I understand the SUPPORT rules for stopping the study oximetry.

What I would like to know is this: Was there a difference in the duration of time the two groups spent on the study oximeters?

I would suspect that – on average – kids in the low saturation target group should have spent less time on the study oximeters because they had a lower threshold for getting into air. Is this correct?
Barbara

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Tuesday, October 04, 2011 1:08 PM
To: Schmidt, Barbara (Neonatology); nfiner@ucsd.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT trial publication

Hi Barbara:

Here is a quote from the Methods in the paper.

"Altered pulse oximetry was initiated within the first 2 hours after birth and was continued until 36 weeks of postmenstrual age or until the infant was breathing ambient air and did not require ventilator support or CPAP for more than 72 hours, whichever occurred first. Infants who were weaned to room air but who subsequently received oxygen supplementation before 36 weeks of postmenstrual age were placed back on the assigned study pulse oximeter. The target ranges were kept unchanged from birth until 36 weeks of postmenstrual age."

We did not report duration of O2 supplementation.
Wally

Wally Carlo, M.D.
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University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
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Birmingham, AL 35233-7335
Phone: 205 934 4680
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Cell: 205 (b)(6)

From: Schmidt, Barbara (Neonatology) [mailto:barbara.schmidt@uphs.upenn.edu]
Sent: Tuesday, October 04, 2011 9:49 AM
To: Wally Carlo, M.D.; nfiner@ucsd.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: SUPPORT trial publication

Dear Wally and Neil,

In your protocol, study oximetry stopped when the babies were breathing room air. Have you reported the average duration of the study oximetry in each of the two saturation target groups? I cannot find this information in the NEJM paper?

Barbara

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From: Finer, Neil
To: Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; Navarrete, Cristina; Duara, Shahnaz; Rich, Wade; richard.ehrenkranz@yale.edu; bpoindex@iupui.edu; kurt.schibler@cchmc.org; mcw3@cwru.edu; Roger Faix; Bradley Yoder; Das, Abhik; Gantz, Marie; Nancy Newman; Wrage, Lisa Ann
Subject: RE: Abstract_Growth_Outcomes_SUPPORT1
Date: Thursday, October 06, 2011 3:55:08 AM

This reads well
My only question is whether growth is adequately defined by weight? Could length be added?
Nicely done
Neil

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Wednesday, October 05, 2011 3:23 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; Navarrete, Cristina; Duara, Shahnaz; Rich, Wade; richard.ehrenkranz@yale.edu; bpoindex@iupui.edu; kurt.schibler@cchmc.org; mcw3@cwru.edu; Roger Faix; Bradley Yoder; Das, Abhik; Gantz, Marie; Nancy Newman; Wrage, Lisa Ann
Subject: RE: Abstract_Growth_Outcomes_SUPPORT1

Great job, Tina and Shanaz.

Enclosed are some tracked suggestions.

wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
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Director, Division of Neonatology
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1700 6th Avenue South
176F Suite 9380R
Birmingham, AL 35233-7335
Phone: 205 934 4680
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From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, October 05, 2011 1:13 PM
To: nfiner@ucsd.edu; Wally Carlo, M.D.; 'Navarrete, Cristina'; Duara, Shahnaz; 'Rich, Wade'; 'Richard, MD Ehrenkranz (richard.ehrenkranz@yale.edu)'; Brenda Poindexter [bpoindex@iupui.edu]; 'kurt.schibler@cchmc.org'; mcw3@cwru.edu; 'Roger Faix'; 'Bradley Yoder'; Das, Abhik; 'Gantz, Marie'; 'Nancy Newman'; Wrage, Lisa Ann
Subject: Abstract_Growth_Outcomes_SUPPORT1

HI,
Here is the SUPPORT GROWTH OUTCOMES draft abstract. Please send comments back to Shahnaz and Tina.

Thanks
Rose

From: Phelps, Dale
To: Higgins, Rosemary (NIH/NICHD) [E]; "wrage@rti.org"; "Kathleen.A.Kennedy@uth.tmc.edu"
Cc: "adas@rti.org"
Subject: RE: PAS Abstract
Date: Wednesday, October 05, 2011 2:41:16 PM

Since we have the date of surgery for ROP, and we have the date of transfer or discharge home in the GDB, I believe we should be able to get this easily. Of course it is never as easy as we think it should be. ☺
Dale

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, October 05, 2011 7:50 AM
To: 'wrage@rti.org'; 'Kathleen.A.Kennedy@uth.tmc.edu'; Phelps, Dale
Cc: 'adas@rti.org'
Subject: Re: PAS Abstract

Some of the children may have been discharged, so there may be three categories:
In hospital
Transferred back
Admitted from home for treatment

Not sure how much detail we have on this

Rose

From: Wrage, Lisa Ann <wrage@rti.org>
To: Kennedy, Kathleen A <Kathleen.A.Kennedy@uth.tmc.edu>; Phelps, Dale <Dale_Phelps@URMC.Rochester.edu>
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik <adas@rti.org>
Sent: Wed Oct 05 10:34:34 2011
Subject: RE: PAS Abstract

Hi,
I have two other abstracts so I won't be able to finish up all the analysis for your paper in the next week and a half, but I can work on the specific items for the abstract, i.e what is in red: what proportion of cases that received treatment were treated before discharge home, and what proportion were treated after back transfer.
I will finish up everything else asap after all the abstracts are done.
Thanks.
Lisa

From: Kennedy, Kathleen A [mailto:Kathleen.A.Kennedy@uth.tmc.edu]
Sent: Wednesday, October 05, 2011 10:28 AM
To: Phelps, Dale
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Wrage, Lisa Ann
Subject: RE: PAS Abstract

I'm revising the abstract based on Dale's comments. Please see the one in red. I'd love to add that

but I don't have the data. Would it be possible to get the rest of the data we requested soon?

Kathleen A. Kennedy, MD, MPH
Richard W. Mithoff Professor of Pediatrics
Director, MS in Clinical Research Degree Program
UT-Houston Medical School
6431 Fannin, Suite 2.106
Houston, TX 77030
713 500-6708

From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Tuesday, October 04, 2011 6:05 PM
To: Kennedy, Kathleen A
Cc: Archer, Stephanie (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Wrage, Lisa Ann
Subject: RE: PAS Abstract

Had these last pm and didn't hit 'send'. Apologies.

The last sentence in the background. I suggest you use instead: "The timing of onset of ROP is related most closely to postmenstrual age (PMA = Gestational + chronologic ages)."
This will help since the full rest of the abstract refers only to PMA.

In the nest to the last sentence of the results, it says ".... White race (44% vs 35%) than infants without ROP. "
It is not clear whether you meant "infants with no ROP" or if you meant "infants without serious ROP". ... I think you mean without serious ROP, but just can't be sure. Could be infants with no ROP plus those with ROP that never got serious enough for treatment.

I like the Table.

In the last paragraph:
Do the current guidelines really suggest that screening can stop at 45 weeks? I don't think so. (can't access them at the moment). I think they say that screening can stop at xx weeks if the vessels are in zone III, and there has been no stage 2 or 3 ROP" or something similar to that. We have to be careful to quote them precisely.

I would reword your second sentence to read:
"Our data are consistent with the current ROP screening guidelines: in a large cohort, we did not observe ROP needing treatment before 32 weeks PMA, nor after 45 weeks PMA. A limitation.... "

Nice abstract. I would still like to add: what proportion of cases that received treatment were treated before discharge home, and what proportion were treated after back transfer. ☺

Dale

From: Kennedy, Kathleen A [mailto:Kathleen.A.Kennedy@uth.tmc.edu]
Sent: Tuesday, October 04, 2011 3:37 PM
To: Phelps, Dale

Subject: Re: PAS Abstract

It's kluged but you can make it work by entering "the NICHD Neonatal Research Network" as the name of the last author. As far as I can tell, you really don't need to enter an email address or institution for every author even though it looks like you do.

Do you want to suggest any changes? Once I get your input, I'm going to send it on to the subcommittee? Do you want me to list an institution for you?
Kathleen A. Kennedy, MD, MPH
Director, Neonatal-Perinatal Division
Director, MS in Clinical Research Degree Program

From: Phelps, Dale <Dale_Phelps@URMC.Rochester.edu>
To: Archer, Stephanie (NIH/NICHD) [E] <archerst@mail.nih.gov>; Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov>; Kennedy, Kathleen A; Wrage, Lisa Ann <wrage@rti.org>
Cc: Das, Abhik <adas@rti.org>
Sent: Tue Oct 04 17:21:36 2011
Subject: RE: PAS Abstract

Let me know how you do it ! I will need to do the same for Inositol.
Dale

From: Archer, Stephanie (NIH/NICHD) [E] [mailto:archerst@mail.nih.gov]
Sent: Tuesday, October 04, 2011 8:15 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; 'Kennedy, Kathleen A'; Wrage, Lisa Ann; Phelps, Dale
Cc: Das, Abhik
Subject: RE: PAS Abstract

Hi Kathleen,

Just looking at some of the submission forms from last year, it looks like most people listed this under the Title area? See the attached sample. Will this year's system let you do this?

Stephanie

Stephanie Wilson Archer
The Eunice Kennedy Shriver
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Pregnancy & Perinatology Branch
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From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tuesday, October 04, 2011 10:58 AM
To: 'Kennedy, Kathleen A'; Wrage, Lisa Ann; dale_phelps@urmc.rochester.edu
Cc: Das, Abhik; Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: PAS Abstract

Kathleen
I included Stephanie as she may know how to get on behalf of NCHD NRN into the template.

The next step is to send to the SUPPORT subcommittee
Thanks
rose

Rosemary D. Higgins, MD
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From: Kennedy, Kathleen A [mailto:Kathleen.A.Kennedy@uth.tmc.edu]
Sent: Tuesday, October 04, 2011 10:56 AM
To: Wrage, Lisa Ann; dale_phelps@urmc.rochester.edu; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik
Subject: RE: PAS Abstract

Thanks for the suggestions. I'll make all the changes. Rose, I don't see how to put the "on behalf of..." as part of the authorship in the PAS electronic format. Do you know if/how others have done it? I've thought about entering that text as your institution, but I don't think that will look right because it will come after the institution for the first author. Maybe the text could be entered as the first name for the last author?

Lisa and Dale, could you tell me how you'd like your institution and city listed?

Lisa, please see answers below.

Rose, what's the next step. When I make these changes (and hopefully get comments from Dale), should it go to the SUPPORT subcommittee since they'll be authors on the subsequent paper?

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From: Wrage, Lisa Ann [mailto:wrage@rti.org]
Sent: Tuesday, October 04, 2011 9:33 AM
To: Kennedy, Kathleen A; dale_phelps@urmc.rochester.edu; Higgins, Rosemary (NIH/NICHD)
Cc: Das, Abhik
Subject: RE: PAS Abstract

Thanks for this. I think it looks great. A couple of comments:

--I assume that you meant to include the 'no ROP' group when you say that n=984 had sufficient exam data to determine the age of onset of ROP? **Yes. I did that because it expresses the proportion of the full cohort for whom we had adequate data. If we have space, I might add a sentence there about the proportion who had ROP. I could also add more detail about missing data.**
--I can get those p-values for you for the baseline characteristic comparisons of severe ROP to no ROP. **Thanks.** I'll get the min/max values for the table as well in case you want to include them. **I'd like to have the min/max values for the manuscript, but I can't add any more columns to the table in the abstract form, so I think we'll just leave those out of the abstract.**
--it does not look like it is causing confusion for the abstract, but I see that I did not update the very last box in the flowchart so I will also fix that. **Thanks.**

As we've discussed before, I probably should change "onset" to "diagnosis".

Thanks.
Lisa

From: Kennedy, Kathleen A [mailto:Kathleen.A.Kennedy@uth.tmc.edu]
Sent: Monday, October 03, 2011 5:40 PM
To: Wrage, Lisa Ann; dale_phelps@urmc.rochester.edu; Higgins, Rosemary (NIH/NICHD)
Subject: PAS Abstract

I've attached an initial draft of a PAS abstract for the SUPPORT secondary study on timing of onset of ROP. I'd appreciate your suggestions. Based on what I've entered into the online system so far, we have room to add more. I'm not sure what will happen when I finish adding authors, affiliations, etc.

Rose, I need a little procedural help with this.

1) Based on your email about the recent votes, I think we don't need to include as authors members of the subcommittee that weren't involved in the secondary study. Is that correct? I think the rule applies if the space is limited for authors and I can't tell if that's true with the PAS application or not. Adding these 4 authors only took up a few % of the space allocation.
2) The online application asks for email addresses and institutions and addresses for each of the authors. Do we usually include that or do we just put the Network as the institution for everyone? I don't see another obvious way to include the network name as an author.

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713 500-6708

From: Finer, Neil
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Wally Carlo, M.D.; Rich, Wade
Subject: Re: SUPPORT trial publication
Date: Wednesday, October 05, 2011 12:56:34 AM

Rose
We do hive the time in oxygen for each group
Marie can easily provide the requested data
Neil

On Oct 4, 2011, at 5:40 PM, "Higgins, Rosemary (NIH/NICHD) [E]"
<higginsr@mail.nih.gov<mailto:higginsr@mail.nih.gov>> wrote:

Barbara
The infants had the study oximeter discontinued if there were on room air (and off respiratory support) for 3 days. I do not think that the information you are requesting was reported. I have attached a supplemental appendix from Neil's CPAP paper, but this doesn't answer your question.
I also included Marie as she would know if we reported the days on oxygen for the saturation arm of the trial

Thanks
rose

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From: Schmidt, Barbara (Neonatology) [mailto:barbara.schmidt@uphs.upenn.edu]
Sent: Tuesday, October 04, 2011 10:49 AM
To: Wally Carlo, M.D.; <mailto:nfiner@ucsd.edu> nfiner@ucsd.edu<mailto:nfiner@ucsd.edu>
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: SUPPORT trial publication

Dear Wally and Neil,

In your protocol, study oximetry stopped when the babies were breathing room air. Have you reported the average duration of the study oximetry in each of the two saturation target groups? I cannot find this information in the NEJM paper?

Barbara

<nejm_support_1970sa1.pdf>

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Schmidt, Barbara (Neonatology)"; "Wally Carlo, M.D."; "nfiner@ucsd.edu"; "Gantz, Marie"
Subject: RE: SUPPORT trial publication
Date: Tuesday, October 04, 2011 11:40:00 AM
Attachments: nejm_support_1970sai.pdf

Barbara
The infants had the study oximeter discontinued if there were on room air (and off respiratory support) for 3 days. I do not think that the information you are requesting was reported. I have attached a supplemental appendix from Neil's CPAP paper, but this doesn't answer your question. I also included Marie as she would know if we reported the days on oxygen for the saturation arm of the trial

Thanks
rose

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From: Schmidt, Barbara (Neonatology) [mailto:barbara.schmidt@uphs.upenn.edu]
Sent: Tuesday, October 04, 2011 10:49 AM
To: Wally Carlo, M.D.; nfiner@ucsd.edu
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: SUPPORT trial publication

Dear Wally and Neil,

In your protocol, study oximetry stopped when the babies were breathing room air. Have you reported the average duration of the study oximetry in each of the two saturation target groups? I cannot find this information in the NEJM paper?

Barbara

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network. Early CPAP versus surfactant in extremely preterm infants. N Engl J Med 2010;362:1970-9.
DOI: 10.1056/NEJMoa0911783.

Web Appendix Tables

Table A1. Pre-Specified Outcomes for 24 to 25 week Stratum

Characteristic	CPAP (N=285)	Surfactant (N=280)	Relative Risk or Difference in Means for CPAP vs. Surfactant (95% CI)	Adjusted P-value
BPD (physiologic definition) or death by 36 weeks PMA	63.9% (182/285)	67.9% (190/280)	0.96 (0.85, 1.07)	0.45
BPD (supplemental oxygen) or death by 36 weeks PMA	62.8% (179/285)	67.1% (188/280)	0.95 (0.84, 1.06)	0.36
BPD (physiologic definition) by 36 weeks PMA	54.8% (125/228)	54.5% (108/198)	1.06 (0.91, 1.25)	0.46
BPD (supplemental oxygen) by 36 weeks PMA	53.5% (122/228)	53.5% (106/198)	1.05 (0.9, 1.23)	0.53
Death by 36 weeks PMA	20.0% (57/285)	29.3% (82/280)	0.68 (0.5, 0.92)	0.01
Days on supplemental oxygen† Adjusted Mean±StdErr, Unadjusted Median (IQR) (N=421)	80.8 ± 2.3 79.5 (51.5, 108.5)	80.3 ± 2.4 79 (52, 110)	0.5 (-5.8, 6.9)	0.86
Days on mechanical vent (HFV & CV) † Adjusted Mean±StdErr, Unadjusted Median (IQR) (N=421)	35.8 ± 1.5 29.5 (10, 48)	38.7 ± 1.6 33 (14, 56)	-3.0 (-7.2, 1.3)	0.17
Alive and off MV (HFV/CV) at 7 days	34.3% (97/283)	26.4% (74/280)	1.29 (1, 1.66)	0.049
Any air leak in first 14 days	8.1% (23/285)	9.6% (27/280)	0.79 (0.47, 1.35)	0.40
Medical or surgical NEC	15.1% (42/279)	13.1% (35/268)	1.13 (0.74, 1.71)	0.58
IVH grade 3-4	19.8% (54/273)	17.0% (45/265)	1.17 (0.82, 1.68)	0.39
Postnatal steroids for BPD	13.0% (36/276)	20.5% (54/264)	0.66 (0.46, 0.94)	0.02

† Among survivors to discharge, transfer or 120 days; maximum value is 120 days

Table A2. Cause of Death for 24 to 25 week stratum

Contributory Cause of Death	CPAP (N=68)	Surfactant (N=90)
Respiratory distress syndrome	13/68 (19.1)	31/90 (34.4)
Bronchopulmonary dysplasia	10/68 (14.7)	7/90 (7.8)
Infection	14/68 (20.6)	15/90 (16.7)
Necrotizing enterocolitis	10/68 (14.7)	16/90 (17.8)
Central nervous center insult	11/68 (16.2)	5/90 (5.6)
Immaturity	3/68 (4.4)	5/90 (5.6)
Other	7/68 (10.3)	11/90 (12.2)

Table A3. Pre-Specified Outcomes for 26 to 27 week Stratum

Characteristic	CPAP (N=378)	Surfactant (N=373)	Relative Risk or Difference in Means for CPAP vs. Surfactant (95% CI)	Adjusted P-value
BPD (physiologic definition) or death by 36 weeks PMA	35.7% (135/378)	38.3% (143/373)	0.94 (0.78, 1.13)	0.48
BPD (supplemental oxygen) or death by 36 weeks PMA	38.1% (144/378)	44.2% (165/373)	0.87 (0.74, 1.03)	0.12
BPD (physiologic definition) by 36 weeks PMA	28.7% (98/341)	32.6% (111/341)	0.92 (0.74, 1.15)	0.46
BPD (supplemental oxygen) by 36 weeks PMA	31.4% (107/341)	39.0% (133/341)	0.84 (0.69, 1.02)	0.08
Death by 36 weeks PMA	9.8% (37/378)	8.6% (32/373)	1.12 (0.72, 1.75)	0.61
Days on mechanical vent (HFV & CV) † Adjusted Mean±StdErr, Unadjusted Median (IQR) (N=677)	13.7 ± 1.3 4 (0, 15)	16.7 ± 1.3 6 (2, 21)	-3.0 (-6.4, 0.4)	0.08
Alive and off MV (HFV/CV) at 7 days	71.2% (265/372)	65.6% (244/372)	1.09 (0.98, 1.2)	0.10
Any air leak in first 14 days	5.8% (22/378)	5.6% (21/373)	1.01 (0.57, 1.81)	0.97
Medical or surgical NEC	10.9% (41/375)	7.6% (28/368)	1.42 (0.9, 2.25)	0.14
IVH grade 3-4	10.3% (38/369)	7.4% (27/363)	1.41 (0.86, 2.3)	0.17
Postnatal steroids for BPD	2.9% (11/373)	7.9% (29/367)	0.4 (0.2, 0.78)	0.008

† Among survivors to discharge, transfer or 120 days; maximum value is 120 days

From: Rich, Wade
To: Newman, Nancy S (Nancy.Newman2@UHhospitals.org); ahensman@wihri.org; ehale@emory.edu; auten002@mc.duke.edu; kurt.schibler@cchmc.org; Bradley.yoder@hsc.utah.edu; Laptook, Abbot (ALaptook@WIHRI.org); adas@rti.org
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: Antenatal Consent Outcomes Rev NF Sept 30 2011
Date: Monday, October 03, 2011 11:46:53 AM
Attachments: Antenatal Consent Outcomes Rev NF Sept 30 2011.docx

All,

Here is the Antenatal Consent Outcomes paper with revisions. The paper has been accepted for publication in Peds. The reviewers were positive. We were asked to include the BPD, ROP, and NEC analyses, and to make other minor changes which have been done. We would like to get this sent back to the journal in the next couple of weeks. I would appreciate your comments.

Tx.

Wade

Enrollment of ELBW Infants in a Clinical Research Study May Not Be Representative

Wade Rich, BSHS RRT[1]; Neil N. Finer, MD[1]; Nancy S. Newman, RN[2]; Angelita M. Hensman, RN BSN[3]; Ellen C. Hale, RN BS CCRC[4]; Kathy J. Auten, MSHS[5]; Kurt Schibler, MD[6]; Roger G. Faix, MD[7]; Abbot R. Laptook, MD[4]; Bradley A. Yoder, MD[8]; Marie G. Gantz, PhD[8],Abhik Das, PhD[8]; Seetha Shankaran, MD[9]; and for the SUPPORT and Generic Database Subcommittees of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network

Short title: Antenatal Consent in a Large Multicenter Trial

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Keywords: Clinical Research/Trials, Informed Consent, Antenatal Steroids, Neonatal

The authors have no financial disclosures or conflicts of interest.

Acknowledgements

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The National Institutes of Health, the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), and the National Heart, Lung, and Blood Institute (NHLBI) provided grant support for the Neonatal Research Network's SUPPORT Trial.

Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Drs. Abhik Das (DCC Principal Investigator) and Marie Gantz (DCC Statistician) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study. The following investigators, in addition to those listed as authors, participated in this study:

NRN Steering Committee Chairs: Alan H. Jobe, MD PhD, University of Cincinnati (2003-2006); Michael S. Caplan, MD, University of Chicago, Pritzker School of Medicine (2006-2011).

Alpert Medical School of Brown University and Women & Infants Hospital of Rhode Island (U10 HD27904) - William Oh, MD; Dan Gingras, RRT; Susan Barnett, RRT; Sarah Lillie, RRT; Kim Francis, RN; Dawn Andrews, RN; Kristen Angela, RN.

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MD MHS; Ronald N. Goldberg, MD; Kimberly A. Fisher, PhD, FNP-BC, IBCLC; Katherine A. Foy, RN; Gloria Siaw, BSN CRA.

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Eunice Kennedy Shriver National Institute of Child Health and Human Development - Rosemary D. Higgins, MD; Stephanie Wilson Archer, MA.

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National Heart, Lung, and Blood Institute - Mary Anne Berberich, PhD; Carol J. Blaisdell, MD; Dorothy B. Gail, PhD; James P. Kiley, PhD.

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University of Miami Holtz Children's Hospital (U10 HD21397, M01 RR16587) - Shahnaz Duara, MD; Ruth Everett-Thomas, RN MSN.

University of New Mexico Health Sciences Center (U10 HD53089, M01 RR997) - Kristi L. Watterberg, MD; Robin K. Ohls, MD; Julie Rohr, MSN RNC CNS; Conra Backstrom Lacy, RN.

University of Rochester Medical Center, Golisano Children's Hospital (U10 HD40521, M01 RR44) - Nirupama Laroia, MD; Dale L. Phelps, MD; Linda J. Reubens, RN CCRC; Erica Burnell, RN.

University of Texas Southwestern Medical Center at Dallas, Parkland Health & Hospital System, and Children's Medical Center Dallas (U10 HD40689, M01 RR633) - Pablo J. Sánchez, MD; Charles R. Rosenfeld, MD; Walid A. Salhab, MD; James Allen, RRT; Alicia Guzman; Gaynelle Hensley, RN; Melissa H. Lepps, RN; Melissa Martin, RN; Nancy A. Miller, RN; Araceli Solis, RRT; Diana M Vasil, RNC-NIC; Kerry Wilder, RN.

University of Texas Health Science Center at Houston Medical School and Children's Memorial Hermann Hospital (U10 HD21373) - Kathleen A. Kennedy, MD MPH; Jon E. Tyson, MD MPH; Brenda H. Morris, MD; Beverly Foley Harris, RN BSN; Anna E. Lis, RN BSN; Sarah Martin, RN BSN; Georgia E. McDavid, RN; Patti L. Tate, RCP; Sharon L. Wright, MT (ASCP).

University of Utah Medical Center, Intermountain Medical Center, LDS Hospital, and Primary Children's Medical Center (U10 HD53124, M01 RR64) - Jill Burnett, RN; Jennifer J. Jensen, RN BSN; Karen A. Osborne, RN BSN CCRC; Cynthia Spencer, RNC; Kimberlee Weaver-Lewis, RN BSN.

Wake Forest University, Baptist Medical Center, Brenner Children's Hospital, and Forsyth Medical Center (U10 HD40498, M01 RR7122) - T. Michael O'Shea, MD MPH; Nancy J. Peters, RN CCRP.

Wayne State University, Hutzel Women's Hospital, and Children's Hospital of Michigan (U10 HD21385) - Beena G. Sood, MD MS; Rebecca Bara, RN BSN; Elizabeth Billian, RN MBA; Mary Johnson, RN BSN.

Yale University, Yale-New Haven Children's Hospital, and Bridgeport Hospital (U10 HD27871, UL1 RR24139, M01 RR125, M01 RR6022) - Vineet Bhandari, MD DM; Richard A. Ehrenkranz, MD; Harris C. Jacobs, MD; Pat Cervone, RN; Patricia Gettner, RN; Monica Konstantino, RN BSN; JoAnn Poulsen, RN; Janet Taft, RN BSN.

Abstract

Background

The results of the SUPPORT antenatal consent study (Pediatrics 2010, 126: e215-e221) demonstrated that mothers of infants enrolled in the SUPPORT trial had significantly different demographics when compared to mothers of eligible but not enrolled infants.

Objective

The objective of this analysis was to compare the outcomes of BPD, ROP, severe intraventricular hemorrhage or periventricular leukomalacia (IVH/PVL), death and death/severe IVH/PVL for infants enrolled in SUPPORT compared with eligible non-enrolled infants.

Methods:

Perinatal characteristics and neonatal outcomes were compared for enrolled and non-enrolled infants in bivariate analyses using t tests and chi-square tests. Logistic regression models were created to test the Hawthorn effect of enrollment in SUPPORT on outcomes, controlling for baseline perinatal characteristics.

Results

1316 infants were enrolled in SUPPORT, and 3053 infants were eligible but not enrolled. A full course of ANS was provided to 71.7% of enrollees, and 49.4% of eligible infants not enrolled ($p<.001$). Delivery room interventions, including intubation, compressions and epinephrine

were significantly more frequent in the non-enrolled group (p<.001). Infants enrolled in SUPPORT had significantly lower rates of death before discharge, BPD, severe IVH/PVL, death/severe IVH/PVL when compared to infants eligible but not enrolled (p<.001). The rate of ROP was not different. After adjustments for maternal factors, enrollment in the trial alone was not a significant predictor of any of the tested clinical outcomes in a logistic regression model.

Conclusions

The results demonstrate significant outcome differences among enrolled and non-enrolled infants in a trial employing antenatal consent much of which is related to differences in the receipt of ANS. In future trials requiring antenatal consent, there may be a need to balance such factors as receipt of ANS and prenatal care in selecting the approached families.

Introduction

The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants (SUPPORT) was a randomized, 2X2 factorial designed multi-center trial conducted by the *Eunice Kennedy Shriver* NICHD Neonatal Research Network (NRN) (Clinical Trials Gov. Number, NCT 00233324). [1,2] The trial prospectively compared Continuous Positive Airway Pressure and a protocol driven limited ventilatory strategy begun in the delivery room and continuing in the Neonatal Intensive Care Unit with the early (< 1 hour) intratracheal administration of surfactant followed by conventional mechanical ventilation. Infants were also randomized to a prospective comparison of a lower oxygen saturation target range (85% to 89%) with a higher, more conventional target range (91% to 95%) until the infant was no longer requiring ventilatory support or oxygen, using purpose altered oximeters. Eligible infants were those born at NRN centers at 24 0/7 to 27 6/7 weeks gestational age (GA), without known major congenital malformations, and with full resuscitation intended. Antenatal consent was required for enrollment.

A prospective cohort study of the antenatal consenting practices of SUPPORT research personnel was conducted during the last half of the trial and the results published.[3] As part of the ongoing NRN Generic Database (GDB) observational study, data were collected routinely for inborn infants at NRN centers, including most of those who met the GA eligibility criteria for SUPPORT. These data were used to identify eligible, non-enrolled infants. In this previous analysis comparisons were made between enrolled vs non-enrolled eligible infants as well as between infants whose mothers were approached vs. not approached. Comparing all GDB infants who were eligible for SUPPORT but whose mothers were not approached to those whose mothers were approached and consented revealed that mothers in the latter group were significantly more likely to be older, to have a high school degree, private medical insurance, and at least one prenatal care (PNC) visit. Infants of these mothers were more likely to be non-

Hispanic white. Failure to be treated with antenatal steroids (ANS) was over 4 times more prevalent among infants who were eligible but not enrolled in SUPPORT compared to those enrolled.

In view of these results, we felt that it was essential to determine if the outcomes of infants enrolled in SUPPORT differed in substantial ways from infants enrolled in the GDB during the same period who were SUPPORT eligible but were not enrolled.

Based on the differences in prenatal care and antenatal steroid use between the populations that we had found previously, we postulated that the infants enrolled in SUPPORT would have lower rates of BPD, ROP, mortality, and death or IVH or PVL compared with infants of the same gestational ages who were entered into the NRN GDB during the period of SUPPORT recruitment (March 2005 through February 2009) but not enrolled in the trial. Previous trials have compared contemporaneous controls to study subjects to determine if just being in the trial affected outcomes, and have found that enrolled subjects did better overall than their contemporaneous comparison groups.[4,5] Because this trial had no placebo group, we created a statistical model that corrected for demographic and receipt of ANS differences between the groups to test for this trial affect.

Methods

This analysis compared 1316 infants enrolled in SUPPORT to 3053 infants born at NRN centers who met the eligibility criteria for the SUPPORT trial, but were not enrolled. Perinatal characteristics, delivery room interventions, and neonatal outcomes were compared for enrolled and non-enrolled infants in bivariate analyses using t-tests and chi-square tests. Data for SUPPORT infants was obtained from trial documents, and non-enrolled infant data was collected from the Neonatal Research Network Generic Database. Because not all of the data collected for the trial subjects was available for non-enrolled infants, the comparison of

retinopathy of prematurity included only those infants who had retinal detachment or documented surgery, and BPD was compared using the conventional definition of oxygen at 36 weeks only, and does not include the NRN physiologic definition of BPD.

Logistic regression models were created to test the 'trial effect' of enrollment in SUPPORT on outcomes, controlling for gestational age, sex, race, center, and antenatal steroid exposure .

Results

Infants in the non-enrolled group were significantly more likely to have an APGAR score of less than 3 at both 1 and 5 minutes, and delivery room interventions, including intubation, compressions and epinephrine were significantly more frequent in the non-enrolled group. (Table 2) In unadjusted analysis of outcomes, infants enrolled in SUPPORT had significantly lower rates of BPD, death before discharge, severe intraventricular hemorrhage or periventricular leukomalacia (IVH/PVL), and death/severe IVH/PVL when compared to infants eligible but not enrolled. Rates of ROP and NEC were not different. (Table 3)

In the logistic regression models used to test whether there was a 'trial effect' related to enrollment in SUPPORT , we found that enrollment in the SUPPORT trial itself was not a significant predictor of BPD, ROP, death, IVH 3-4, or PVL when we controlled for GA, sex, race, center and antenatal steroid exposure.

Discussion

When providing the enrollment tables for their trials, authors generally start with an enumeration of eligible subjects, and then describe how many refused, had missing data, etc. This group of eligible subjects is better described as "identified eligible subjects," in other words, those whom the investigator identified as eligible at the time they would normally be approached for consent. There were additional mothers who were missed by the investigators

due to time of day, rapidity of admission, duration of stay, etc. Due to the nature of the GDB database of the Neonatal Research Network, which identifies and tracks all infants fitting broad gestational age criteria, we were able to look not just at the enrolled subjects, but also those who were not enrolled or in some cases were not even identified as eligible by the research team. This allowed us to make a unique comparison of all infants who were born in NRN centers who met the SUPPORT study criteria, both those who were enrolled and those who were not.

Our findings suggest that using antenatal consent to carry out a trial such as SUPPORT under the constraints of pre-intervention informed consent creates a situation where population bias is a significant issue. We agree with the concerns expressed by Schmidt et al. that this circumstance can create a threat to the external validity of the trial.4 Title 45 of the Code of Federal Regulations allows institutional review boards to waive some or all elements of consent.[6] Our previous observations, combined with the further analysis of this trial, suggest that allowing for the deferral of consent until after birth for trials comparing routinely used interventions can help to insure that we include the sickest and most at-risk populations, and thus contribute to a more generalizable study population

What remains unclear is how to deal with trials of greater than minimal risk that require antenatal consentCurrent standards for waiver of consent would be the same as those used for 'emergency' trials, such as the use of a blood substitute in a pre-hospital environment. These requirements include high risk balanced with a life-threatening situation, a direct benefit, public disclosure, and the existence of an independent data safety board. Most near-birth trials would not meet the standard of a life-threatening situation, and neonatal trials with pre-specified direct benefit are also extremely uncommon. In a review of clinical research in critically ill patients, Truog et al. concluded that informed consent is required for research interventions

that, if they were clinical interventions, would not require specific consent. They suggest that the requirement for consent in a clinical trial be based on 5 criteria: 1) whether all of the treatments in the trial could be offered outside the trial, 2) whether there is minimal additional risk compared to the alternative clinical treatment 3) whether there is equipoise, 4) whether a reasonable person would have a preference between the two treatments, and 5) that the subject be informed that the previous four criteria are the basis for determining the need for specific rather than general consent in the institution involved. [7] Based on these characteristics, one could make the argument that the SUPPORT trial could have been carried out under waiver. Luce countered this argument with the statement that informed consent in critically ill subjects is necessary to promote respect for patients and their right of self-determination, and because investigator self-regulation is inadequate. [8]

In trials that compare currently used interventions and are minimal risk, it is suggested that a waiver of consent and a postnatal written consent to utilize the infant's information be sought. This stipulation allows parents to decide if they want their infant's information included in the study. This type of delayed consent has been successfully applied in non-US clinical trials requiring near-birth interventions. However, more complex trials requiring antenatal consent are still at risk for the lack of generalizability seen in our results. , Further dialogue with regulatory agencies needs to be conducted to determine the best method of balancing the safety and security of subjects with the need for the evidence that can be properly obtained from large trials that are generalizable to the intended populationor population at risk

Conclusion

The results of this analysis demonstrate significant outcome differences between enrolled and non-enrolled infants in the eligible population of a trial employing antenatal consent. In minimal-risk trials for minimal-risk trials of interventions in the delivery room or shortly after

birth, a waiver or delay of parental consent should be considered in order to promote generalizability of results. Further research and regulatory review need to be carried out in order to ensure that large moderate risk trials that currently require antenatal consent are able to be conducted in such a way as to ensure generalizability of results.

Table 1.

Variable	Enrolled (N=1316)	Non-Enrolled (N=3053)	P-value
GA (weeks) (mean ± standard deviation)	26.2 +/- 1.1	26.0 +/- 1.2	<0.001
Birth weight (grams) (mean ± standard deviation)	830.1 +/- 193.2	812.5 +/- 191.8	0.006
Male	54.1%	52.6%	0.373
White, non-Hispanic	39.6%	36.1%	0.030
Prenatal Antibiotics	78.1%	65.4%	<0.001
Antenatal steroids (any)	96.2%	84.4%	<0.001
Antenatal steroids (full course)	71.7%	49.4	<0.001

Table 2.

Variable	Enrolled (N=1316)	Non-Enrolled (N=3053)	P-value
Apgar < 3 at 1 minute	24.4%	31.9%	<0.001
Apgar < 3 at 5 minutes	4.4%	8.4%	<0.001
Intubated in DR	63.6%	75.8%	<0.001
Surfactant in DR or NICU	82.5%	86.5%	<0.001
Chest compressions in DR	5.9%	9.7%	<0.001
Epinephrine in DR	3.1%	6.0%	<0.001

Table 3.

Outcome	SUPPORT Enrolled (N=1316)	Non-Enrolled (N=3053)	p-value
Death	18.0%	24.1%	<0.001*
BPD (Oxygen at 36 wks)	42.4	47.7	.0027*

BPD or Death by 36 wks	51.3	59.2	<.0001*
ROP (Surgery or Retinal Detachment)	10.4	12.4	0.101
NEC (Medical or Surgical)	11.3	12.7	0.214
Intraventricular Hemorrhage (IVH) grade 3-4	13.0	17.6	<0.001*
Periventricular Leukomalacia (PVL)	3.8%	5.1%	0.068
IVH 3-4 or PVL	15.1%	19.8%	<0.001*
Death or IVH 3-4 or PVL	27.4%	35.6%	<0.001*

Legends

Table 1 - **Demographic information for randomized versus non enrolled infants**

Table 2 - **Delivery room status and interventions**

Table 3 – **Neonatal outcomes.**

---

[1] SUPPORT Study Group of the *Eunice Kennedy Schriver* NICHD Neonatal Research Network, Finer, N. N. ; Carlo, W. A.; Walsh, M. C.; Rich, W.; Gantz, M. G.; Laptook, A. Ret al. Early CPAP versus Surfactant in Extremely Preterm Infants. N Engl J Meds. 2010; 362(21):1970-1979.

[2] SUPPORT Study Group of the *Eunice Kennedy Shriver* NICHD Neonatal Research Network, Carlo WA, Finer NN, Walsh MC, Rich W, Gantz MG, Laptook AR, et al. Target ranges of oxygen saturation in extremely preterm infants. N Engl J Med. 2010; 362(21):1959-69.

[3] Rich W, Auten K, Gantz M, Hale E, Hensman A and for the National Institute of Child Health and Human Development Neonatal Research Network. Antenatal Consent in the SUPPORT Trial: Challenges, Costs, and Representative Enrollment. Pediatrics 2010;126;e215-e221

[4] Schmidt B, Gillie P, Caco C, Roberts J, Roberts R. Do sick newborn infants benefit from participation in a randomized clinical trial? Journal of Pediatrics 1999;134:151–5.

[5] Davis, S., Wright, P. W., Schulman, S. F., Hill, L. D., Pinkham, R. D., Johnson, L. P., Jones, T. W., Kellogg, H. B., Radke, H. M., Sikkema, W. W., Jolly, P. C. and Hammar, S. P. (1985), Participants in prospective, randomized clinical trials for resected non-small cell lung cancer have improved survival compared with nonparticipants in such trials. Cancer, 56: 1710–1718. doi: 10.1002/1097-0142

[6] US Department of Health and Human Services. General requirements for informed consent, 45 CFR §46.116d

[7] Truog RD, Robinson W, Randolph A, Morris A. Is informed consent always necessary for randomized, controlled trials? . N Engl J Med. 1999;340(10):804-7

[8] Luce JM. Is the concept of informed consent applicable to clinical research involving critically ill patients? Crit Care Med. 2003:31(3 Suppl):S153-60. Review.

From: Finer, Neil
To: Wally Carlo, M.D.; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; Myriam Peralta, M.D.; Vaucher, Yvonne; Das, Abhik
Subject: RE: SUPPORT OXIMETRY abstract draft
Date: Monday, October 03, 2011 6:02:58 AM

This looks very complete to me.

Thanks Myriam

Neil

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Friday, September 30, 2011 4:54 PM
To: Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; Myriam Peralta, M.D.; Finer, Neil; Vaucher, Yvonne; Das, Abhik
Subject: RE: SUPPORT OXIMETRY abstract draft

Great job, Myriam.

I have added my changes/comments to the draft sent by Marie.

Wally

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Sent: Friday, September 30, 2011 3:05 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Myriam Peralta, M.D.; Wally Carlo, M.D.; Finer, Neil; Vaucher, Yvonne; Das, Abhik
Subject: RE: SUPPORT OXIMETRY abstract draft

Myriam,

My suggested edits are attached. FYI, I will be out of town next week, and I will not have a chance to review the current draft of the full paper before I leave, but I will be sure to get any edits or comments back to you by the 13th as requested in Rose's email.

Marie

Marie Gantz, Ph.D.
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RTI International
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From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, September 30, 2011 8:28 AM
To: Myriam Peralta, M.D.; 'Wally Carlo, M.D.'; 'Finer, Neil'; 'Vaucher, Yvonne'; kurt.schibler@cchmc.org; 'mcw3@cwru.edu'; Roger Faix;

Laptook, Abbot; Bradley Yoder; Das, Abhik; Gantz, Marie; 'Nancy Newman'; Rich, Wade
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: SUPPORT OXIMETRY abstract draft
Importance: High

Here is the SUPPORT OXIMETRY PAS abstract- please send comments to Myriam Peralta by October 7.

Thanks

Rose

From: Myriam Peralta, M.D. [mailto:MPeralta@peds.uab.edu]
Sent: Thursday, September 29, 2011 8:24 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Wally Carlo, M.D.
Subject: abstract draft

Draft Preview of Abstract #750268
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First Author: Myriam Peralta-Carcelen **Filename:** 750268
Responsible Author: Myriam Peralta-Carcelen
Presenting Author: Myriam Peralta-Carcelen
Contact Person: Myriam Peralta-Carcelen

2012 Pediatric Academic Societies' Annual Meeting

Subspecialty: Not yet indicated
Theme: Not yet indicated

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Eastern Society for Pediatric Research: Not yet indicated
Pediatric Hospital Medicine: Not yet indicated
Research Type: Not yet indicated
Presentation Sabbath Conflict on:

APA Special Interest Groups, Committees or Regions: Not yet indicated

Awards Applied for:

No awards selected

Sponsor Information

You must indicate to which meeting(s) you would like to submit your abstract on the Questionnaire

Title: Neurodevelopmental Outcome of Extremely Preterm Infants in a trial of Different Oxygen Saturation Targets

Myriam Peralta-Carcelen[UAB] and SUPPORT Group[NICHD]. [1]Pediatrics, UAB, Birmingham, United States.

Background: The previous SUPPORT multicenter randomized controlled trial showed the benefits of lower oxygen saturation targets on extremely preterm infants in reducing retinopathy of prematurity however higher oxygen saturation targets increased survival by discharge.

Objective: To evaluate the long term neurodevelopmental effects of different oxygen saturation target levels. We hypothesized that relative lower oxygen saturation levels will be associated with lower death or neurodevelopmental impairment at 18 to 22 months of age

Design/Methods: 1316 infants 24 to 27 weeks gestation were enrolled in the SUPPORT trial. Infants were randomized to higher (91 to 95%) or lower oxygen saturation targets (85 to 89%) starting at birth and up to 36 weeks corrected age. Infants were randomized within each center by gestational age strata group (24 0/7-25 6/7 and 26 0/7 - 27 6/7 wks). The primary outcome was a composite of death or neurodevelopmental impairment at 18 to 22 months of age. Neurodevelopmental Impairment was defined as a cognitive composite score of Bayley Scales of Infant Development 3rd edition < 70, motor score less than 70, modified Gross Motor function classification system > 1, presence of moderate to severe cerebral palsy, permanent hearing loss or bilateral blindness. Analyses were adjusted for gestational age strata group, center and familial clustering.

Results: Primary outcome data was available for 93.8% of enrolled infants (1234/1316). 93.6% of survivors were evaluated at 18-22 months adjusted age. [table 1]

Conclusions: Among extremely preterm infants exposed to different levels of oxygen saturation targets, there is increased mortality in the lower oxygen saturation group and no difference in neurodevelopmental impairment at 18 to 22 months of age.

Characteristic	Low SpO2 n=654	High SpO2 n=662	Relative risk (95% CI)	Adjusted p value
Death or NDI	185/612 (30.2%)	171/622 (27.5%)	1.12 (0.94, 1.32)	0.2098
Death by 18-22m	140/633 (30.2%)	118/648 (18.2%)	1.25 (1, 1.55)	0.0462
NDI	45/472 (9.5%)	53/504 (10.5%)	0.87 (0.6, 1.28)	0.492
CP mod/severe	20/479 (4.2%)	20/511 (4.5%)	1 (0.54, 1.83)	0.9971
Blindness both eyes	5/479 (1%)	6/511 (1.2%)	0.9 (0.28, 2.9)	0.8636
Blind one eye	5/479 (1%)	8/511 (1.6%)	0.67 (0.22, 2.02)	0.4784

Other Previews:

Abstract Disclosure Info: [Disclosures]

[Print]

From: Vaucher, Yvonne
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Final Hot Topics slides
Date: Friday, September 30, 2011 11:20:43 PM
Attachments: SUPPORT CPAP Hot Topics CPAP slides09302011ver5.0.pptx

Rose,

Here is the final for the Hot topics syllabus. I changed the format a bit to make it more congruent with Myriam's. I also added the RR and CI in slide # 5. It looks more crowded but I think it is OK.

Yvonne

Yvonne E. Vaucher, M.D., M.P.H.
Division of Neonatal/Perinatal Medicine
Clinical Professor of Pediatrics
UCSD School of Medicine

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Neurodevelopmental Outcome of Extremely Preterm Infants in the SUPPORT trial Early CPAP vs. Surfactant

Presented for the

SUPPORT study group

Eunice Kennedy Shriver NICHD

Neonatal Research Network

Introduction

- Extremely premature infants have high rates of disability including cognitive impairment, neurosensory deficits and cerebral palsy.

- Neonatal complications (e.g., IVH, PVL, NEC, PDA, ROP, BPD) each contribute independently to the adverse neurodevelopmental outcomes of extremely premature infants

- The goals of neonatal interventions are to increase survival, decrease the risk of acute and chronic complications and reduce the risk of adverse neurodevelopmental outcomes

h1

Respiratory Interventions

- Surfactant treatment reduces the rates of death and BPD
- Reducing mortality without increasing adverse complications (e.g., IVH, PVL, PDA, ROP, BPD) is the goal of respiratory interventions.
- Multiple RCTs have failed to demonstrate consistent superiority of any respiratory intervention (e.g. HFOV, HFJV, iNO) over conventional ventilation in neurodevelopmental outcome

Slide 3

h1

higginsr, 9/27/2011

SUPPORT Trial

- Randomized 24-27 week newborns (N=1316) to treatment in the delivery room with CPAP vs. intubation and surfactant administration

- After adjustment for gestational age, center, familial clustering there was no difference in the **composite primary outcome of death or BPD** at 36 weeks post-menstrual age (PMA).

- Early CPAP is an alternative to immediate intubation and surfactant administration.

SUPPORT Study Group. **NEJM** 2010; 362:1970-9

SUPPORT Trial

- Infants treated with CPAP had significantly
  - fewer days of mechanical ventilation among survivors
    [25 vs. 28 days, -3.0 (-5.6 to 0.3) p=0.03]
  - increased survival without need for HFOV or CV at 7 days
    [55% vs. 49%, RR 1.14 (1.03 to 1.25) p=0.01]
  - less need for postnatal steroids
    [7% vs. 13%, RR 0.57 (0.41-0.78) p=0.001]

- Infants treated with CPAP showed a trend towards decreased death by 36 wks PMA (14.2 vs. 17.5%, p=0.09)

SUPPORT Study Group. NEJM 2010; 362:1970-9

Hypothesis

- Compared to immediate intubation and surfactant administration, early CPAP decreases the **composite outcome of mortality or neurodevelopmental impairment** at 18-22 months corrected age.

SUPPORT trial: Methods

- Enrollment criteria:
  - EGA 24 0/7 to 27 6/7 weeks (best obstetrical estimate)
  - no known malformation
  - decision for full resuscitation
  - consent obtained before delivery

- Inborn at one of the 20 US NICHD Neonatal Research Network centers

- Randomization in the delivery room to either early CPAP application (CPAP) or intubation with surfactant administration (SURF) within one hour

SUPPORT trial: Methods

- Randomization stratified according to center and gestational age
  - 24 0/7 to 25 6/7 weeks
  - 26 0/6 to 27 6/7 weeks
- Ventilation strategies
  - CPAP arm: limited ventilation
  - Surfactant arm: conventional ventilation
- Using a 2X2 factorial design infants were also randomly assigned to lower (85-89%) vs. higher (91-95%) target ranges of oxygen saturation

SUPPORT trial: Methods

- Sample size:
  - based on NRN neurodevelopmental outcome data (birth yr 2000)
  - powered to detect a difference of 10% for primary outcome at 18-22 months corrected age

- Approved by the IRB of each participating institution and RTI International

SUPPORT trial: Data collection and analyses

- Demographic, neonatal and neurodevelopmental outcome data were collected and entered in standardized forms which were transmitted to, stored and analyzed by Research Triangle Institute International

- Analyses:
  - Intention to treat
  - Adjustment for gestational age stratum, center, familial clustering
  - Relative risks and 95% CI for categorical variables were estimated using robust Poisson regression in a generalized-estimating-equation model; adjusted means and 95% CI for continuous variables were estimated using linear mixed models
  - Significant if 2-sided $p < 0.05$

SUPPORT trial: Neurodevelopmental Follow-up

- Comprehensive, standardized physical, neurologic (Amiel-Tison) and developmental (BSID-III) evaluations performed at 18-22 months corrected age by annually certified examiners

Primary composite outcome

Death or neurodevelopmental impairment (NDI)

Neurodevelopmental Impairment (NDI)

- **NDI defined as having any of the following:**
  - Cognitive composite score < 70 (BSID-III)
  - Gross Motor Function Classification System Score ≥ 2
  - Moderate/severe cerebral palsy (CP)
  - Hearing impairment with or without amplification
  - Blind in both eyes (vision < 20/200)

Results and Conclusions

To be presented at

Hot Topics 2011

From: Vaucher, Yvonne
To: Higgins, Rosemary (NIH/NICHD) [E]; Myriam Peralta, M.D.; "Wally Carlo, M.D."; Finer, Neil; kurt.schibler@cchmc.org; "mcw3@cwru.edu"; Roger Faix; Laptook, Abbot; Bradley Yoder; "Das, Abhik"; Gantz, Marie; "Nancy Newman"; Rich, Wade
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: SUPPORT OXIMETRY abstract draft
Date: Friday, September 30, 2011 3:03:52 PM
Attachments: SUPPORTOXimeter Abstract093011YEV.docx

Looks good. A few edits.

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, September 30, 2011 5:28 AM
To: Myriam Peralta, M.D.; 'Wally Carlo, M.D.'; Finer, Neil; Vaucher, Yvonne; kurt.schibler@cchmc.org; 'mcw3@cwru.edu'; Roger Faix; Laptook, Abbot; Bradley Yoder; 'Das, Abhik'; Gantz, Marie; 'Nancy Newman'; Rich, Wade
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: SUPPORT OXIMETRY abstract draft
Importance: High

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Thanks
Rose

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To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Wally Carlo, M.D.
Subject: abstract draft

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First Author: Myriam Peralta-Carcelen **Filename:** 750268
Responsible Author: Myriam Peralta-Carcelen
Presenting Author: Myriam Peralta-Carcelen
Contact Person: Myriam Peralta-Carcelen

2012 Pediatric Academic Societies' Annual Meeting

Subspecialty: Not yet indicated
Theme: Not yet indicated

Contact Author: Myriam Peralta-Carcelen
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Responsible Author Declaration: As the responsible author, I confirm that the individual listed as the sponsor has been contacted and given the opportunity to review the abstract and has subsequently agreed to sponsor this abstract.

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The presenting author is member of these Alliance Societies:
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Questionnaire Information

Eastern Society for Pediatric Research: Not yet indicated
Pediatric Hospital Medicine: Not yet indicated
Research Type: Not yet indicated
Presentation Sabbath Conflict on:
APA Special Interest Groups, Committees or Regions: Not yet indicated

Awards Applied for:

No awards selected

Sponsor Information

You must indicate to which meeting(s) you would like to submit your abstract on the Questionnaire

Title: Neurodevelopmental Outcome of Extremely Preterm Infants in a trial of Different Oxygen Saturation Targets

Myriam Peralta-Carcelen[UAB] and SUPPORT Group[NICHD]. [1]Pediatrics, UAB, Birmingham, United States.

Background: The previous SUPPORT multicenter randomized controlled trial showed the benefits of lower oxygen saturation targets on extremely preterm infants in reducing retinopathy of prematurity however higher oxygen saturation targets increased survival by discharge.

Objective: To evaluate the long term neurodevelopmental effects of different oxygen saturation target levels. We hypothesized that relative lower oxygen saturation levels will be associated with lower death or neurodevelopmental impairment at 18 to 22 months of age.

Design/Methods: 1316 infants 24 to 27 weeks gestation were enrolled in the SUPPORT trial. Infants were randomized to higher (91 to 95%) or lower oxygen saturation targets (85 to 89%) starting at birth and up to 36 weeks corrected age. Infants were randomized within each center by gestational age strata group (24 0/7-25 6/7 and 26 0/7 - 27 6/7 wks). The primary outcome was a composite of death or neurodevelopmental impairment at 18 to 22 months of age. Neurodevelopmental impairment was defined as a cognitive composite score of Bayley Scales of Infant Development 3rd edition < 70, motor score less than 70, modified Gross Motor function classification system > 1, presence of moderate to severe cerebral palsy, permanent hearing loss or bilateral blindness. Analyses were adjusted for gestational age strata group, center and familial clustering.

Results: Primary outcome data was available for 93.8% of enrolled infants (1234/1316). 93.6% of survivors were evaluated at 18-22 months adjusted age. [table 1]

Conclusions: Among extremely preterm infants exposed to different levels of oxygen saturation targets there is increased mortality in the lower oxygen saturation group and no difference in neurodevelopmental impairment at 18 to 22 months of age.

Characteristic	Low SpO2 n=654	High SpO2 n=662	Relative risk (95% CI)	Adjusted p value
Death or NDI	185/612 (30.2%)	171/622 (27.5%)	1.12 (0.94, 1.32)	0.2098
Death by 18-22m	140/633 (30.2%)	118/648 (18.2%)	1.25 (1, 1.55)	0.0462
NDI	45/472 (9.5%)	53/504 (10.5%)	0.87 (0.6, 1.28)	0.492
CP mod/severe	20/479 (4.2%)	20/511 (4.5%)	1 (0.54, 1.83)	0.9971
Blindness both eyes	5/479 (1%)	6/511 (1.2%)	0.9 (0.28, 2.9)	0.8636
Blind one eye	5/479 (1%)	8/511 (1.6%)	0.67 (0.22, 2.02)	0.4784

Other Previews:

Abstract Disclosure Info: [Disclosures]

[Print]

Title: Neurodevelopmental Outcome of Extremely Preterm Infants in a trial of Different Oxygen Saturation Targets

Myriam Peralta-Carcelen[UAB] and SUPPORT Group[NICHD]. [1]Pediatrics, UAB, Birmingham, United States.

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Death by 18-22m	140/633 (30.2%)	118/648 (18.2%)	1.25 (1, 1.55)	0.046~~2~~
NDI	45/472 (9.5%)	53/504 (10.5%)	0.87 (0.6, 1.28)	0.49~~2~~
CP mod/severe	20/479 (4.2%)	20/511 (4.5%)	1 (0.54, 1.83)	0.997~~1~~
Blindness both eyes	5/479 (1%)	6/511 (1.2%)	0.9 (0.28, 2.9)	0.86~~36~~
Blind one eye	5/479 (1%)	8/511 (1.6%)	0.67 (0.22, 2.02)	0.48~~784~~

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Vaucher, Yvonne"
Cc: "Wally Carlo"
Subject: FW: SUPPORT OXIMETRY abstract draft
Date: Friday, September 30, 2011 2:48:00 PM

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301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Walsh, Michele [mailto:Michele.Walsh@UHhospitals.org]
Sent: Friday, September 30, 2011 2:45 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT OXIMETRY abstract draft

This one looks superb.

Michele Walsh, MD

Chief, Division of Neonatology

216.844.3759

It's not what you look at that matters, it's what you see. Thoreau

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, September 30, 2011 8:28 AM
To: Myriam Peralta, M.D.; 'Wally Carlo, M.D.'; 'Finer, Neil'; 'Vaucher, Yvonne'; kurt.schibler@cchmc.org; 'mcw3@cwru.edu'; Roger Faix; Laptook, Abbot; Bradley Yoder; 'Das, Abhik'; Gantz, Marie; 'Nancy Newman'; Rich, Wade
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: SUPPORT OXIMETRY abstract draft
Importance: High

Here is the SUPPORT OXIMETRY PAS abstract- please send comments to Myriam Peralta by October 7.

Thanks
Rose

From: Myriam Peralta, M.D. [mailto:MPeralta@peds.uab.edu]
Sent: Thursday, September 29, 2011 8:24 PM

To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Wally Carlo, M.D.
Subject: abstract draft

Draft Preview of Abstract #750268
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First Author: Myriam Peralta-Carcelen **Filename:** 750268
Responsible Author: Myriam Peralta-Carcelen
Presenting Author: Myriam Peralta-Carcelen
Contact Person: Myriam Peralta-Carcelen

2012 Pediatric Academic Societies' Annual Meeting

Subspecialty: Not yet indicated
Theme: Not yet indicated

Contact Author: Myriam Peralta-Carcelen
Department/Institution/Address: 1600 7th Avenue South, Birmingham, United States
Phone: 205=939-9585 **Fax:** **E-mail:** mperalta@peds.uab.edu

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Phone: 205-939-9585 **Fax:**
Responsible Author E-mail: mperalta@peds.uab.edu
Responsible Author Declaration: As the responsible author, I confirm that the individual listed as the sponsor has been contacted and given the opportunity to review the abstract and has subsequently agreed to sponsor this abstract.

Presenting Author: Myriam Peralta-Carcelen
Department/Institution/Address:
Phone: **Fax:**
Presenting Author E-mail: mperalta@peds.uab.edu
The presenting author is member of these Alliance Societies:
Is Presenting Author a Trainee? No, Not a Trainee
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Questionnaire Information

Eastern Society for Pediatric Research: Not yet indicated
Pediatric Hospital Medicine: Not yet indicated
Research Type: Not yet indicated
Presentation Sabbath Conflict on:
APA Special Interest Groups, Committees or Regions: Not yet indicated

Awards Applied for:

No awards selected

Sponsor Information

You must indicate to which meeting(s) you would like to submit your abstract on the Questionnaire

Title: Neurodevelopmental Outcome of Extremely Preterm Infants in a trial of Different Oxygen Saturation Targets

Myriam Peralta-Carcelen[UAB] and SUPPORT Group[NICHD]. [1]Pediatrics, UAB, Birmingham, United States.

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Blind one eye	5/479 (1%)	8/511 (1.6%)	0.67 (0.22, 2.02)	0.4784

Other Previews:

Abstract Disclosure Info: [Disclosures]

[Print]

From: Walsh, Michele
To: Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo; Finer, Neil; kurt.schibler@cchmc.org; mcw3@cwru.edu; Roger Faix; Bradley Yoder; Laptook, Abbot; Das, Abhik; Gantz, Marie; Nancy Newman; Rich, Wade; Vaucher, Yvonne; Myriam Peralta, M.D.
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: Finer PAS abstract
Date: Friday, September 30, 2011 2:41:26 PM

Neil; Thanks for tackling this!
1. The methods don't seem to be pertinent to the data presented. No neuro outcome?
2. I find the abbreviation EPS- unclear: is there another way to say this. Not intuitive: perhaps 24/25w
3. Results: realize this is complex to present. Table is very helpful, I get lost between what I think is
The overall analysis, and the sub analysis. I have highlighted below where I begin to lose it completely.
I can not follow the results cited clearly in the table.
3. I find the conclusions to be unclear:
The first sentence seems to contradict the last sentence.

: **Overall,** The lowest death rate was seen in the CPAP infants treated with a high SpO2 approach, supporting the use of a higher SpO2 approach. However in the 24/25w strats death/ROP was significantly lower in the low SpO2. In addition the other large randomized trials comparing SpO2 ranges did not randomize infants to a respiratory support strategy and their preliminary results support a higher mortality in the Low SpO2 range infamnts. (*This doesn't seem to belong here.*) For extremely immature infants a strategy of early CPAP with a limited ventilator approach combined with a lower SpO2 target may be optimal. While unlikely (*why?*) , further trials should evaluate this approach

Are we prepared to contradict the conclusions of the main trial on the basis of a sub-analysis?
Even though prespecified?
I think we need to be very very cautious here.

Michele Walsh, MD
Chief, Division of Neonatology
216.844.3759

It's not what you look at that matters, it's what you see. Thoreau

---

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, September 30, 2011 10:21 AM
To: Wally Carlo; 'Finer, Neil'; kurt.schibler@cchmc.org; 'mcw3@cwru.edu'; Roger Faix; Bradley Yoder; Laptook, Abbot; 'Das, Abhik'; Gantz, Marie; 'Nancy Newman'; Rich, Wade; 'Vaucher, Yvonne'; Myriam Peralta, M.D.
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW:

HI,
Here is a secondary SUPPORT analysis. Please send Neil comments by the end of next week. We have a SUPPORT call set up on 10/11 at noon and will discuss.

Thanks
Rose

Rosemary D. Higgins, MD
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From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Friday, September 30, 2011 9:58 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Wally Carlo
Subject:

HI Rose
Can you circulate this to the SUPPORT Subcommittee for their review and then can we have a call to discuss
Ita about 95% full
Thanks
Neil

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Draft Preview of Abstract #750127
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First Author: Neil N Finer, MD **Filename:** 750127
Responsible Author: Neil N Finer, MD
Presenting Author: Neil N Finer, MD
Contact Person: Neil N Finer, MD

2012 PAS Annual Meeting

Subspecialty: Neonatology - General
Theme: Neonatal - Patient-Oriented Research

Contact Author: Neil N Finer, MD
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Responsible Author E-mail: nfiner@ucsd.edu
Responsible Author Declaration: As the responsible author, I confirm that the individual listed as the sponsor has been contacted and given the opportunity to review the abstract and has subsequently agreed to sponsor this abstract.

Presenting Author: Neil N Finer, MD
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The presenting author is member of these Alliance Societies:
Is Presenting Author a Trainee? No, Not a Trainee
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QUESTIONNAIRE INFORMATION
Eastern Society for Pediatric Research: No, Do not consider this abstract for the Eastern SPR
Pediatric Hospital Medicine: No, Do not consider this abstract for presentation at the Pediatric Hospital Medicine, July 19-21, 2012
Research Type: Clinical
Presentation Sabbath Conflict on: N/A
APA Special Interest Groups, Committees or Regions: None

AWARDS APPLIED FOR:
No awards selected

SPONSOR INFORMATION
Sponsoring Member for PAS/ASPR abstract:
Sponsor Name: Neil Norman Finer
Email: nfiner@ucsd.edu
Is the Sponsor an Author? Yes
Sponsoring Societies:
Society for Pediatric Research

Title: Early CPAP Versus Surfactant: The Effect Of A Lower SpO2 Range: Secondary Outcomes Of The SUPPORT Trial.

Neil N Finer, MD[UCSD], Waldemar Carlo, MD[University of A] and Support Group[NICHD 1]. [1]Neonatology, Pediatrics, University California San Diego, San Diego, Ca, 92103, United States.

Background: The SUPPORT Trial prospectively compared early CPAP and a limited ventilator strategy to early surfactant and also randomized all infants to a lower (85-89%) versus a higher (91-95%) SpO2 range from 2 hours of birth.(NEJM 2010) The results demonstrated a significant reduction in death for infants who were randomized to CPAP in the extremely premature strata (EPS, 24 to 25 wk, 23.9% vs 32.1%, p=0.028).Infants randomized to the lower SpO2 range had less ROP (8.6% vs 17.9%, p=0.001) and increased death (19.9% vs 16.2%, p=0.04).A prespecified secondary outcome for the SUPPORT Trial was that infants randomized to CPAP and a low SpO2 strategy would have a lower rate of death/ROP. There was no overall interaction between the respiratory arms and the SpO2 ranges. We did not initially evaluate the gestational age strata for such an interaction.

Objective: This study evaluated the effect of the SpO2 range on the outcomes for infants in the 2 gestational age strata, 24-25 wks, and 26-27 weeks

Design/Methods: The surviving infants were assessed at 18 to 22 months for full neurodevelopmental evaluation, which included hearing, vision, and mental and motor outcomes using the Bayley 3. Tests for interaction were adjusted for GA center and family clustering.

Results: There were 1316 infants randomized in the SUPPORT Trial and deaths prior to discharge, (16.4% vs 19.6%), and follow-up (18.4% vs 21.9%) Overall?? ROP rates among survivors (13.1% vs 13.7%) were not different between CPAP and Surf. ROP was less frequent in the EPS, (22.2% vs 31.6%, p=0.04)whereas ROP was greater in CPAP infants in the 26-27 wh strata (7.3% vs 3.6% p=0.04) ***this is very confusing to me.***. Death at follow-up for the EPS infants remained significantly lower for the CPAP infants (26.4% vs 35.5%, p=0.019). For the overall study and for the 26-27 wk strata there were no significant intercations between SpO2 group and the intervention groups for death/ROP or death/NDI. There was a significant interaction between SpO2 low vs high and CPAP vs Surf in the EPS, the p value for the interaction between CPAP/surfactant and SpO2 was .05. ROP was significantly lower for those randomized to CPAP vs. surf in the Low SpO2 target group (p=.01) but not those in the High SpO2 group (p=.71). For the outcome of death or ROP, while no interaction was seen in the overall study, the EPS infants in the Low SpO2 strata had a lower rate of ROP/death (p=.001), such differences were not seen in the High SpO2 group (p=.2)

Death/ROP for 24-25 wk Strata and 26-27 wk Strata - Low vs High SpO2

SpO2 Range	CPAP/Surf	Death - (24-25)	ROP - (24-25)	Death/ROP - (24-25)	Death - (26-27)	ROP - (26-27)	Death/ROP (26-27)
Low	CPAP	37/142 (26%)	11/95 (12%)	48/132 (36%)*	25/194(13%)	8/153(5%)	33/176(19%)
	Surf	48/134 (36%)	21/76 (28%)	69/124 (56%)*	20/184(11%)	1/151(1%)	21/171(12%)
High	CPAP	31/143 (22%)	33/103 (32%)	64/134 (48%)	15/185(9%)	15/160(9%)	31/176(18%)
	Surf	42/146 (29%)	33/95 (35%)	75/137 (55%)	18/189(10%)	10/141(7%)	28/189(17%)

* p = 0.001

There was no differences in death/NDI comparing SPO2 strategy overall or for either strata.

Conclusions: The lowest death rate was seen in the CPAP infants treated with a high SpO2 approach, supporting the use of a higher SpO2 approach. However death and ROP were significantly lower in the low SpO2 arm in the EPS. In addition the other large randomized trials comparing SpO2 ranges did not randomize infants to a respiratory support strategy and their preliminary results support a higher mortality in the Low SpO2 range infamnts. For extremely immature infants a strategy of early CPAP with a limited ventilator approach combined with a lower SpO2 target may be optimal. While unlikely, further trials should evaluate this approach

Other Previews:
Abstract Disclosure Info:

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From: Walsh, Michele
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Finer abstract
Date: Friday, September 30, 2011 2:41:21 PM

HI Rose: Im really concerned about the SUPPORT subanalysis.
Can the data on which this is based be shared prior to the call?

Michele
email: michele.walsh@cwru.edu
Phone: (216) 844-3387
Fax: (216) 844-3380

From: Juliann Di Fiore
To: Finer, Neil
Cc: Michele Walsh; Richard Martin; Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade; Wally Carlo; Wrage, Lisa Ann
Subject: Re: Final Version IH events and O2 target range
Date: Thursday, September 29, 2011 3:00:44 PM

Hi Neil,

The text regarding event severity and duration refers to Figure 3. Does that help or is it still not clear?
I will change the wording regarding the trials.
Pertaining to interpretation of the results, this study speaks to timing and patterns of IH. We are currently working on another manuscript in a comparable infant cohort not enrolled in the SUPPORT trial and we are seeing IH patterns associated with ROP that are different to what we are seeing in this cohort. So, the bottom line is that, I believe, it is not just the # of IH but at what age they occur and the timing between events that matter.

Julie

On 9/29/2011 12:36 PM, Finer, Neil wrote:

> Hi Julie
> Nice work as always
> I have been traveling without internet and am late getting back to you
> I think the manuscript reads well
> I have just a few questions – what do you mean by severity worsened – how low where the SpO2 values and for how long
> Could you calculate the duration of SpO2 below 80% < 70% and where these different between low and high groups in this small cohort?
> In the discussion you say 2 clinical trials have demonstrated increased death in the low SpO2 arms
> This is technically not correct – the second paper- really a letter to NEJM describes the results of 4 trails including SUPPORT, of which 2 were stopped before completion
> UK and Aust BOOST2 -- New Zealand was completed
> You may want to change the wording
> I am personally not clear how to interpret the results of this study
> Thanks for a really complete and well written manuscript
> Good luck
> Neil
>
> **From:** Juliann Di Fiore [mailto:jmd3@case.edu]
> **Sent:** Thursday, September 29, 2011 6:33 AM
> **To:** Michele Walsh; Richard Martin; Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; Rich, Wade; Wally Carlo; Wrage, Lisa Ann
> **Subject:** Final Version IH events and O2 target range
>
> Hi Everyone,
>
> Thanks for all of your comments. Attached is the final version of the *Low O2 Saturation Target Range .....and IH* paper along with the authorship form. Please

fill it out and fax it back to me at (216) 844-3380. (with a cover letter to my attention).

Take Care,

Julie

--
Juliann Di Fiore
Research Engineer
Case Western Reserve University
Rainbow Babies & Children's Hospital
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by law.

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Vaucher, Yvonne"
Subject: RE: SUPPORT PAS CPAP abstract
Date: Thursday, September 29, 2011 2:13:00 PM

Take
Me off – save the space – everyone can be on the paper. If you can keep you, Peralta, Carlo, Finer and Gantz, that would be great. If they don't all fit, we will re-discuss.

Thanks for all the effort!

Rose

Rosemary D. Higgins, MD
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From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]
Sent: Thursday, September 29, 2011 2:12 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: SUPPORT PAS CPAP abstract

Rose,

Could you look at the authors section and advise me how to list/arrange /change it?

Thanks.

Yvonne

Yvonne E. Vaucher, M.D., M.P.H.
Division of Neonatal/Perinatal Medicine
Clinical Professor of Pediatrics
UCSD School of Medicine

tele: 619-543-3759
FAX: 619-543-3812

From: Vaucher, Yvonne
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: SUPPORT PAS CPAP abstract
Date: Thursday, September 29, 2011 2:11:38 PM
Attachments: PAS 2012SUPPORTCPAPAbstract09292011 AD_MG_WC_RH_YV ver3.0.docx

Rose,

Could you look at the authors section and advise me how to list/arrange /change it?

Thanks.

Yvonne

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PAS 2012 Abstract

Title: Neurodevelopmental Outcome after Early CPAP versus Intubation with Surfactant Administration in Extremely Preterm Infants Enrolled in the SUPPORT Trial

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Background: The recent multicenter SUPPORT randomized, controlled trial demonstrated that initial treatment with early, non-invasive CPAP is an alternative to early surfactant administration after intubation and is associated with similar rates of death or BPD in infants born at 24 to 27 weeks gestation.

Objective: We hypothesized that, compared to treatment with surfactant administration after intubation, treatment with early CPAP would decrease the composite outcome of mortality or neurodevelopmental impairment by 18-22 months corrected age.

Design/Methods: The SUPPORT trial enrolled 1316 infants, 24 to 27 weeks gestation, who were randomized to receive either CPAP in the delivery room with limited ventilation as needed (CPAP) or intubation with surfactant administration within one hour after birth (SURF). Infants were randomized within each center by two gestational age strata (24 0/7-25 6/7 and 26 0/7-27 6/7 weeks). A standardized neurodevelopmental assessment was performed on survivors at 18-22 months corrected age. The primary composite outcome was death or neurodevelopmental impairment (NDI) which included at least one of the following: Bayley Scales of Infant Development, 3rd ed., cognitive composite score < 70, Gross Motor Function Classification score of ≥2, moderate/severe cerebral palsy, bilateral blindness or permanent hearing impairment. Results were adjusted for gestational age stratum, center and familial clustering.

Results: Death or NDI was determined for 1234/1316 (93.8%) of infants enrolled in SUPPORT; 990 children were evaluated at 18-22 months corrected age. Death or NDI occurred in 27.9% (173/621) of the CPAP and in 29.9% (183/613) of the SURF infants (p=0.39). Rates of death (CPAP-18.4 vs. SURF-21.9%, p=0.10), and outcomes among survivors, including NDI alone (CPAP-10.9 vs. SURF 9.1%, p=0.44), cognitive score < 70 (CPAP-7.2 vs. SURF-7.6%, p=0.84), moderate/severe cerebral palsy (CPAP-4.1 vs. SURF-4.0%, p=0.82), blindness (CPAP-0.8 vs. SURF 1.5%, p=0.31), and permanent hearing impairment (CPAP-3.3 vs. SURF-1.5%, p=0.06) were similar in both treatment arms. Except for fewer deaths in the most immature GA stratum [CPAP-26.4% (73/277) vs. SURF-35.5% (97/273), aRR 0.73 (0.57,0.96), p=0.022], there were no statistically significant differences in these outcomes between CPAP and SURF groups within each GA stratum.

Conclusions: In extremely premature children born at 24-27 weeks gestation, there were no significant differences in death or neurodevelopmental outcomes at 18-22months corrected age between those treated with early CPAP in the delivery room and those treated with intubation and surfactant administration.

From: Vaucher, Yvonne
To: Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie; Das, Abhik; Wally Carlo, M.D.; Finer, Neil
Cc: Vaucher, Yvonne
Subject: PAS 2012 SUPPORT CPAP abstract
Date: Thursday, September 29, 2011 2:06:57 PM
Attachments: PAS 2012SUPPORTCPAPAbstract09292011 AD MG WC RH YV ver3.0.docx

All,

Here is the latest version incorporating everyone's recommendations (I think).

Yvonne

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From: Karen Osborne RN
To: Poundstone, Margaret; Higgins, Rosemary (NIH/NICHD) [E]
Cc: "Auman, Jeanette O."
Subject: RE: SUPPORT TRACKING
Date: Thursday, September 29, 2011 1:13:47 PM

Margaret,
If there's anything we can do here at UT to help with contacting the family please let me know. We're only too glad to help!

Thanks,
Karen

From: Poundstone, Margaret [mailto:Margaret.Poundstone@uth.tmc.edu]
Sent: Thursday, September 29, 2011 10:46 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Karen Osborne RN
Cc: 'Auman, Jeanette O.'
Subject: RE: SUPPORT TRACKING

Got it, thanks!

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, September 29, 2011 11:44 AM
To: Poundstone, Margaret; 'Karen Osborne RN'
Cc: 'Auman, Jeanette O.'
Subject: RE: SUPPORT TRACKING

The Site that originally recruited the patient into the trial gets the % credit for those seen at the FU time points. The site actually doing the work gets the financial reimbursement for tracking and/or seeing the patient.

Thanks
Rose

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301-496-5575
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higginsr@mail.nih.gov

From: Poundstone, Margaret [mailto:Margaret.Poundstone@uth.tmc.edu]
Sent: Thursday, September 29, 2011 12:43 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; 'Karen Osborne RN'
Cc: 'Auman, Jeanette O.'
Subject: RE: SUPPORT TRACKING

OK so (b)(6) is now responsible for this patient and (b)(6) (b)(6)

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, September 29, 2011 11:40 AM
To: Poundstone, Margaret; 'Karen Osborne RN'
Cc: 'Auman, Jeanette O.'
Subject: RE: SUPPORT TRACKING

If you are able to contact the family, please try. I think the (b)(6) (b)(6)

Thanks
Rose

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301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Poundstone, Margaret [mailto:Margaret.Poundstone@uth.tmc.edu]
Sent: Thursday, September 29, 2011 12:39 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; 'Karen Osborne RN'
Cc: 'Auman, Jeanette O.'
Subject: RE: SUPPORT TRACKING

Rose,

I don't understand the question. The (b)(6) for his 18 month visit. I have all contact information for the family. I just need to know who should be tracking the patient for the extended SUPPORT, and who is responsible for entering the 3-4 yr tracking form.

--Margaret

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]

Sent: Thursday, September 29, 2011 7:38 AM
To: 'Karen Osborne RN'; Poundstone, Margaret
Cc: 'Auman, Jeanette O.'
Subject: RE: SUPPORT TRACKING

Karen and Margaret –
Do we have permission from the family to exchange the information obtained from (b)(6) (b)(6)
Thanks
Rose

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higginsr@mail.nih.gov

From: Karen Osborne RN [mailto:Karen.Osborne@hsc.utah.edu]
Sent: Wednesday, September 28, 2011 8:05 PM
To: Poundstone, Margaret; Higgins, Rosemary (NIH/NICHD) [E]
Cc: 'Auman, Jeanette O.'
Subject: RE: SUPPORT TRACKING

Hi Margaret,
I responded to Rose's query and let her know that this patient now lives in (b)(6) so their closest NRN F/U unit would be (b)(6) I assumed (maybe incorrectly?) that (b)(6) (b)(6) for school age Follow Up as this is what we've done with patients transferred to us from other sites, and that we have transferred to other sites. Please let me know if this is incorrect!

Thanks,
Karen

From: Poundstone, Margaret [mailto:Margaret.Poundstone@uth.tmc.edu]
Sent: Wednesday, September 28, 2011 2:21 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Karen Osborne RN
Cc: 'Auman, Jeanette O.'
Subject: RE: SUPPORT TRACKING

Any update on this? Should I be (b)(6) I've attached Karen on this email so she can be in the loop.

Layne

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, September 14, 2011 3:58 PM
To: Poundstone, Margaret; Kennedy, Kathleen A; Evans, Patricia W; Mcdavid, Georgia E
Cc: 'Auman, Jeanette O.'
Subject: RE: SUPPORT TRACKING

Were the patients (b)(6) told they could have their school age FU in (b)(6) Do they live close – these patients have also gone in a query to (b)(6) but I haven't heard back from them.

Jenny – can you check to see why the other child isn't showing up I the DMS>

Thanks
Rose

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From: Poundstone, Margaret [mailto:Margaret.Poundstone@uth.tmc.edu]
Sent: Wednesday, September 14, 2011 4:56 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Kennedy, Kathleen A; Evans, Patricia W; Mcdavid, Georgia E
Cc: 'Auman, Jeanette O.'
Subject: RE: SUPPORT TRACKING

Rose,

(b)(6) was entered at the end of (b)(6) so they will show up completed for next month's report.

As for (b)(6) am I supposed to be tracking him? He was originally (b)(6) we just saw him for his 18 month visit.

Layne

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, September 14, 2011 2:42 PM
To: Kennedy, Kathleen A; Poundstone, Margaret; Evans, Patricia W; Mcdavid, Georgia E
Cc: 'Auman, Jeanette O.'
Subject: SUPPORT TRACKING

Hi,

We are missing tracking outcome form(s) for SUPPORT NEUROIMAGING tracking. Please let us know how you are doing.

Thanks for all the effort!!
Rose

CENTER	NETWORK	FOLNUM	_3YRDT	_4YRDT	Follow-up CENTER	NICU CENTER	
18	79821	1981	10/2/2009	10/2/2010	.	.	
18	80631	1887	2/3/2010	2/3/2011	.	.	
18	81851	1922	7/22/2010	7/22/2011	.	.	
25	66611	1127	11/16/2009	11/16/2010		18	25
18	66611	2075	11/16/2009	11/16/2010		18	25

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301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "mcw3@cwru.edu"; "jmd3@case.edu"
Subject: FW: Final Version IH events and O2 target range
Date: Thursday, September 29, 2011 11:44:00 AM
Attachments: fig1.jpg
fig2.jpg
fig3.jpg
fig4.jpg
Final Draft effect of low target range on the incidence of IH.docx
NRN Authorship Responsibility[1]-1.pdf
Table.docx

FYI

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From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Thursday, September 29, 2011 11:44 AM
To: 'Truog, William (MD)'; Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: Final Version IH events and O2 target range

For publications subcommittee review, boilerplate and NICHD clearance.

Thanks
Rose

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From: Juliann Di Fiore [mailto:jmd3@case.edu]
Sent: Thursday, September 29, 2011 9:33 AM

To: Michele Walsh; Richard Martin; Higgins, Rosemary (NIH/NICHD) [E]; Neil Finer; Wade Rich; Wally Carlo; Wrage, Lisa Ann
Subject: Final Version IH events and O2 target range

Hi Everyone,

Thanks for all of your comments. Attached is the final version of the *Low O2 Saturation Target Range .....and IH* paper along with the authorship form. Please fill it out and fax it back to me at (216) 844-3380. (with a cover letter to my attention).

Take Care,

Julie

--
Juliann Di Fiore
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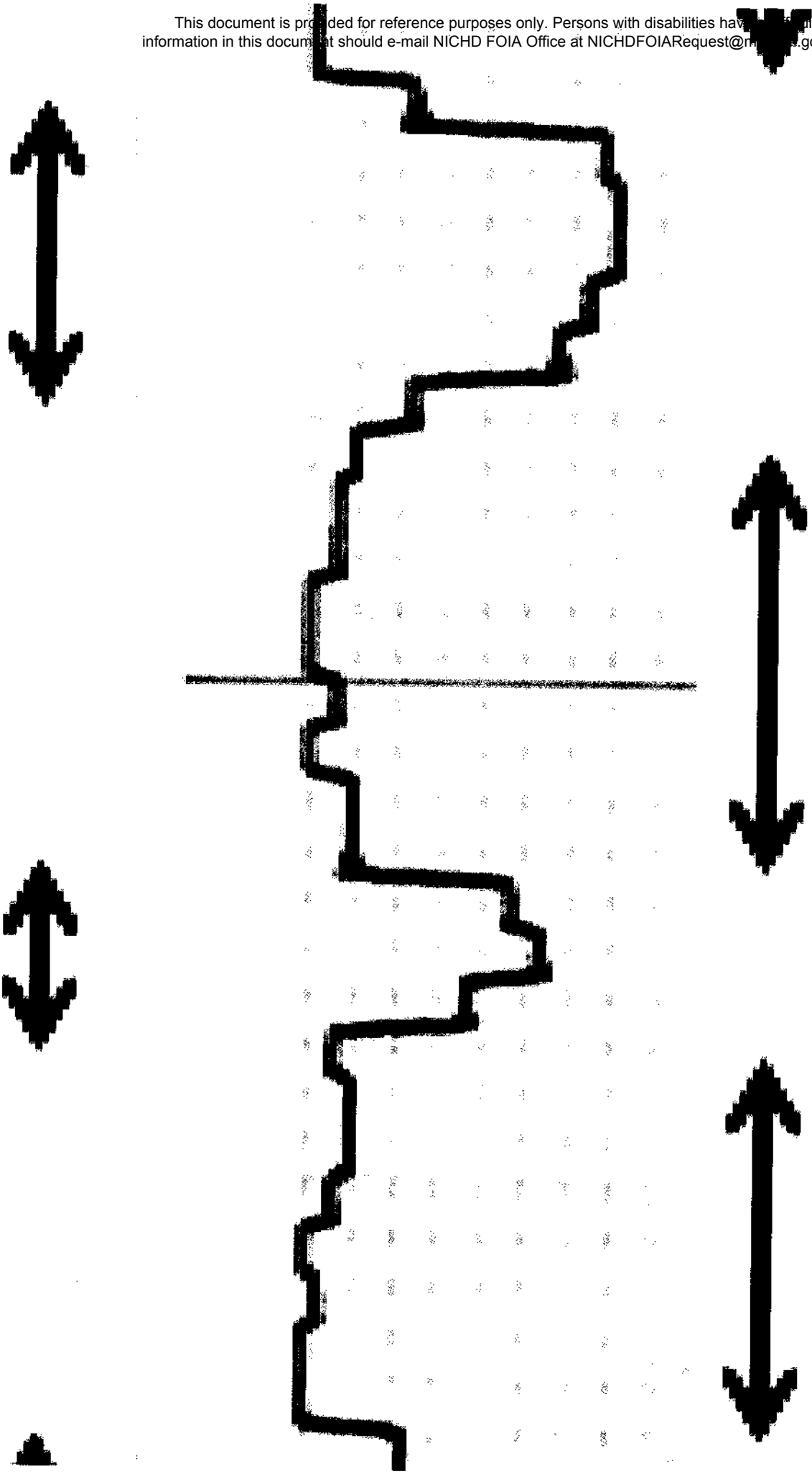

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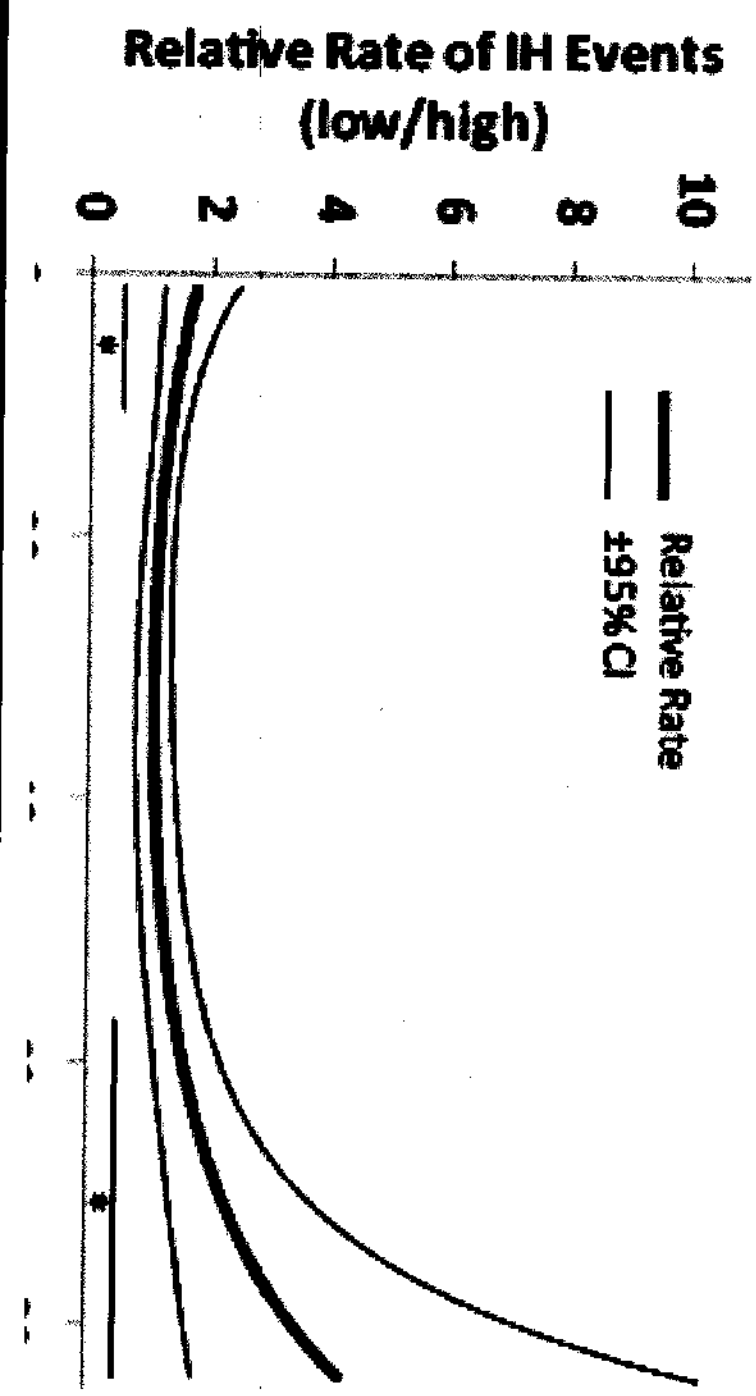
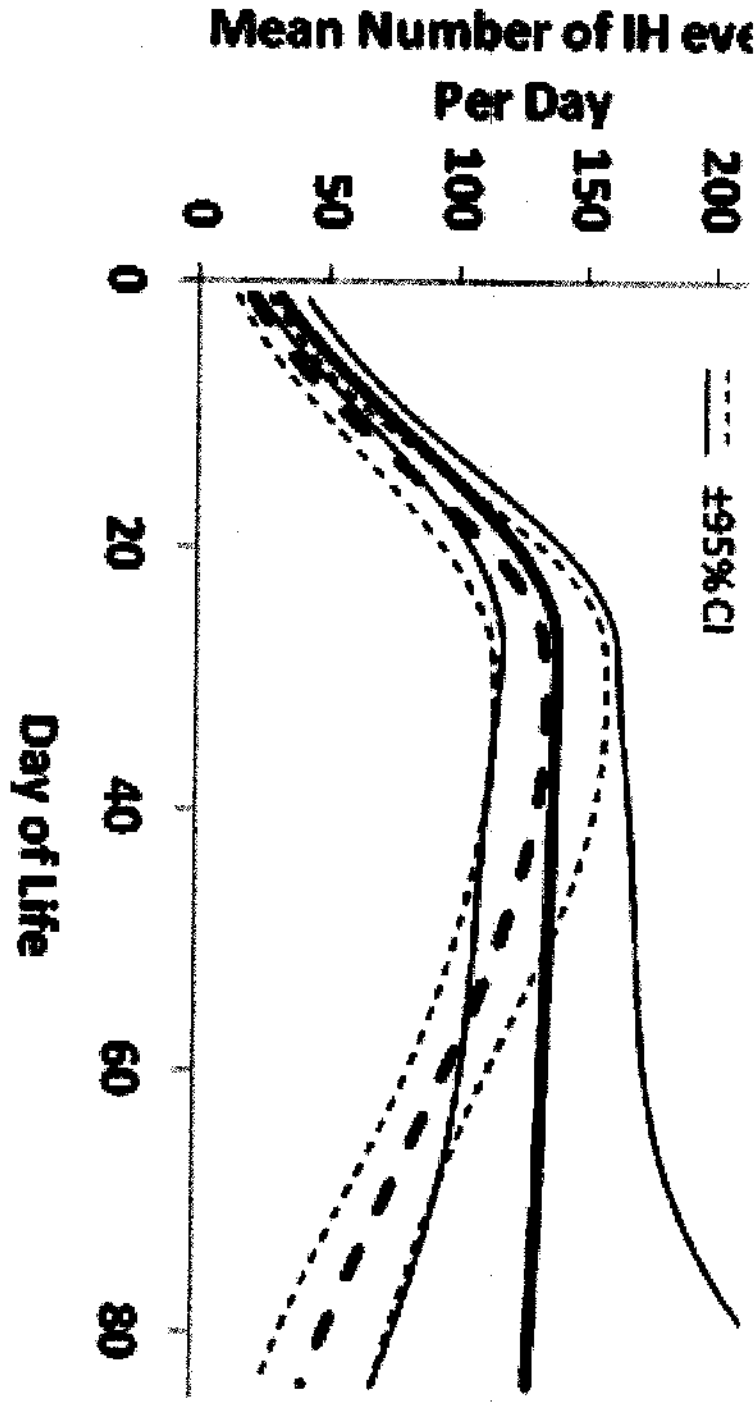
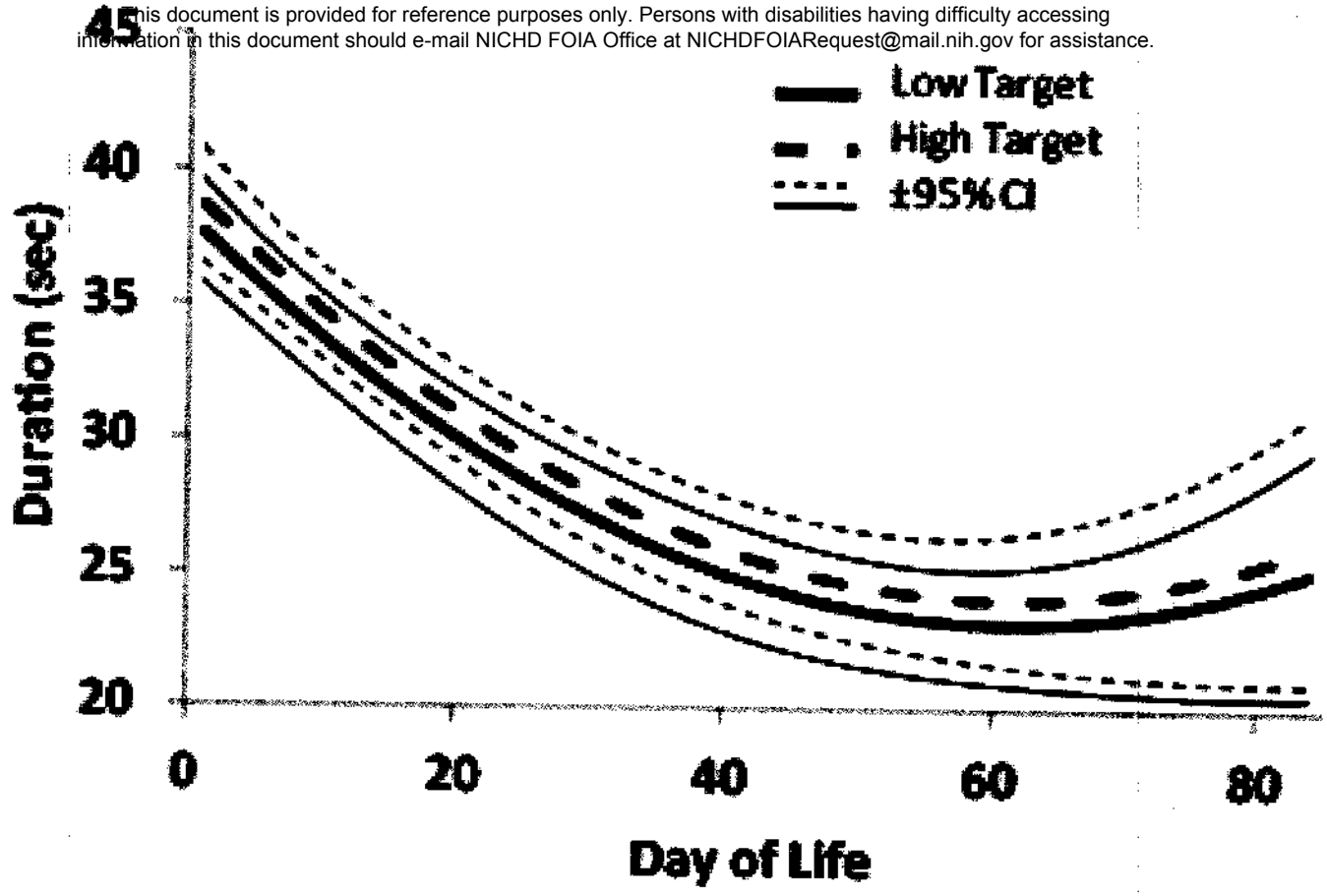
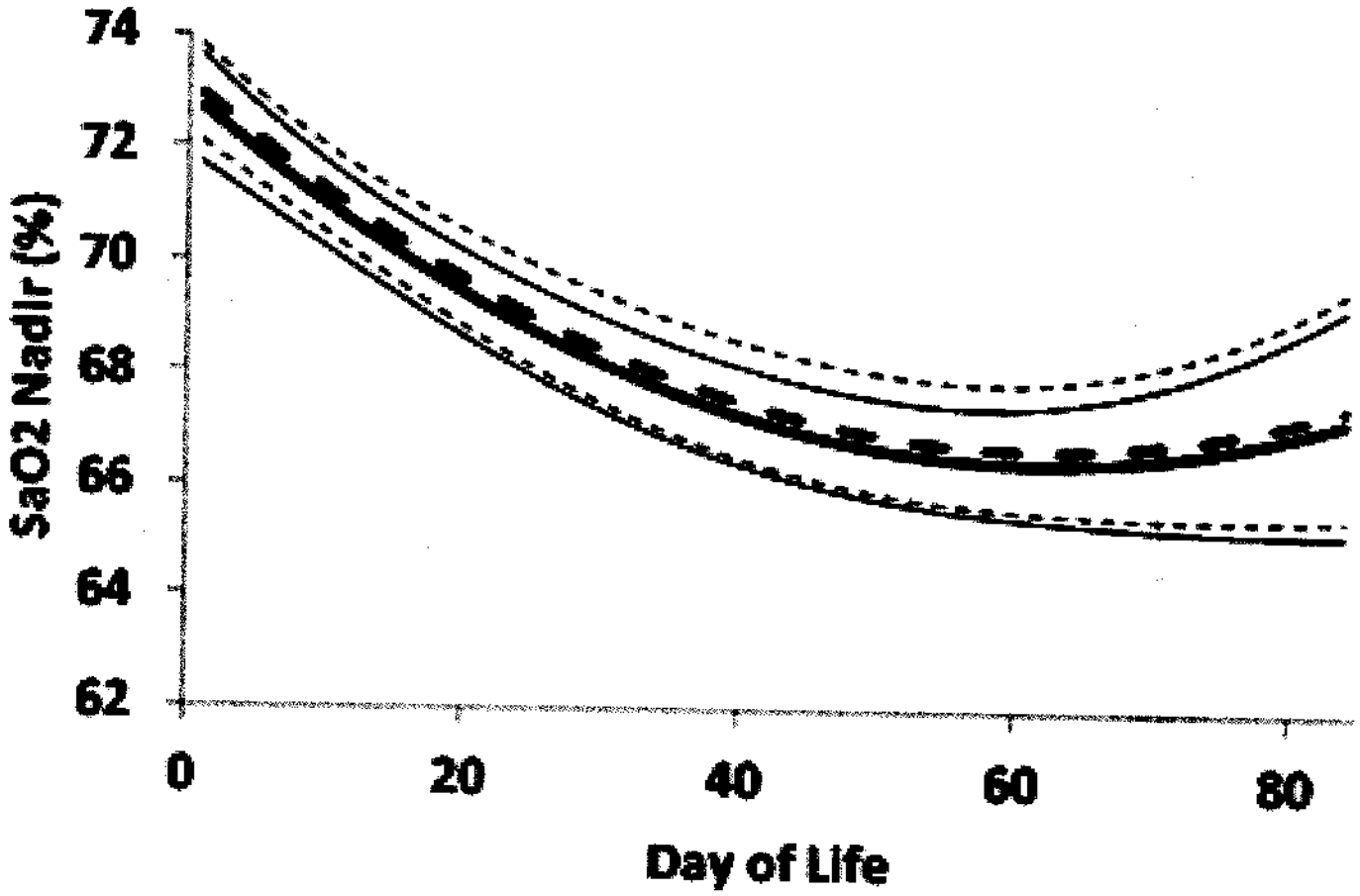
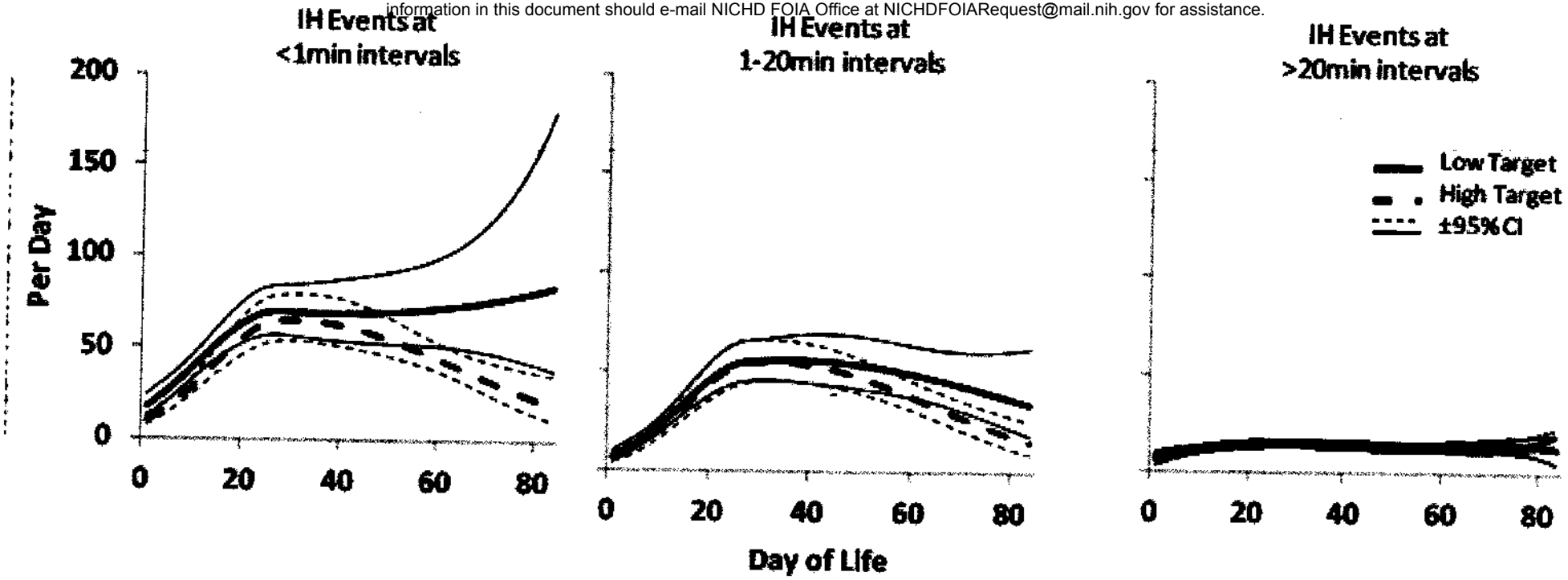








A



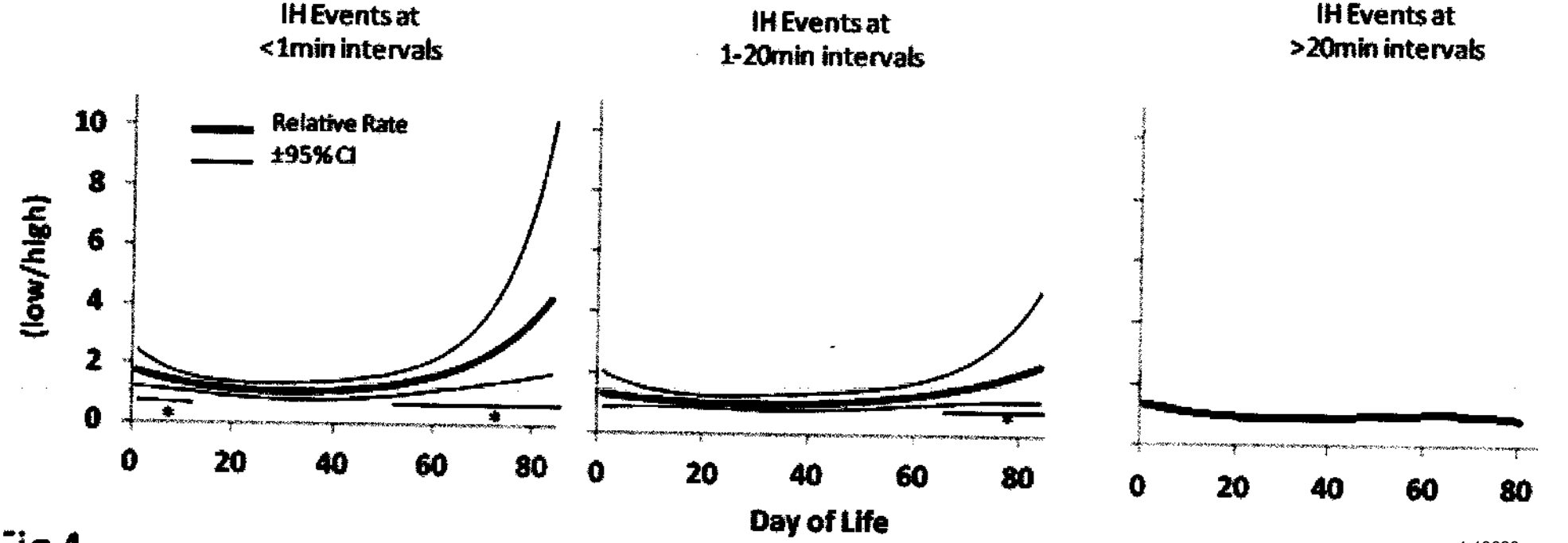


Fig 4

4-13628

Low oxygen saturation target range is associated with increased incidence of intermittent hypoxemia

Juliann M. Di Fiore, BSEE[1], Michele Walsh, MD[1], Lisa Wrage, MPH[2], Wade Rich, RRT[3], Neil Finer,MD[3], Waldemar A. Carlo, MD[4], Richard J. Martin, MD[1], and the SUPPORT Study Group of the NICHD Neonatal Network

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[2] RTI International Research Triangle Park, North Carolina

[3] Division of Neonatology, Department of Pediatrics, University of California, San Diego, California

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Financial Assistance:

Supported by the National Institute of Child Health and Human Development Cooperative Multicenter Neonatal Research Network (Grant HD021364-23)

4-13629

Juliann Di Fiore wrote the first draft of the manuscript.

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Keywords: preterm infants, hypoxia

The authors state no conflicts of interest

Abstract:

Objective:

To test the hypothesis that preterm infants randomized to a low versus high O_2 saturation target range have a higher incidence of intermittent hypoxemia (IH).

Study Design:

A subcohort of 115 preterm infants with high resolution pulse oximetry (2 sec sample rate and 2 sec averaging) enrolled in the SUPPORT trial, were randomized to low (85-89%) or high (90-95%) oxygen saturation target ranges. Oxygen saturation was monitored until 36wks postmenstrual age or until the infant was breathing room air without respiratory support for ≥72hrs.

Results:

The low target oxygen saturation group had a higher rate of IH events prior to 12 days and beyond 57 days of life ($p<0.05$). The duration shortened ($p<0.01$) and the severity increased ($p<0.01$) with increasing postnatal age with no differences between target saturation groups. The higher rate of IH events in the low target group was associated with a time interval between events of <1min.

Conclusion:

A low oxygen saturation target was associated with an increased rate of IH events that was dependent on postnatal age. The duration and severity of events was comparable between target groups. Further investigation is needed to assess the role of IH events and their timing on neonatal morbidity.

Background:

There is increasing evidence that intermittent hypoxemia (IH) may be associated with perinatal morbidity. In newborn animal models, administered IH paradigms have been shown to impair dopamine signaling[1], contribute to neurological handicap[1-3], and exacerbate retinal neovascularization[4]. Although it is known that IH events are common in preterm infants, data relating to the prevalence of these events have been limited. Pulse oximetry technology has enabled non-invasive recording of spontaneous intermittent hypoxemic events in preterm infants over prolonged periods of time. This has allowed for accurate documentation of the temporal changes in the incidence of IH events over the first few months of life. Recent data in preterm infants of 24-28 weeks gestation have shown relatively few IH events over the first week of life, a progressive increase in events until approximately 5 weeks post natal age followed by a decline thereafter[5]. In contrast, a sustained increase in the incidence of IH events was shown to be associated with severe retinopathy of prematurity (ROP)[5].

The multi-center SUPPORT trial examined the role of high versus low O_2 saturation target ranges on retinopathy of prematurity. Following randomization to lower (85-89%) or higher (91-95%) oxygen saturation target ranges, infants in the lower target group were found to have a lower incidence of severe ROP. This was associated with an unexpected higher mortality in infants targeted to low baseline oxygen saturation[6,7]. The effect of these oxygenation target ranges on the occurrence of intermittent hypoxemia (IH) is unknown. Therefore, the purpose of

this study was to test the hypothesis that infants randomized to a low compared to high O_2 saturation target range would have an increase in the incidence of intermittent hypoxemia.

Methods:

The study population included a subcohort of 115 preterm infants enrolled in the multi-center SUPPORT study from two sites: Rainbow Babies & Children's Hospital, Cleveland, and University of California San Diego. The study was approved by the Institutional Review Board at each site and by RTI Internatinal, which is the independent data coordinating center for the Neonatal Research Network. Written informed consent was obtained from the parent or guardian of each child before delivery.

Enrollment criteria included infants who were born between 24 weeks 0 days and 27 weeks 6 days of gestation for whom a decision had been made to provide full resuscitation. Infants born in other hospitals and those known to have major anomalies were excluded. Using a permuted-block randomization design, with stratification according to study center and gestational age (24 weeks 0 days to 25 weeks 6 days or 26 weeks 0 days to 27 weeks 6 days), infants were randomized to a low (85-89%) or high (91-95%) oxygen saturation target group within two hours of birth. Infants who were part of multiple births were randomly assigned to the same group.

Electronically altered pulse oximeters (Radical SET, Masimo, Irvine, CA) were used to blind the staff to the randomization group. The clinical staff was instructed to maintain infants in an oxygen saturation range of 88-92%, with altered monitors showing target levels of 88-92% with a maximum offset of 3%. For example a displayed value of 90% corresponded to an actual

oxygen saturation value of 87% in the low target group and 93% in the high target group[6]. Actual values were displayed when the oxygen saturation values were <85% or ≥95% in both treatment groups.

Targeting of oxygen saturation and high resolution (2 sec sample rate and 2 sec time averaging) data collection began within 2 hours after birth and continued until 36 wks postmenstrual age or until the infant was breathing air without respiratory support, defined as high frequency ventilation, conventional mechanical ventilation, Nasal SIMV, CPAP, nasal cannula, or hood, for ≥ 72 hours, whichever came first. Infants weaned to room air but re-administered supplemental oxygen were returned to the original randomization group. As previous studies have suggested that the timing and pattern of IH events may play a role in morbidity[4], the number of IH (≤80% for ≥10sec and ≤3min), the duration of IH events and the time interval between events (Figure 1) were calculated for each day.

Demographic and clinical variables were compared between high and low SaO_2 target groups using Generalized Estimating Equation (GEE) regression models, adjusting for SUPPORT study stratification variables site and gestational age group, where appropriate. Due to sparse data a Fisher's exact test was used to evaluate death prior to 36 weeks. To model counts of intermittent hypoxemia events a GEE regression model assuming a negative binomial distribution was used. The GEE model provided robust standard error estimates which take into account the correlations within multiple-birth clusters, including correlations between repeated measurements. Variables included in the final model for intermittent hypoxemia events were treatment group, linear and quadratic terms for postnatal age, interactions

between treatment group and postnatal age variables, gestational age group, and respiratory support (yes or no, per day). An additional quadratic term which allowed the quadratic relationship of postnatal age and IH events to vary before and after 28 days was also included; this spline regression approach provided a better fit than simpler models[8]. Also considered were interactions between GA group and postnatal age, between GA group and treatment group, and between the additional quadratic term and treatment group, as well as variables for gender, race, center, CPAP versus surfactant treatment group (an additional randomization of the main SUPPORT trial protocol), and caffeine use. Each of these additional terms considered were not significant and thus were not included in the final model. Similar models for the <1 minute and 1 to 20 minute time interval between event subsets of intermittent hypoxemia events were run with the same final set of variables as the overall model. Additional models were run to model duration and severity of intermittent hypoxemia events. These models included variables for treatment group, linear and quadratic terms for age, gestational age group, and center.

Results:

The population of 115 infants had a mean birth weight of 830±181gm and gestational age of 25.8 ±1.0wks. There were 50 infants in the gestational age range of 24 to 25 weeks 6 days and 65 infants in the gestational age range of 26 to 27 weeks 6 days range. Fifty one percent of the infants were male and 35% were non-Hispanic white. Characteristics of infants randomized to the high (n=62) and low (n=53) target group are presented in Table 1. There were no differences between groups in birth weight, gestational age, incidence of bronchopulmonary

dysplasia or severe retinopathy of prematurity (ROP). In this small cohort, there was a trend towards a higher mortality in the low target group (p=.09), mirroring the finding in the main trial, but this did not reach statistical significance. Caffeine use occurred on approximately 80% of days during the monitoring period in both infant groups. Infants in the low target group received respiratory support for 86% of the monitoring period compared with 92% in the high target group (adjusted RR low versus high target, .93, 95% CI 0.86-0.99, p=.029).

The model based estimates showed an increase in IH events over the first 3 weeks of life in both infant groups followed by a decrease in IH events in the high target group compared to a plateau in the low target group (Figure 2a). The adjusted relative rate of IH events (RR), (the ratio of the adjusted mean number of IH events in the low target group/ the adjusted mean number of IH events in the high target group, per day), revealed a significantly higher rate of IH events prior to 12 days, and beyond 57 days of age in the low target group ($p<0.05$, Figure 2b). Higher rates of IH events were associated with lower gestational age, (adjusted RR 1.24, 95% CI 1.01-1.5, p=.032), and respiratory support, adjusted (RR 1.85, 95% CI 1.52-2.49, $p<.0001$).

The mean duration of IH events shortened ($p<.01$) and the severity worsened ($p<.01$) with increasing day of life (Figure 3). However, there were no differences in duration or severity between infant groups.

There was a wide range in the time interval between sequential IH events both within and between infants. To address the association between the timing of IH events and the oxygen saturation target group, the number of IH events was documented for three time interval

ranges 1) <1 minute, 2) 1-20 minutes and, 3) >20 minutes between IH events. The highest incidence of events occurred with a time interval between events of <1 min, followed by a time interval of 1-20 minutes between events. There were relatively few IH events that occurred with a time interval of >20 minutes between events (Figure 4). IH events occurring with a time interval between events of <1 minute were associated with a significantly higher relative rate of IH events in the low target group at <15 and >54 days of life ($p<0.05$). After 65 days of life, there were a significantly higher number of IH events with a time interval of 1-20 minutes between events in the low target group ($p<.05$) with no differences between groups for IH events with a time interval of >20 minutes between events.

The above analysis examined the characteristics of IH events with increasing postnatal age. In addition, the effect of post menstrual age on the occurrence of IH events was also assessed. While the number of IH events decreased with postmenstrual age, the number of IH events was not significantly different by treatment group, at any post menstrual age.

Discussion:

This study showed an association between a low oxygen saturation target range and an escalation in the incidence of IH events that changed with increasing day of life. Infants in the low target range had a higher number of IH events during the first two weeks and after 57 days of life but followed a similar trajectory as the high saturation target group between these time periods. IH events became shorter and more severe with increasing post natal age, however, there were no differences in duration or severity between infant groups. Lastly, the higher

incidence of IH events in the low target group was predominantly associated with a time interval between IH events of <1minute in duration.

Intermittent hypoxemic events are ubiquitous in preterm infants, both ventilated[9,10] and spontaneously breathing[11]. Nonetheless, the precise incidence of these events has not been well documented. This is important in order to address their potential pathophysiological consequences. This study showed a higher incidence of IH in the low target group which is consistent with McEvoy et al[12] showing a relationship between oxygen levels and IH in former preterm infants with chronic lung disease. Although these events are thought to be a consequence of immature respiratory control, this study and previous data in a similar infant cohort[5] suggest that other developmental phases may be contributing. There were relatively few IH events during the 1st week of life regardless of the level of oxygen exposure. This early phase was followed by a linear increase in IH events through weeks two to three of life that was not affected by the oxygen saturation target range. The third phase of IH events began after four weeks of age with a plateau in IH events. After this time group differences emerge with a decline in events in the high target group while remaining relatively constant in the low target group. This may be due to a low baseline alveolar PO2 in the low target group which, in a model based analysis, has been shown to cause early onset of desaturation[13]. It remains unclear why this low reserve did not consistently result in a higher number of IH events at earlier post natal ages.

Caffeine use and respiratory support are the main clinical therapies for apnea and accompanying desaturation. Although caffeine has been shown to decrease apnea[14],

interestingly, it has been shown to have little if any effect on desaturation episodes[15] although this is based on a single small series. Both infant groups spent a high percentage of the monitoring period on caffeine therapy with no significant difference in caffeine usage between infant groups, therefore, it is unlikely that caffeine use affected the results of this study. Respiratory support was associated with a higher incidence of IH events within each treatment group. However, with the high target group having a higher percentage of time receiving respiratory support, this cannot explain the increased incidence of IH in the low target infants.

Both groups showed a comparable decrease in duration and increase in severity of IH events during the first four weeks of life with no further changes throughout the study monitoring period. Previous data have suggested that infants with increased spontaneous apnea have an augmented ventilatory response to acute hypoxia[16]. Thus, although infants in the low target group may have been more susceptible to initiation of a hypoxic event, they may have been able to rally a compensatory ventilatory response and recover as well as infants in the high target group.

The lower incidence of severe ROP in the main trial is in contrast to our previous findings of an association between IH and severe ROP[5]. This discrepancy may relate to the fact that the initial hyperoxia induced inhibition of angiogenesis is enhanced in the high oxygen target group at a time when IH episodes are not prominent. Time interval between IH events may also play a role. Previous data in animal models have suggested that the timing of patterns of IH events are important and may affect morbidity. Clustered patterns of IH events have been shown to be associated with enhanced retinal neovascularization when compared to equally dispersed

patterns[4]. This may be mediated by a hypoxia induced factor (HIF)[17] or reactive oxygen species (ROS) cascade known to occur in response to IH[18]. In response to hypoxic exposure, measurements of reactive oxygen species have shown an increase in superoxide anion concentration during the recovery phase, with a delayed response of several minutes[19]. Current preterm infant data from our group suggest that ROP is associated with a time interval between events of 1-20 min potentially consistent with the ability to initiate an increase in reactive oxygen species (ROS). In contrast, the higher number of IH events in the low target group predominantly occurred with a time interval between events of less than 1 minute which may have limited the ROS response. The effect of the duration of recovery time between IH events on the resultant oxidative stress response has yet to be determined and merits further investigation.

There are limited data on the long term consequences of IH events in preterm infants[20]. A history of apnea of prematurity during hospitalization[21] and cardiorespiratory events in the home[22] have been associated with neurodevelopmental impairment. These studies have focused on apnea rather than the accompanying hypoxemic events. The only study to address the latter issue is the observation that mean oxygen saturation during apnea has been shown to predict motor scores[23]. Further analysis is ongoing to assess the relationship between IH events and neurodevelopmental outcome in this infant cohort.

This study was limited by the known challenge of keeping infants in a designated oxygen saturation target range[24,25]. The main SUPPORT trial revealed overlap in the median level of oxygen saturation between target groups with actual median oxygen saturation levels slightly

higher than targeted levels in both treatment groups[6]. This may have affected the number of IH events as lowering the median baseline saturation and increasing the time in the actual low target level may have resulted in an even higher incidence of IH events. In addition, the data used in this analysis were collected via pulse oximeters which remained in use from birth up to 36 weeks postmenstrual age (PMA), but only during times when the infants were receiving respiratory support and during the three days after respiratory support was discontinued. Thus, data do not exist for time points four or more days after discontinuation of respiratory support, transfer to a non-study hospital, discharge, or 36 weeks PMA (whichever came first). The GEE models used in this analysis assume that any missing data are missing completely at random. This assumption may be violated by these data, because infants who dropped out of the data due to a poor outcome such as death, or a favorable outcome such as discharge or being able to breathe room air without support, are likely to differ from those who remained on respiratory support through 36 weeks PMA. Thus, this should be considered a conditional analysis; that is, it is conditioned upon being alive and on respiratory support, and the results provided by the GEE model for any given point in time should be interpreted as applying only to the subset of infants who were alive and on respiratory support at that time. Lastly, enrollment for this study was limited by the pulse oximeter settings per the main SUPPORT trial protocol. Sites not participating in this ancillary trial had a prolonged averaging time of 16 seconds and a low sample rate of 10 seconds thus potentially limiting the ability to detect IH events with such a low resolution waveform.

In conclusion, a low oxygen saturation target range is associated with an increased incidence of intermittent hypoxemic events that is dependent on postnatal age. These events tend to occur

less than one minute apart but are of comparable duration and severity regardless of level of oxygen exposure. Two clinical trials have now demonstrated an association between low oxygen targets and increased mortality. While the etiology of such a mortality increase is unknown at this time, we speculate that the association between a low oxygen saturation target and increasing incidence of IH might provide insight to unraveling underlying pathophysiology. Further studies are needed to assess the contribution of timing of IH events on neonatal morbidity. We speculate that, to minimize episodes of IH, the optimal O_2 saturation target may need to be adjusted by postnatal age.

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Figure Legends:

Figure 1

A raw SaO2 waveform with the duration of the event and the time interval between events denoted by the arrows.

Figure 2

A) The model based estimates showed an increase in IH events over the first 3 weeks of life in both infant groups followed by a decrease in IH events in the high target group (- - -)compared to a plateau in the low target group (—) . B) The relative rate of IH events (RR), (the ratio of the adjusted mean number of IH events in the low target group/ the adjusted mean number of IH events in the high target group, per day), revealed a higher rate of IH events from <12 days, and >57 days of age in the low target group (* $p<0.05$).

Figure 3

IH event duration decreased and severity worsened with increasing postnatal age in both the low and high target groups with no differences between groups.

Figure 4

A) The number of IH events was documented for three time interval ranges; <1 minute, 1-20 minutes and, >20 minutes between IH events. The highest incidence of events occurred with a time interval between events of <1 min, followed by a time interval of 1-20 minutes. There were relatively few IH events that occurred with a time interval of >20 minutes between

events. B) IH events occurring with a time interval between events of <1 minute were associated with a significantly higher relative rate of IH events in the low target group at <15 and >54 days of life ($p<0.05$). IH events occurring with a time interval of 1-20 minutes between event had a higher relative rate of IH events >65 days of life ($p<0.05$). IH events occurring >20 min apart were comparable between target groups with a relative rate of approximately one throughout the monitoring period.

NICHD Neonatal Research Network

Authorship Responsibility (adapted from ICMJE and JAMA)

Prior to submission of a Network manuscript for NICHD clearance, each author should meet all criteria below (A, B and C) and should indicate general and specific contributions by reading criteria A, B and C and checking the appropriate boxes.

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   ☐ administrative, technical, or material support
   ☐ supervision
   ☐ no additional contributions
   ☐ other (specify)
   ☐ or are disclosed in an attachment.

Your Signature _____ Date Signed _____

	Low Target (53)	High Target (62)	p value*
Birth Weight (gm), mean(SD)	855(191)	808(171)	0.47
Gestational Age (wk), mean(SD)	25.8(1.1)	25.8(1.0)	0.76
BPD (O_2 @ 36 wk), n/N(%)	14/50(28%)	24/62(39%)	0.45
Death before 36 wk PMA, n(%)	3 (6%)	0 (0%)	0.09
Severe ROP, n/N(%)	8/49(16%)	13/58(22%)	0.41
Caffeine, n/N(%) of monitored days	2245/2838 (79%)	2757/3417 (81%)	0.87
Respiratory Support[t], n/N(%) of monitored days	2451/2849 (86%)	3085/3369 (92%)	0.03

*results adjusted for stratification factors (study center and gestational age group) and familial clustering except for gestational age (adjusted for study center and familial clustering) and death (Fisher's exact test).

[t]High frequency jet ventilation, CPAP, conventional ventilation, nasal cannula, Nasal SIMV, or hood

From: Walsh, Michele
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Final Version IH events and O2 target range
Date: Thursday, September 29, 2011 11:45:06 AM

Thought so: thanks.

Michele Walsh, MD
Chief, Division of Neonatology
216.844.3759

It's not what you look at that matters, it's what you see. Thoreau

---

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, September 29, 2011 11:44 AM
To: Walsh, Michele
Subject: RE: Final Version IH events and O2 target range

This should go to pubs sub as it was partially nrn funded.
Also, I should not be an author.

I will send it on and copy you and Julie

Rose

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higginsr@mail.nih.gov

From: Walsh, Michele [mailto:Michele.Walsh@UHhospitals.org]
Sent: Thursday, September 29, 2011 11:43 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Final Version IH events and O2 target range

It would be great if Stephanie can do.
Does this need pub sub review before submission-
Or not bc only 2 centers.

Michele Walsh, MD
Chief, Division of Neonatology
216.844.3759

It's not what you look at that matters, it's what you see. Thoreau

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From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, September 29, 2011 11:41 AM
To: 'jmd3@case.edu'; Walsh, Michele
Subject: RE: Final Version IH events and O2 target range

Just faxed the form

Did we do a boilerplate for you or do I need to get Stephanie to do it?
Thanks
Rose

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From: Juliann Di Fiore [mailto:jmd3@case.edu]
Sent: Thursday, September 29, 2011 9:33 AM
To: Michele Walsh; Richard Martin; Higgins, Rosemary (NIH/NICHD) [E]; Neil Finer; Wade Rich; Wally Carlo; Wrage, Lisa Ann
Subject: Final Version IH events and O2 target range

Hi Everyone,

Thanks for all of your comments. Attached is the final version of the *Low O2 Saturation Target Range .....and IH* paper along with the authorship form. Please fill it out and fax it back to me at (216) 844-3380. (with a cover letter to my attention).

Take Care,

Julie

--
Juliann Di Fiore
Research Engineer
Case Western Reserve University

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From: Juliann Di Fiore
To: Michele Walsh; Richard Martin; Higgins, Rosemary (NIH/NICHD) [E]; Neil Finer; Wade Rich; Wally Carlo; Wrage, Lisa Ann
Subject: Final Version IH events and O2 target range
Date: Thursday, September 29, 2011 9:36:40 AM
Attachments: fig1.jpg
fig2.jpg
fig3.jpg
fig4.jpg
Final Draft_ effect of low target range on the incidence of IH.docx
NRN Authorship Responsibility[1]-1.pdf
Table.docx

Hi Everyone,

Thanks for all of your comments. Attached is the final version of the *Low O2 Saturation Target Range .....and IH* paper along with the authorship form. Please fill it out and fax it back to me at (216) 844-3380. (with a cover letter to my attention).

Take Care,

Julie

--
Juliann Di Fiore
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From: Walsh, Michele
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Hot Topics slides for Oximetry arm FU from SUPPORT Trial
Date: Wednesday, September 28, 2011 4:41:50 PM

Yes: good news yesterday ☺

Michele Walsh, MD
Chief, Division of Neonatology
216.844.3759

It's not what you look at that matters, it's what you see. Thoreau

---

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, September 28, 2011 3:42 PM
To: Walsh, Michele
Subject: RE: Hot Topics slides for Oximetry arm FU from SUPPORT Trial

Will let them know

Glad to see you answering email!!
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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From: Walsh, Michele [mailto:Michele.Walsh@UHhospitals.org]
Sent: Wednesday, September 28, 2011 3:42 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Hot Topics slides for Oximetry arm FU from SUPPORT Trial

Initial slides have typos and need to be proof read.

Michele Walsh, MD
Chief, Division of Neonatology
216.844.3759

It's not what you look at that matters, it's what you see. Thoreau

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, September 27, 2011 3:41 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; 'Roger Faix'; 'Richard, MD Ehrenkranz (richard.ehrenkranz@yale.edu)'; 'Frantz, Ivan'; 'Finer, Neil'; 'Vaucher, Yvonne'; 'Michael O`Shea'; 'Bauer, Charles R'; 'Duara, Shahnaz'; 'Gantz, Marie'; 'Rich, Wade'; 'Nancy Newman'; 'Bradley Yoder'; (suhas.kallapur@cchmc.org); Abbot Laptook (alaptook@wihri.org); Abhik Das (adas@rti.org); Ambal (ambal@uab.edu); Anna Maria Hibbs (AnnaMaria.hibbs@cwru.edu); barbara_stoll@oz.ped.emory.edu; bpoindex@iupui.edu; carl_dangio@urmc.rochester.edu; Carlton, David P; cotte010@mc.duke.edu; dstevenson@stanford.edu; dwallace@rti.org; Ed Bell (edward-bell@uiowa.edu); goldb008@mc.duke.edu; Greg Sokol (gsokol@iupui.edu); Haresh Kirpalani (KIRPALANIH@email.chop.edu); 'John Barks'; Jon.E.Tyson@uth.tmc.edu; Kennedy, Kathleen A; Krisa Van Meurs (vanmeurs@stanford.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); Kurt Schibler [kurt.schibler@cchmc.org]; Luc Brion (luc.brion@utsouthwestern.edu); Martin Keszler (mkeszler@wihri.org); mcw3@po.cwru.edu; Meena Garg (mgarg@mednet.ucla.edu); Nelin, Leif; Pablo.Sanchez@UTSouthwestern.edu; Polin, Richard; Robin Ohls (rohls@salud.unm.edu); ronnie_guillet@urmc.rochester.edu; Satyan Lakshminrusimha; Schmidt, Barbara (Neonatology); Seetha Shankaran ; Sood, Beena [bsood@med.wayne.edu]; Truog, William (MD); Uday Devaskar (UDEVASKAR@MEDNET.UCLA.EDU); Wally Carlo (wacarlo@uab.edu); (apappas@med.wayne.edu); (EMcGowan@tufts-nemc.org); Acarregui, Michael; Betty Vohr (bvohr@wihri.org); Costello, Frank; golds005@mc.duke.edu; 'ira adams-chapman'; JaFuller@salud. unm. edu (JaFuller@salud.unm.edu); Jean Steichen (steichjj@uc.edu); 'Kim Yolton'; Myriam Peralta-Carcelen (MPeralta@peds.uab.edu); 'Roy Heyne'; 'Susan Hintz'
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: Hot Topics slides for Oximetry arm FU from SUPPORT Trial

Here is the attachment

Thanks
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From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tuesday, September 27, 2011 3:35 PM
To: 'Roger Faix'; 'Richard, MD Ehrenkranz (richard.ehrenkranz@yale.edu)'; 'Frantz, Ivan'; 'Finer, Neil'; 'Vaucher, Yvonne'; 'Michael O`Shea'; 'Bauer, Charles R'; Duara, Shahnaz; 'Gantz, Marie'; 'Rich, Wade'; 'Nancy Newman'; 'Bradley Yoder'; (suhas.kallapur@cchmc.org); Abbot Laptook (alaptook@wihri.org); Abhik Das (adas@rti.org); Ambal (ambal@uab.edu); Anna Maria Hibbs (AnnaMaria.hibbs@cwru.edu); barbara_stoll@oz.ped.emory.edu; bpoindex@iupui.edu; carl_dangio@urmc.rochester.edu; Carlton, David P; cotte010@mc.duke.edu; dstevenson@stanford.edu; dwallace@rti.org; Ed Bell (edward-bell@uiowa.edu); goldb008@mc.duke.edu; Greg Sokol (gsokol@iupui.edu); Haresh Kirpalani

(KIRPALANIH@email.chop.edu); John Barks; Jon.E.Tyson@uth.tmc.edu; Kennedy, Kathleen A; Krisa Van Meurs (vanmeurs@stanford.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); Kurt Schibler [kurt.schibler@cchmc.org]; Luc Brion (luc.brion@utsouthwestern.edu); Martin Keszler (mkeszler@wihri.org); mcw3@po.cwru.edu; Meena Garg (mgarg@mednet.ucla.edu); Nelin, Leif; Pablo.Sanchez@UTSouthwestern.edu; Polin, Richard; Robin Ohls (rohls@salud.unm.edu); ronnie_guillet@urmc.rochester.edu; Satyan Lakshminrusimha; Schmidt, Barbara (Neonatology); Seetha Shankaran ; Sood, Beena [bsood@med.wayne.edu]; Truog, William (MD); Uday Devaskar (UDEVASKAR@MEDNET.UCLA.EDU); Wally Carlo (wacarlo@uab.edu); (apappas@med.wayne.edu); (EMcGowan@tufts-nemc.org); Acarregui, Michael; Betty Vohr (bvohr@wihri.org); drfjcmd@aol.com; golds005@mc.duke.edu; ira adams-chapman; JaFuller@salud. unm. edu (JaFuller@salud.unm.edu); Jean Steichen (steichjj@uc.edu); Kim Yolton; Myriam Peralta-Carcelen (MPeralta@peds.uab.edu); Roy Heyne; Susan Hintz
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: Hot Topics slides for Oximetry arm FU from SUPPORT Trial

Hi

Attached are the draft slides for submission for the HOT OPICS program for the December 2011 meeting.

Please send comments to Myriam Peralta by September 30.

Thanks

Rose

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3701.243 prohibit disclosure of this information without the specific
written consent of the person to whom it pertains, or as otherwise permitted
by law.

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From: Walsh, Michele
To: jmd3@case.edu; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Draft effect of low target range on the incidence of IH_9_14
Date: Wednesday, September 28, 2011 4:40:09 PM
Attachments: NRN Authorship Responsibility[1].pdf

Looks good Julie. If this is final, would send to all authors.
Attached is the authorship form they need to fill out and FAX to you.

Rose: I assume this needs to go to the Pub Sub committee?
If so, can you forward when Julie provides final draft? Tx.

Michele Walsh, MD
Chief, Division of Neonatology
216.844.3759

It's not what you look at that matters, it's what you see. Thoreau

-----Original Message-----
From: Juliann Di Fiore [mailto:jmd3@case.edu]
Sent: Friday, September 16, 2011 12:30 PM
To: Walsh, Michele; Richard Martin; Neil Finer; Wally Carlo; Wade Rich; Wrage, Lisa Ann; Higgins, Rosemary (NIH/NICHD) [E]
Subject: Draft effect of low target range on the incidence of IH_9_14

Hi Everyone,

Here is the next draft of the IH paper for your comments. It has been decided to send it Journal of Pediatrics.

Thanks,

Julie

PS- Could you please send me any financial support and conflict of interest information that is relevant for submitting to the journal? Thanks!

--
Juliann Di Fiore
Research Engineer
Case Western Reserve University
Rainbow Babies& Children's Hospital
Division of Neonatology, room 3100
11100 Euclid Ave
Cleveland, OH 44106
(216) 844-1478
---

addressee.

Federal and Ohio law protect patient medical information, including psychiatric_disorders, (H.I.V) test results, A.I.Ds-related conditions, alcohol, and/or drug_dependence or abuse disclosed in this email. Federal regulation (42 CFR Part 2) and Ohio Revised Code section 5122.31 and 3701.243 prohibit disclosure of this information without the specific written consent of the person to whom it pertains, or as otherwise permitted
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Federal and Ohio law protect patient medical information, including psychiatric_disorders, (H.I.V) test results, A.I.Ds-related conditions, alcohol, and/or drug_dependence or abuse disclosed in this email. Federal regulation (42 CFR Part 2) and Ohio Revised Code section 5122.31 and 3701.243 prohibit disclosure of this information without the specific written consent of the person to whom it pertains, or as otherwise permitted by law.

NICHD Neonatal Research Network

Authorship Responsibility (adapted from ICMJE and JAMA)

Prior to submission of a Network manuscript for NICHD clearance, each author should meet all criteria below (A, B and C) and should indicate general and specific contributions by reading criteria A, B and C and checking the appropriate boxes.

Title of manuscript _____
First author _____

☐ A. I certify that the manuscript represents valid work and that neither this manuscript nor one with substantially similar content under my authorship has been published or is being considered for publication elsewhere. I agree to allow the corresponding author to serve as the primary correspondent with the journal editorial office, to review the edited typescript and proof.

☐ B. I have read and given final approval of the submitted manuscript.

C. To qualify for authorship, you must check at least 1 box for each of the 3 categories of contributions listed below.

I have made substantial contributions to the intellectual content of the paper as described below.

1. (check at least 1 of the 3 below)

   ☐ conception and design
   ☐ acquisition of data
   ☐ analysis and interpretation of data

2. (check at least 1 of 2 below)

   ☐ drafting of the manuscript
   ☐ critical revision of the manuscript for important intellectual content

3. (check at least 1 below)

   ☐ statistical analysis
   ☐ obtaining funding
   ☐ administrative, technical, or material support
   ☐ supervision
   ☐ no additional contributions
   ☐ other (specify)
   ☐ or are disclosed in an attachment.

Your Signature _____ Date Signed _____

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Myriam Peralta, M.D."
Cc: "Wally Carlo, M.D."
Subject: SUPPORT OXIMETRY FOLLOW UP PAPER
Date: Wednesday, September 28, 2011 3:18:00 PM

Hi Myriam,

Please send me the latest version of the SUPPORT FU paper. I know that you have a lot on your plate and we would like to get this finalized. You will be maintained as the first author, but we want to get it to the subcommittee and co-authors asap.

I am happy to discuss.

Thanks

Rose

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Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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higginsr@mail.nih.gov

From: Walsh, Michele
To: Higgins, Rosemary (NIH/NICHD) [E]; suhas.kallapur@cchmc.org; alaptook@wihri.org; adas@rti.org; ambal@uab.edu; AnnaMaria.hibbs@cwru.edu; barbara_stoll@oz.ped.emory.edu; bpoindex@iupui.edu; carl_dangio@urmc.rochester.edu; Carlton, David P; cotte010@mc.duke.edu; dstevenson@stanford.edu; dwallace@rti.org; edward-bell@uiowa.edu; goldb008@mc.duke.edu; gsokol@iupui.edu; KIRPALANIH@email.chop.edu; John Barks; Jon.E.Tyson@uth.tmc.edu; Kennedy, Kathleen A; vanmeurs@stanford.edu; kwatterberg@salud.unm.edu; kurt.schibler@cchmc.org; luc.brion@utsouthwestern.edu; mkeszler@wihri.org; mcw3@po.cwru.edu; mgarg@mednet.ucla.edu; Nelin, Leif; Pablo.Sanchez@UTSouthwestern.edu; Polin, Richard; rohls@salud.unm.edu; ronnie_guillet@urmc.rochester.edu; Satyan Lakshminrusimha; Schmidt, Barbara (Neonatology); Seetha Shankaran ; bsood@med.wayne.edu; Truog, William (MD); UDEVASKAR@MEDNET.UCLA.EDU; wacarlo@uab.edu
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: Safe and Effective Oxygenation in ELBW Infants-June 2011 (2).ppt
Date: Wednesday, September 28, 2011 1:48:56 PM

Yes: he could also site Abbot's paper on targeting saturation during the Benchmarking study.

Michele Walsh, MD
Chief, Division of Neonatology
216.844.3759

It's not what you look at that matters, it's what you see. Thoreau

---

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, September 26, 2011 3:52 PM
To: (suhas.kallapur@cchmc.org); Abbot Laptook (alaptook@wihri.org); Abhik Das (adas@rti.org); Ambal (ambal@uab.edu); Anna Maria Hibbs (AnnaMaria.hibbs@cwru.edu); barbara_stoll@oz.ped.emory.edu; bpoindex@iupui.edu; carl_dangio@urmc.rochester.edu; Carlton, David P; cotte010@mc.duke.edu; dstevenson@stanford.edu; dwallace@rti.org; Ed Bell (edward-bell@uiowa.edu); goldb008@mc.duke.edu; Greg Sokol (gsokol@iupui.edu); Haresh Kirpalani (KIRPALANIH@email.chop.edu); John Barks; Jon.E.Tyson@uth.tmc.edu; Kennedy, Kathleen A; Krisa Van Meurs (vanmeurs@stanford.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); Kurt Schibler [kurt.schibler@cchmc.org]; Luc Brion (luc.brion@utsouthwestern.edu); Martin Keszler (mkeszler@wihri.org); mcw3@po.cwru.edu; Meena Garg (mgarg@mednet.ucla.edu); Nelin, Leif; Pablo.Sanchez@UTSouthwestern.edu; Polin, Richard; Robin Ohls (rohls@salud.unm.edu); ronnie_guillet@urmc.rochester.edu; Satyan Lakshminrusimha; Schmidt, Barbara (Neonatology); Seetha Shankaran ; Sood, Beena [bsood@med.wayne.edu]; Truog, William (MD); Uday Devaskar (UDEVASKAR@MEDNET.UCLA.EDU); Wally Carlo (wacarlo@uab.edu)
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: Safe and Effective Oxygenation in ELBW Infants-June 2011 (2).ppt

Hi,

Dr. Eduardo Bancalari has asked that we share a prior SUPPORT presentation with him so that he can prepare his Hot Topics talk "Oxygen targets: can they be achieved?" Dr. Bancalari will acknowledge the network.

Wally has sent a recent talk that is suitable.

Please send me a yes./No vote by Sept. 30 to share with Eduardo

Just a reminder, Miami did enroll in the SUPPORT Trial as part of their network involvement.

Thanks

Rose

Visit us at www.UHhospitals.org.

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Poindexter, Brenda B"
Subject: RE: Hot Topics slides for Oximetry arm FU from SUPPORT Trial
Date: Wednesday, September 28, 2011 1:37:00 PM

The issue of presenting SUPPORT at Hot Topics was discussed on a steering committee call (June 2011) and at the steering committee in July. The results were preliminary results were presented in July at the SC meeting. The PI's were in favor of presenting the results at Hot Topics. These abstracts will also be submitted for PAS. The CPAP paper is written and with the subcommittee. The oximetry paper is almost done.

You should see both papers shortly.

Thanks for your input
Rose

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From: Poindexter, Brenda B [mailto:bpoindex@iupui.edu]
Sent: Wednesday, September 28, 2011 1:25 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Hot Topics slides for Oximetry arm FU from SUPPORT Trial

Rose,
Can you clarify the last slide? It just says results and conclusions to be presented. Does she mean at Hot Topics or at another meeting (like PAS)? I still feel very uncomfortable having results from our main trials presented first at Hot Topics given the lack of peer review for that meeting – I think it is fine if the results have already been presented at PAS or have already been published. Maybe we discussed this as a Steering Committee and I just don't remember. If she is presenting the primary FU results at Hot Topics, will the PI's have an opportunity to review the results/conclusions prior to the talk in December?
Thanks, Brenda

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, September 27, 2011 3:41 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; 'Roger Faix'; 'Richard, MD Ehrenkranz (richard.ehrenkranz@yale.edu)'; 'Frantz, Ivan'; 'Finer, Neil'; 'Vaucher, Yvonne'; 'Michael O`Shea'; 'Bauer, Charles R'; 'Duara, Shahnaz'; 'Gantz, Marie'; 'Rich, Wade'; 'Nancy Newman'; 'Bradley Yoder';

(suhas.kallapur@cchmc.org); Abbot Laptook (alaptook@wihri.org); Abhik Das (adas@rti.org); Ambal (ambal@uab.edu); Anna Maria Hibbs (AnnaMaria.hibbs@cwru.edu); barbara_stoll@oz.ped.emory.edu; Poindexter, Brenda B; carl_dangio@urmc.rochester.edu; Carlton, David P; cotte010@mc.duke.edu; dstevenson@stanford.edu; dwallace@rti.org; Ed Bell (edward-bell@uiowa.edu); goldb008@mc.duke.edu; Sokol, Gregory M.; Haresh Kirpalani (KIRPALANIH@email.chop.edu); 'John Barks'; Jon.E.Tyson@uth.tmc.edu; Kennedy, Kathleen A; Krisa Van Meurs (vanmeurs@stanford.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); Kurt Schibler [kurt.schibler@cchmc.org]; Luc Brion (luc.brion@utsouthwestern.edu); Martin Keszler (mkeszler@wihri.org); mcw3@po.cwru.edu; Meena Garg (mgarg@mednet.ucla.edu); Nelin, Leif; Pablo.Sanchez@UTSouthwestern.edu; Polin, Richard; Robin Ohls (rohls@salud.unm.edu); ronnie_guillet@urmc.rochester.edu; Satyan Lakshminrusimha; Schmidt, Barbara (Neonatology); Seetha Shankaran ; Sood, Beena [bsood@med.wayne.edu]; Truog, William (MD); Uday Devaskar (UDEVASKAR@MEDNET.UCLA.EDU); Wally Carlo (wacarlo@uab.edu); (apappas@med.wayne.edu); (EMcGowan@tufts-nemc.org); Acarregui, Michael; Betty Vohr (bvohr@wihri.org); (b)(6) @aol.com; golds005@mc.duke.edu; 'ira adams-chapman'; JaFuller@salud.unm. edu (JaFuller@salud.unm.edu); Jean Steichen (steichjj@uc.edu); 'Kim Yolton'; Myriam Peralta-Carcelen (MPeralta@peds.uab.edu); 'Roy Heyne'; 'Susan Hintz'
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: Hot Topics slides for Oximetry arm FU from SUPPORT Trial

Here is the attachment

Thanks
Rose

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301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: Fw: Safe and Effective Oxygenation in ELBW Infants-June 2011 (2).ppt
Date: Wednesday, September 28, 2011 6:19:57 AM

----- Original Message -----
From: Devaskar, Uday <UDevaskar@mednet.ucla.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tue Sep 27 21:21:04 2011
Subject: RE: Safe and Effective Oxygenation in ELBW Infants-June 2011 (2).ppt

yes

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]
Sent: Monday, September 26, 2011 12:51 PM
To: (suhas.kallapur@cchmc.org); Abbot Laptook (alaptook@wihri.org); Abhik Das (adas@rti.org); Ambal (ambal@uab.edu); Anna Maria Hibbs (AnnaMaria.hibbs@cwru.edu); barbara_stoll@oz.ped.emory.edu; bpoindex@iupui.edu; carl_dangio@urmc.rochester.edu; Carlton, David P; cotte010@mc.duke.edu; dstevenson@stanford.edu; dwallace@rti.org; Ed Bell (edward-bell@uiowa.edu); goldb008@mc.duke.edu; Greg Sokol (gsokol@iupui.edu); Haresh Kirpalani (KIRPALANIH@email.chop.edu); John Barks; Jon.E.Tyson@uth.tmc.edu; Kennedy, Kathleen A; Krisa Van Meurs (vanmeurs@stanford.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); Kurt Schibler [kurt.schibler@cchmc.org]; Luc Brion (luc.brion@utsouthwestern.edu); Martin Keszler (mkeszler@wihri.org); mcw3@po.cwru.edu; Garg, Meena; Nelin, Leif; Pablo.Sanchez@UTSouthwestern.edu; Polin, Richard; Robin Ohls (rohls@salud.unm.edu); ronnie_guillet@urmc.rochester.edu; Satyan Lakshminrusimha; Schmidt, Barbara (Neonatology); Seetha Shankaran ; Sood, Beena [bsood@med.wayne.edu]; Truog, William (MD); Devaskar, Uday; Wally Carlo (wacarlo@uab.edu)
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Wally has sent a recent talk that is suitable.
Please send me a yes./No vote by Sept. 30 to share with Eduardo
Just a reminder, Miami did enroll in the SUPPORT Trial as part of their network involvement.

Thanks
Rose

From: Vaucher, Yvonne
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Lastest Hot Topics CPAP slides
Date: Wednesday, September 28, 2011 3:54:56 PM
Attachments: SUPPORT CPAP Hot Topics CPAP slides09282011ver4.0.pptx

Rose,

Here is the latest version taking into account everyone's recommendations.

Yvonne

Yvonne E. Vaucher, M.D., M.P.H.
Division of Neonatal/Perinatal Medicine
Clinical Professor of Pediatrics
UCSD School of Medicine

tele: 619-543-3759
FAX: 619-543-3812

Neurodevelopmental Outcome of Extremely Preterm Infants in the SUPPORT trial Early CPAP vs. Surfactant

Presented for the

SUPPORT study group

Eunice Kennedy Shriver NICHD

Neonatal Research Network

Introduction

- Extremely premature infants have high rates of disability including cognitive impairment, neurosensory deficits and cerebral palsy.

- Neonatal complications (e.g., IVH, PVL, NEC, PDA, ROP, BPD) each contribute independently to the adverse neurodevelopmental outcomes of extremely premature infants

- The goals of neonatal interventions are to increase survival, decrease the risk of acute and chronic complications and reduce the risk of adverse neurodevelopmental outcomes

Respiratory Interventions

- Surfactant treatment reduces the rates of both death and CLD/BPD

- Reducing mortality and the rate of chronic lung disease (BPD) without increasing adverse complications (e.g., IVH, PVL, PDA, ROP) is the goal of respiratory interventions.

- Multiple RCTs have failed to demonstrate consistent superiority of any respiratory intervention (e.g. HFOV, HFJV, iNO) over conventional ventilation in neurodevelopmental outcome

Slide 3

h1

higginsr, 9/27/2011

SUPPORT Trial

- The SUPPORT trial recently demonstrated that early CPAP application in the delivery room and over the first two weeks is an alternative to immediate intubation and surfactant administration.

- After adjustment for gestational age, center, familial clustering there was no difference in the **composite primary outcome of death or BPD** at 36 weeks post-conceptual age (PCA).

SUPPORT Study Group. NEJM 2010; 362:1970-9

SUPPORT Trial

- Infants treated with CPAP had significantly
  - fewer days of mechanical ventilation among survivors (25 vs. 28 days, p=0.03)
  - increased survival without need for HFOV or CV at 7 days (55% vs. 49%, p=0.01)
  - less need for postnatal steroids (7% vs. 13%, p=0.001)

- Infants treated with CPAP showed a trend towards decreased death by 36 wks PCA (14.2 vs. 17.5%, p=0.09)

SUPPORT Study Group. NEJM 2010; 362:1970-9

Objective

- Compare the neurodevelopmental outcome at 18-22 months corrected age for extremely premature infants randomized to the CPAP treatment arm versus the Surfactant treatment arm of the SUPPORT trial.

- Hypothesis: Compared to immediate intubation and surfactant administration, early CPAP decreases the **composite outcome of mortality or neurodevelopmental impairment**.

Methods: SUPPORT RCT

- Enrollment criteria:
  - EGA 24 0/7 to 27 6/7 weeks (best obstetrical estimate)
  - no known malformation
  - decision for full resuscitation
  - consent obtained before delivery
- Inborn at one of the 20 US NICHD Neonatal Research Network centers
- Randomization to either early CPAP application (CPAP) in the delivery room or intubation with surfactant administration (SURF) within one hour

Methods: SUPPORT RCT

- Randomization stratified by center and gestational age group
  - 24 0/7 to 25 6/7 weeks
  - 26 0/6 to 27 6/7 weeks
- Ventilation strategies
  - CPAP arm: limited ventilation
  - Surfactant arm: conventional ventilation
- Using a 2X2 factorial design infants were also randomly assigned to lower (85-89%) vs. higher (91-95%) target ranges of oxygen saturation

Methods (cont'd)

- Sample size:
  - based on NRN neurodevelopmental outcome data (birth yr 2000)
  - powered to detect a difference of 10% for primary outcome at 18-22 months corrected age

- Approved by the IRB of each participating institution and RTI International

Neurodevelopmental Follow-up

- Comprehensive, standardized physical, neurologic (Amiel-Tison) and developmental (BSID-III) evaluations performed at 18-22 months corrected age by annually certified examiners

- Primary composite outcome:

  Death or neurodevelopmental impairment (NDI)

Components of Neurodevelopmental Impairment (NDI)

- NDI defined as having at least one of the following:
  - Cognitive composite score < 70 (BSID-III)
  - Gross Motor Function Classification Score ≥ 2
  - Moderate/severe cerebral palsy (CP)
  - Blind in both eyes (vision < 20/200)
  - Hearing impairment with or without amplification

Methods: Data collection and analyses

- Demographic, neonatal and neurodevelopmental outcome data were collected and entered in standardized forms which were transmitted to, stored and analyzed by Research Triangle Institute International

- Analyses:
  - Intention to treat
  - Adjustment for gestational age stratum, center, familial clustering
  - Relative risks and 95% CI for categorical variables were estimated using robust Poisson regression in a generalized-estimating-equation model; adjusted means and 95% CI for continuous variables were estimated using linear mixed models
  - Significant if 2-sided $p < 0.05$

Results and Conclusions

To be presented at

Hot Topics 2011

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Bell, Edward (Pediatrics)"
Subject: RE: Hot Topics slides for Oximetry arm FU from SUPPORT Trial
Date: Tuesday, September 27, 2011 3:43:00 PM

I just resent it
Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Bell, Edward (Pediatrics) [mailto:edward-bell@uiowa.edu]
Sent: Tuesday, September 27, 2011 3:43 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Hot Topics slides for Oximetry arm FU from SUPPORT Trial

Attachment missing

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, September 27, 2011 2:35 PM
To: 'Roger Faix'; 'Richard, MD Ehrenkranz (richard.ehrenkranz@yale.edu)'; 'Frantz, Ivan'; 'Finer, Neil'; 'Vaucher, Yvonne'; 'Michael O`Shea'; 'Bauer, Charles R'; Duara, Shahnaz; 'Gantz, Marie'; 'Rich, Wade'; 'Nancy Newman'; 'Bradley Yoder'; (suhas.kallapur@cchmc.org); Abbot Laptook (alaptook@wihri.org); Abhik Das (adas@rti.org); Ambal (ambal@uab.edu); Anna Maria Hibbs (AnnaMaria.hibbs@cwru.edu); barbara_stoll@oz.ped.emory.edu; bpoindex@iupui.edu; carl_dangio@urmc.rochester.edu; Carlton, David P; cotte010@mc.duke.edu; dstevenson@stanford.edu; dwallace@rti.org; Bell, Edward (Pediatrics); goldb008@mc.duke.edu; Greg Sokol (gsokol@iupui.edu); Haresh Kirpalani (KIRPALANIH@email.chop.edu); John Barks; Jon.E.Tyson@uth.tmc.edu; Kennedy, Kathleen A; Krisa Van Meurs (vanmeurs@stanford.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); Kurt Schibler [kurt.schibler@cchmc.org]; Luc Brion (luc.brion@utsouthwestern.edu); Martin Keszler (mkeszler@wihri.org); mcw3@po.cwru.edu; Meena Garg (mgarg@mednet.ucla.edu); Nelin, Leif; Pablo.Sanchez@UTSouthwestern.edu; Polin, Richard; Robin Ohls (rohls@salud.unm.edu); ronnie_guillet@urmc.rochester.edu; Satyan Lakshminrusimha; Schmidt, Barbara (Neonatology); Seetha Shankaran ; Sood, Beena [bsood@med.wayne.edu]; Truog, William (MD); Uday Devaskar (UDEVASKAR@MEDNET.UCLA.EDU); Wally Carlo (wacarlo@uab.edu); (apappas@med.wayne.edu); (EMcGowan@tufts-nemc.org); Acarregui, Michael; Betty Vohr (bvohr@wihri.org); (b)(6) @aol.com; golds005@mc.duke.edu; ira adams-chapman; JaFuller@salud. unm. edu (JaFuller@salud.unm.edu); Jean Steichen (steichjj@uc.edu); Kim Yolton; Myriam Peralta-Carcelen (MPeralta@peds.uab.edu); Roy Heyne; Susan Hintz
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: Hot Topics slides for Oximetry arm FU from SUPPORT Trial

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Please send comments to Myriam Peralta by September 30.

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Higgins, Rosemary (NIH/NICHD) [E]; "Roger Faix"; "Richard, MD Ehrenkranz (richard.ehrenkranz@yale.edu)"; "Frantz, Ivan"; "Finer, Neil"; "Vaucher, Yvonne"; "Michael O`Shea"; "Bauer, Charles R"; "Duara, Shahnaz"; "Gantz, Marie"; "Rich, Wade"; "Nancy Newman"; "Bradley Yoder"; " (suhas.kallapur@cchmc.org)"; "Abbot Laptook (alaptook@wihri.org)"; "Abhik Das (adas@rti.org)"; "Ambal (ambal@uab.edu)"; "Anna Maria Hibbs (AnnaMaria.hibbs@cwru.edu)"; "barbara_stoll@oz.ped.emory.edu"; "bpoindex@iupui.edu"; "carl_dangio@urmc.rochester.edu"; "Carlton, David P"; "cotte010@mc.duke.edu"; "dstevenson@stanford.edu"; "dwallace@rti.org"; "Ed Bell (edward-bell@uiowa.edu)"; "goldb008@mc.duke.edu"; "Greg Sokol (gsokol@iupui.edu)"; "Haresh Kirpalani (KIRPALANIH@email.chop.edu)"; "John Barks"; "Jon.E.Tyson@uth.tmc.edu"; "Kennedy, Kathleen A"; "Krisa Van Meurs (vanmeurs@stanford.edu)"; "Kristi Watterberg (kwatterberg@salud.unm.edu)"; "Kurt Schibler [kurt.schibler@cchmc.org]"; "Luc Brion (luc.brion@utsouthwestern.edu)"; "Martin Keszler (mkeszler@wihri.org)"; "mcw3@po.cwru.edu"; "Meena Garg (mgarg@mednet.ucla.edu)"; "Nelin, Leif"; "Pablo.Sanchez@UTSouthwestern.edu"; "Polin, Richard"; "Robin Ohls (rohls@salud.unm.edu)"; "ronnie_guillet@urmc.rochester.edu"; "Satyan Lakshminrusimha"; "Schmidt, Barbara (Neonatology)"; "Seetha Shankaran "; "Sood, Beena [bsood@med.wayne.edu]"; "Truog, William (MD)"; "Uday Devaskar (UDEVASKAR@MEDNET.UCLA.EDU)"; "Wally Carlo (wacarlo@uab.edu)"; " (apappas@med.wayne.edu)"; " (EMcGowan@tufts-nemc.org)"; "Acarregui, Michael"; "Betty Vohr (bvohr@wihri.org)"; (b)(6) @aol.com"; "golds005@mc.duke.edu"; "Ira adams-chapman"; "JaFuller@salud.unm.edu (JaFuller@salud.unm.edu)"; "Jean Steichen (steichj@uc.edu)"; "Kim Yolton"; "Myriam Peralta-Carcelen (MPeralta@peds.uab.edu)"; "Roy Heyne"; "Susan Hintz"
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: Hot Topics slides for Oximetry arm FU from SUPPORT Trial
Date: Tuesday, September 27, 2011 3:41:00 PM
Attachments: Oximetry slides.ppt

Here is the attachment

Thanks
Rose

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Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: Hot Topics slides for Oximetry arm FU from SUPPORT Trial

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Neurodevelopmental Outcome of Extremely Preterm Infants in the SUPPORT trial
Pulse Oximetry Trial

Presented for the SUPPORT study group

Eunice Kennedy Shriver NICHD Neonatal Research Network

Background

- Oxygen supplementation is vital therapy for survival in many preterm infants for respiratory disorder
- Oxygen supplementation may increase risk of retinopathy of prematurity, BPD
- Concern of restrictive oxygen and mortality

- Long term neurodevelopmental outcome is not known regarding effects of different saturation oxygen targets

SUPPORT trial

- Oxygen saturation target groups 85-89% vs. and the higher saturation group 91-95%

SUPPORT study group NEJM 2010; 362: 1959-1969

SUPPORT trial

- Composite outcome of retinopathy and death did not differ significantly between lower oxygen saturation group and higher saturation group
- However death at discharge was increased in the lower saturation group (19.9% vs. 16.2 %, RR 1.27 95% CI, 1.01 to 1.60; P=0.04)
- ROP was reduced in the lower saturation group (8.6% vs. 17.9% RR 0.53; 95% CI 0.37 to 0.73; P<0.001)

SUPPORT study group NEJM 2010; 362: 1959-1969

Objective

- To compare the neurodevelopmental outcome at 18 to 22 months corrected age of infants enrolled in the support trial and who were randomized to lower or higher oxygenation group.

Hypothesis

- The composite outcome of death or neurodevelopmental impairment will be decreased in the lower saturation target oxygenation group compared to the higher oxygen saturation group at 18 to 22 months adjusted age.

Methods

- Study Design
  - Prospective, randomized, controlled follow up cohort of infants that participated in the SUPPORT follow up trial (20 centers)
  - Permuted block randomization with stratification according to center and GA
  - Randomly assigned to receive O2 sat:
    - 85% to 89% (lower) vs. 91% to 95% (higher)
  - 2 by 2 factorial design
  - Approved by IRB and RTI

- Subjects:
  - GA: 24 0/7 to 27 6/7 weeks
    - GA stratified to two groups:
      - 24 0/7 to 25 6/7 weeks
      - 26 0/7 to 27 6/7 weeks
  - Born between Feb 2005 and Feb 2009
  - Survivors at 36 weeks postconceptional age were enrolled
  - Evaluated at 18 to 22 months corrected age for gestational age

Assessments

- Blinded neurodevelopmental examiners, certified yearly
- Bayley Scales of Infant Development 3rd edition: Cognitive Composite Score
- Modified Gross Motor Function Classification System
- Neurologic examination (Amiel Tyson)
- Parental history of vision and hearing exam and medical history

Definitions

- Neurodevelopmental Impairment defined as any of:
  - Bayley III cognitive score < 70
  - GCMFC $\geq$ 2
  - Moderate to Severe Cerebral Palsy
  - Hearing impairment despite amplification or hearing aids
  - Bilateral visual impairment (<20/200)

Outcomes

- Primary: Presence of death or NDI at 18 to 22 months adjusted age
- Other:
  - Presence of CP at 18 to 22 m adjusted age
  - Presence of Blindness at 18 to 22 m adjusted age

Data collection and analysis

- Data collected in standard forms transmitted to RTI
- Analysis
  - Intention to treat
  - Adjusted for GA, center, familial clustering
  - 2 sided P<.05 significant
  - Adjusted RR and 95% CI for categorical and continuous variables estimated using Poisson Regression and mixed linear models.

Results and Conclusions

To be presented

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Myriam Peralta, M.D."
Cc: "Wally Carlo, M.D."; "Finer, Neil"; "Gantz, Marie"; "Vaucher, Yvonne"
Subject: RE: Hot Topics.
Date: Tuesday, September 27, 2011 3:32:00 PM
Attachments: Oximetry slides.ppt

Myriam
I deleted the CONSORT diagram as I don't think we should show any data. I will send this version out to the steering committee and follow up PI's for comments.

Thanks for all the effort!
Rose

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From: Myriam Peralta, M.D. [mailto:MPeralta@peds.uab.edu]
Sent: Tuesday, September 27, 2011 2:52 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Hot Topics.

Rose here are a draft of the slides, please send me any comments thanks

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, September 23, 2011 2:59 PM
To: 'Vaucher, Yvonne'
Cc: Myriam Peralta, M.D.; 'Finer, Neil'; Wally Carlo, M.D.; Gantz, Marie; Das, Abhik
Subject: RE: Hot Topics.

Yes, please send so I can get input.

Also, how are we doing on the papers? I believe we had discussed having them this week to send out for comments.

Thanks
Rose

Rosemary D. Higgins, MD

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From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]
Sent: Friday, September 23, 2011 3:57 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Myriam Peralta, M.D.; Vaucher, Yvonne
Subject: Hot Topics.

Rose,

The Hot Topics syllabus handouts and bibliographies are due October 1. I assume this refers to our background and methods slides. If so, should we send them to you earlier next week for approval? Thanks.

Yvonne

Yvonne E. Vaucher, M.D., M.P.H.
Division of Neonatal/Perinatal Medicine
Clinical Professor of Pediatrics
UCSD School of Medicine

tele: 619-543-3759
FAX: 619-543-3812

From: Higgins, Rosemary (NIH/NICHD) [E]
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Cc: "Wally Carlo, M.D."; "Finer, Neil"; "Gantz, Marie"; "Vaucher, Yvonne"
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tele: 619-543-3759
FAX: 619-543-3812

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To: "Vaucher, Yvonne"; "Finer, Neil"; "Wally Carlo, M.D."; "Myriam Peralta, M.D."
Subject: PAS 2012SUPPORTCPAPAbstract09272011ver2 0
Date: Tuesday, September 27, 2011 2:33:00 PM
Attachments: PAS 2012SUPPORTCPAPAbstract09272011ver2 0.docx

Yvonne – I made a minor change in the methods. For the authors – if you want to save space, you can simply have a few authors on behalf of the NICHD NRN SUPPORT STUDY. Also, for the lower death rate in the CPAP arm of the 24-25 week strata, I think we can make a stronger assertion regarding benefit of a trial of CPAP in this GA group. I would defer to Wally and Neil on this one.

Thanks for getting this to us so quickly

Rose

PAS 2012 Abstract

Title: Neurodevelopmental Outcome after Early CPAP versus Intubation with Surfactant Administration in Extremely Preterm Infants Enrolled in the SUPPORT Trial

Yvonne E Vaucher, MD,MPH[1], Myriam Peralta-Carcelen, MD,MPH[2], Marie G Gantz, PhD[3], Neil N Finer, MD[1], Waldemar A Carlo, MD[2], Rose D Higgins, MD[4], NRN Follow-up PIs and SUPPORT Study Group. [1]Div.ision of Neonatology, Department of Pediatrics, University of California,, San Diego, CA, United States; [2]Division of Neonatology, University of Alabama at Birmingham, Birmingham, AL, United States; [3]Statistics and Epidemiology, RTI International, Research Triangle Park, NC, United States and [4]Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network, Bethesda, MD, United States.

Background: The recent multicenter SUPPORT randomized, controlled trial demonstrated that initial treatment with early, non-invasive CPAP is an alternative to early surfactant administration after intubation and is associated with similar rates of death or BPD in infants born at 24 to 28 weeks gestation.

Objective: We hypothesized that, compared to treatment with surfactant administration after intubation, treatment with early CPAP would decrease the composite outcome of mortality or neurodevelopmental impairment.

Design/Methods: **The SUPPORT Trial enrolled** ~~We followed 1108~~ 1316 infants, 24 to 2~~7~~8 weeks gestation, randomized ~~in the SUPPORT trial~~ to receive either CPAP in the delivery room with limited ventilation if needed (CPAP) or intubation with surfactant administration within one hour after birth (SURF~~)~~. Infants were randomized within each center by two gestational age strata (24 0/7-25 6/7 and 26 0/7-27 6/7 weeks). A standardized neurodevelopmental assessment was performed at 18-22 months corrected age. The primary composite outcome was death or neurodevelopmental impairment (NDI) which included at least one of the following: cognitive score < 70, Gross Motor Function Classification score of ≥2, moderate/severe cerebral palsy, bilateral blindness or permanent hearing impairment. Results were adjusted for gestational age, center and familial clustering.

Results: Death or NDI was determined for 1234/1316 (93.8%) of infants enrolled in SUPPORT; 93.6% (990/1058) of known survivors were evaluated at 18-22 months corrected age. Death or NDI occurred in 27.9% (173/621) CPAP and in 29.9% (183/613) of the SURF infants (p=0.39). Rates of death (CPAP-18.4 vs. SURF-21.9%, p=0.10), NDI alone (CPAP-11.1 vs. SURF 8.9%, p=0.32), cognitive score < 70 (CPAP-7.2 vs. SURF-7.6%, p=0.84), moderate/severe cerebral palsy (CPAP-4.1 vs. SURF-4.0%, p=0.82), blindness (CPAP-0.8 vs. SURF 1.5%, p=0.31), and permanent hearing impairment (CPAP-3.3 vs. SURF-1,5%, p=0.06) were similar in both treatment arms. Except for fewer deaths in the most immature GA stratum [CPAP-26.4% (73/277) vs. SURF-35.5% (97/273), p=0.022], there were no significant differences in neurodevelopmental outcomes between CPAP and SURF groups within each GA stratum.

Conclusions: In extremely premature children, early CPAP, when compared to early intubation and surfactant administration, results in comparable neurodevelopmental outcome at 18-22 months corrected age.

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Laptook, Abbot"
Subject: RE: SUPPORT CPAP Draft
Date: Tuesday, September 27, 2011 1:48:00 PM

Yes, review the paper.
I accidently included Roger Soll so recalled the first one – I called him and told him to delete the email.

Thanks
Rose

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Sent: Tuesday, September 27, 2011 1:33 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: SUPPORT CPAP Draft
Importance: High

I see something was recalled; are we to be reviewing this? AL

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, September 27, 2011 8:41 AM
To: 'Finer, Neil'; 'Wally Carlo, M.D.'; kurt.schibler@cchmc.org; 'mcw3@cwru.edu'; 'Soll, Roger F.'; Laptook, Abbot; 'Bradley Yoder'; Das, Abhik; Gantz, Marie; 'Nancy Newman'; Rich, Wade; Myriam Peralta, M.D.
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: SUPPORT CPAP Draft
Importance: High

Hi,
Here is the draft of the SUPPORT CPAP Follow up paper. Please send comments back to Yvonne by October 7.

I expect the oximetry paper shortly and will send along.

Thanks
rose

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From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]
Sent: Monday, September 26, 2011 8:52 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Gantz, Marie
Subject: FW: SUPPORT CPAP Draft

Rose,
Here is the most recent draft. I could not attach the Tables properly. Will try to do that tomorrow.

Marie, please review consort diagram to be sure the numbers are correct. Also the bolded numbers in the paper. Thanks.

I have left the percentages in the paper so the reader can see them while reading without referring to the tables but they can be removed or stay depending upon what is included in the final tables. Tables can be combined or deleted (Tables 3 &/or 4) and the relevant data included in the text instead. I have included the GA strata in the Tables for Subcommittee review as the strata are very different. Again we don't need to put them in the final paper or they could be another Appendix.

Yvonne

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Clinical Professor of Pediatrics
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From: Vaucher, Yvonne
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: PAS Deadlines
Date: Tuesday, September 27, 2011 1:42:43 PM
Attachments: PAS 2012SUPPORTCPAPAbstract09272011ver2.0.docx

Rose,
PAS 2012 SUPPORT CPAP abstract attached. Still room for more results. Only 62% of maximum allowance.

Yvonne

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, September 27, 2011 8:27 AM
To: 'Beau Batton'; Phelps, Dale; 'Bell, Edward (Pediatrics)'; Michael Cotten; 'Myriam Peralta, M.D.'; Vaucher, Yvonne; Susan Hintz; 'Navarrete, Cristina'; 'Erika Fernandez'; Shankaran, Seetha; 'James Wynn, M.D.'; William MD Oh (woh@wihri.org); 'Kennedy, Kathleen A'; 'Natarajan, Girija'; alaptook@WIHRI.org; Pappas, Athina; 'vohr'
Cc: 'mcw3@cwru.edu'; 'D'Angio, Carl'; 'Ron, MD Goldberg (goldb008@mc.duke.edu)'; 'Wally Carlo (wacarlo@uab.edu)'; Finer, Neil; 'vanmeurs@leland.stanford.edu'; Duara, Shahnaz; 'Das, Abhik'; Wallace, Dennis; Archer, Stephanie (NIH/NICHD) [E]; 'Zaterka-Baxter, Kristin'; Cunningham, Meg; Gabrio, Jenna; 'Newman, Jamie'
Subject: PAS Deadlines

Please note—I have included you on this email as you have a PAS abstract (s) listed on the spreadsheet.

September 30, 2011 – Initial abstract draft due to subcommittee. This need not contain final data analyses results.

October 17, 2011 – Final abstract due to subcommittee. Approvals for abstracts must be obtained in advance of NICHD Clearance

Let me know if there are any questions.

Thanks
Rose

PAS 2012 Abstract

Title: Neurodevelopmental Outcome after Early CPAP versus Intubation with Surfactant Administration in Extremely Preterm Infants Enrolled in the SUPPORT Trial

Yvonne E Vaucher, MD,MPH[1], Myriam Peralta-Carcelen, MD,MPH[2], Marie G Gantz, PhD[3], Neil N Finer, MD[1], Waldemar A Carlo, MD[2], Rose D Higgins, MD[4], NRN Follow-up PIs and SUPPORT Study Group. [1]Div.ision of Neonatology, Department of Pediatrics, University of California,, San Diego, CA, United States; [2]Division of Neonatology, University of Alabama at Birmingham, Birmingham, AL, United States; [3]Statistics and Epidemiology, RTI International, Research Triangle Park, NC, United States and [4]Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network, Bethesda, MD, United States.

Background: The recent multicenter SUPPORT randomized, controlled trial demonstrated that initial treatment with early, non-invasive CPAP is an alternative to early surfactant administration after intubation and is associated with similar rates of death or BPD in infants born at 24 to 28 weeks gestation.

Objective: We hypothesized that, compared to treatment with surfactant administration after intubation, treatment with early CPAP would decrease the composite outcome of mortality or neurodevelopmental impairment.

Design/Methods: We followed 1108 infants, 24 to 28 weeks gestation, randomized in the SUPPORT trial to receive either CPAP in the delivery room with limited ventilation if needed (CPAP) or intubation with surfactant administration within one hour after birth (SURF). Infants were randomized within each center by two gestational age strata (24 0/7-25 6/7 and 26 0/7-27 6/7 weeks). A standardized neurodevelopmental assessment was performed at 18-22 months corrected age. The primary composite outcome was death or neurodevelopmental impairment (NDI) which included at least one of the following: cognitive score < 70, Gross Motor Function Classification score of ≥2, moderate/severe cerebral palsy, bilateral blindness or permanent hearing impairment. Results were adjusted for gestational age, center and familial clustering.

Results: Death or NDI was determined for 1234/1316 (93.8%) of infants enrolled in SUPPORT; 93.6% (990/1058) of known survivors were evaluated at 18-22 months corrected age. Death or NDI occurred in 27.9% (173/621) CPAP and in 29.9% (183/613) of the SURF infants (p=0.39). Rates of death (CPAP-18.4 vs. SURF-21.9%, p=0.10), NDI alone (CPAP-11.1 vs. SURF 8.9%, p=0.32), cognitive score < 70 (CPAP-7.2 vs. SURF-7.6%, p=0.84), moderate/severe cerebral palsy (CPAP-4.1 vs. SURF-4.0%, p=0.82), blindness (CPAP-0.8 vs. SURF 1.5%, p=0.31), and permanent hearing impairment (CPAP-3.3 vs. SURF-1,5%, p=0.06) were similar in both treatment arms. Except for fewer deaths in the most immature GA stratum [CPAP-26.4% (73/277) vs. SURF-35.5% (97/273), p=0.022], there were no significant differences in neurodevelopmental outcomes between CPAP and SURF groups within each GA stratum.

Conclusions: In extremely premature children, early CPAP, when compared to early intubation and surfactant administration, results in comparable neurodevelopmental outcome at 18-22 months corrected age.

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Wally Carlo, M.D."
Subject: RE: Safe and Effective Oxygenation in ELBW Infants-June 2011 (2).ppt
Date: Tuesday, September 27, 2011 1:05:00 PM

You are welcome!!
Rose

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From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Tuesday, September 27, 2011 1:05 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Safe and Effective Oxygenation in ELBW Infants-June 2011 (2).ppt

Thx

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
1700 6th Avenue South
176F Suite 9380R
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 (b)(6)

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, September 27, 2011 12:04 PM
To: Wally Carlo, M.D.
Subject: FW: Safe and Effective Oxygenation in ELBW Infants-June 2011 (2).ppt

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From: Archer, Stephanie (NIH/NICHD) [E]
Sent: Tuesday, September 27, 2011 12:55 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Safe and Effective Oxygenation in ELBW Infants-June 2011 (2).ppt

I have 16 yeses for this so far. So it passes.

Stephanie Wilson Archer
The Eunice Kennedy Shriver
National Institute of Child Health and Human Development
Pregnancy & Perinatology Branch
6100 Executive Boulevard, Room 4B03
Rockville, MD 20852

Tel. 301-496-0430
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archerst@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, September 26, 2011 3:52 PM
To: (suhas.kallapur@cchmc.org); Abbot Laptook (alaptook@wihri.org); Abhik Das (adas@rti.org); Ambal (ambal@uab.edu); Anna Maria Hibbs (AnnaMaria.hibbs@cwru.edu); barbara_stoll@oz.ped.emory.edu; bpoindex@iupui.edu; carl_dangio@urmc.rochester.edu; Carlton, David P; cotte010@mc.duke.edu; dstevenson@stanford.edu; dwallace@rti.org; Ed Bell (edward-bell@uiowa.edu); goldb008@mc.duke.edu; Greg Sokol (gsokol@iupui.edu); Haresh Kirpalani (KIRPALANIH@email.chop.edu); John Barks; Jon.E.Tyson@uth.tmc.edu; Kennedy, Kathleen A; Krisa Van Meurs (vanmeurs@stanford.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); Kurt Schibler [kurt.schibler@cchmc.org]; Luc Brion (luc.brion@utsouthwestern.edu); Martin Keszler (mkeszler@wihri.org); mcw3@po.cwru.edu; Meena Garg (mgarg@mednet.ucla.edu); Nelin, Leif; Pablo.Sanchez@UTSouthwestern.edu; Polin, Richard; Robin Ohls (rohls@salud.unm.edu); ronnie_guillet@urmc.rochester.edu; Satyan Lakshminrusimha; Schmidt, Barbara (Neonatology); Shankaran, Seetha; Sood, Beena; Truog, William (MD); Uday Devaskar (UDEVASKAR@MEDNET.UCLA.EDU); Wally Carlo (wacarlo@uab.edu)
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: Safe and Effective Oxygenation in ELBW Infants-June 2011 (2).ppt

HI,

Dr. Eduardo Bancalari has asked that we share a prior SUPPORT presentation with him so that he can prepare his Hot Topics talk "Oxygen targets: can they be achieved?" Dr. Bancalari will acknowledge the network.

Wally has sent a recent talk that is suitable.

Please send me a yes./No vote by Sept. 30 to share with Eduardo

Just a reminder, Miami did enroll in the SUPPORT Trial as part of their network involvement.

Thanks
Rose

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: Safe and Effective Oxygenation in ELBW Infants-June 2011 (2).ppt
Date: Tuesday, September 27, 2011 12:49:00 PM

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higginsr@mail.nih.gov

From: Shankaran, Seetha [mailto:sshankar@med.wayne.edu]
Sent: Tuesday, September 27, 2011 12:49 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Safe and Effective Oxygenation in ELBW Infants-June 2011 (2).ppt

Rose
My vote is yes
Seetha

Seetha Shankaran, MD
Professor of Pediatrics
Wayne State University School of Medicine
Director, Division of Neonatal/Perinatal Medicine
Children's Hospital of Michigan and
Hutzel Women's Hospital
313-745-1436 (o)
313-745-5867 (f)
sshankar@med.wayne.edu

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, September 26, 2011 3:52 PM
To: (suhas.kallapur@cchmc.org); Abbot Laptook (alaptook@wihri.org); Abhik Das (adas@rti.org); Ambal (ambal@uab.edu); Anna Maria Hibbs (AnnaMaria.hibbs@cwru.edu); barbara_stoll@oz.ped.emory.edu; bpoindex@iupui.edu; carl_dangio@urmc.rochester.edu; Carlton, David P; cotte010@mc.duke.edu; dstevenson@stanford.edu; dwallace@rti.org; Ed Bell (edward-bell@uiowa.edu); goldb008@mc.duke.edu; Greg Sokol (gsokol@iupui.edu); Haresh Kirpalani (KIRPALANIH@email.chop.edu); John Barks; Jon.E.Tyson@uth.tmc.edu; Kennedy, Kathleen A; Krisa Van Meurs (vanmeurs@stanford.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); Kurt Schibler [kurt.schibler@cchmc.org]; Luc Brion (luc.brion@utsouthwestern.edu); Martin Keszler (mkeszler@wihri.org); mcw3@po.cwru.edu; Meena Garg (mgarg@mednet.ucla.edu); Nelin, Leif; Pablo.Sanchez@UTSouthwestern.edu; Polin, Richard; Robin Ohls (rohls@salud.unm.edu); ronnie_guillet@urmc.rochester.edu; Satyan Lakshminrusimha; Schmidt, Barbara (Neonatology);

Shankaran, Seetha; Sood, Beena; Truog, William (MD); Uday Devaskar (UDEVASKAR@MEDNET.UCLA.EDU); Wally Carlo (wacarlo@uab.edu)
Cc: Archer, Stephanie (NIH/NICHD) [E]
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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Susan Hintz"
Subject: Confidential FW: SUPPORT CPAP Draft
Date: Tuesday, September 27, 2011 11:48:00 AM
Attachments: AppendixA_BSIDIIIabcCompositeCogLangMotorScoresMean less than70_85_CPAP09222011.docx
Table1_DemoNeoCharacteristicsCPAP09222011.docx
Table2_abcNDIOutcomesCPAP09222011.docx
Table3_abcDeathNDIComponentsGACompCPAP09222011.docx
Table4_abcMedicalrOutcomesCPAP09222011.docx
Figure ConsortCPAP09262011.doc
Vaucher SUPPORT FU CPAP PAPERwithoutTables9262011_YEVver3.5 SUPPORTSubCommittee.docx
Importance: High

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From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tuesday, September 27, 2011 9:03 AM
To: 'Finer, Neil'; 'Wally Carlo, M.D.'; 'kurt.schibler@cchmc.org'; 'mcw3@cwru.edu'; 'Roger Faix'; 'Laptook, Abbot'; 'Bradley Yoder'; 'Das, Abhik'; 'Gantz, Marie'; 'Nancy Newman'; 'Rich, Wade'; 'Myriam Peralta, M.D.'
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: SUPPORT CPAP Draft
Importance: High

Hi,
Here is the draft of the SUPPORT CPAP Follow up paper. Please send comments back to Yvonne by October 7.

I expect the oximetry paper shortly and will send along.

Thanks
rose

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From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]
Sent: Monday, September 26, 2011 8:52 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Gantz, Marie
Subject: FW: SUPPORT CPAP Draft

Rose,
Here is the most recent draft. I could not attach the Tables properly. Will try to do that tomorrow.

Marie, please review consort diagram to be sure the numbers are correct. Also the bolded numbers in the paper. Thanks.

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Yvonne

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BSID-III at 18-22 months Corrected Age

a. Entire cohort:CPAP vs. Surfactant

	CPAP	SURF	RR**	p
Cognitive Composite score (N=974,mean±SEM)	91±0.74	90±0.75	0.92(-0.94, 2.79)	0.33
Language composite score (N=960,mean±SEM)	86±0.87	86±0.88	0.57 (-1.63, 2.77)	0.61
Composite motor score (N=277,mean±SEM)	88±1.45	88±1.37	0.72(-3.14, 4.58	0.7
Cognitive Composite score < 70*	36/502(7.2)	36/472(7.6)	0.95(0.61, 1.5)	0.84
Language composite score <70*	73/479(14.7)	81/463(17.5)	0.83 (0.62, 1.12)	0.23
Composite motor score < 70*	16/135(11.9)	18/142(12.7)	0.92(0.51, 1.66)	0.77
Cognitive Composite score < 85*	111/502(22.1)	26/472(26.7)	0.82(0.66, 1.02)	0.08
Language composite score <85*	214/497(43.1)	214/463(46.2)	0.91 (0.79, 1.06)	0.23
Composite motor score < 85*	41/135(30.4)	45/142(31.7)	0.88 (0.63, 1.25)	0.48

b. 24 0/7-25 6/7 weeks Gestational Age

Cognitive Composite score (N=352,mean±SEM)	89±0.1.09	88±1,17	1.06(-1./96 4.08)	0.49
Language composite score (N=361,mean±SEM)	84±1.28	83±1.38	1.47 (-2.09, 5.02)	0.42
Composite motor score (N=106,mean±SEM)	88±1.45	88±1.37	0.72(-3.14, 4.58	0.7
Cognitive Composite score < 70*	23/198(11.6)	16/167(9.6)	1.16(0.64, 2.12)	0.62
Language composite score <70*	44/196(22.4)	37/165(22.4)	1.01 (0.68, 1.49)	0.97
Composite motor score < 70*	12/53(22.6)	11/53(20.8)	1.09(0.53, 2.22)	0.82
Cognitive Composite score < 85*	57/198(28.8)	55/167(32.9)	0.9(0.66, 1.22)	0.5
Language composite score <85*	97/196(49.5)	92/165(55.8)	0.9 (0.73, 1.1)	0.3
Composite motor score < 85*	27/53(50.9)	25/53(47.2)	1.04 (0.69, 1.585)	0.84

c. 26 0/7-27 6/7 weeks Gestational Age

Cognitive Composite score (N=609,mean±SEM)	93±0.91	93±0.88	0.84(-1.53, 3.21)	0.49
Language composite score (N=599,mean±SEM)	88±1.07	88±1.04	0.02 (-2.77, 2.81)	0.99
Composite motor score (N=171,mean±SEM)	93±1.83	92±1.70	1.19(-3.72, 6.11)	0.62
Cognitive Composite score < 70*	13/304(4.3)	20/305(6.6)	0.74(0.36, 1.51)	0.42
Language composite score <70*	29/301(9.6)	44/298(14.8)	0.67 (0.43, 1.06)	0.08
Composite motor score < 70*	4/82(4.9)	20/89(22.5)	0.68(0.36, 1.28)	0.46
Cognitive Composite score < 85*	54/304(17.8)	71/305(23.3)	0.75(0.55, 1.03)	0.08
Language composite score <85*	117/301(38.9)	122/298(40.9)	0.93 (0.75, 1.14)	0.48
Composite motor score < 85*	14/82(17.1)	20/89(22.5)	0.68 (0.36, 1.26)	0.23

* -no./total no.(%)

** Adjusted difference in means(95% CI)

Table 1: Demographics and Characteristics of Trial Cohort and Follow-up Cohorts

	Trial Cohort		Follow-up Cohort	
	CPAP	SURFACTANT	CPAP	SURFACTANT
	N=663	N=653	N=511	N=479
Birth weight (grams, Mean ± SD)	835±188	825±198	849±186	852±193
Gestational age (weeks, Mean ± SD)	26.2±1.1	26.2±1.1	26.3±1.1	26.3±1.1
Small for gestational age < 10-no./total no.(%)	37/663(5.6)	59/653(9)**	23/511(4.5)	32(479(6.7)
Male-no./total no.(%)	342/663(51.6)	370/653(56.7)	256/511(50.1)	266/479(55.5)
Race				
Non-Hispanic White-no./total no.(%)	250/663(39.1	271/653(41.5)	196/511(38.4)	200/479(41.8)
Non-Hispanic Black-no./total no.(%)	254/663(38.3)	235/653(36)	200/511(39.1)	177/479(37)
Hispanic-no./total no.(%)	138/663(20.8)	121/653(18.5)	98/511(19.2)	85/479(17.7)
Other or unknown-no./total no.(%)	21/663(3.2)	26/653(4)	17/511(3.3)	17/479(3.5)
Multiples-no./total no.(%)	178/663(26.8)	159/653(24.3)	138/511(27)	114/470(23.8)
Antenatal steroids(any)-no./total no.(%)	642/663(96.8)	623/652(95.6)	493/511(96.5)	456/479(95.2)
Cesarean section-no./total no.(%)	449/663(67.7)	434/653(66.5)	352/511(68.9)	315/479(65.8)
Public health insurance only-no./total no.(%)	351/661(53.1)	353/649(54.4)	262/511(51.3)	257/479(53.7)

Mother married-no./total no.(%)	305/662(46.1)	287/651(44.1)	244/511(47.7)	221/479(46.1)
With both biological parents-no./total no.(%)	365/539(67.7)	353/516(68.4)	348/510(68.2)	329/479(68.7)
Maternal education < 12-no./total no.(%)	161/616(26.1)	152/590(25.8)	128/506(25.3)	116/469(24.7)
Income < $30,000/year†-no./total no.(%)	270/514(52.5)	268/488(54.9)	260/493(52.7)	251/461(54.4)
English as primary language-no./total no.(%)	427/511(83.6)	403/478(84.3)	426/510(83.5)	403/478(84.3)
Severe ROP-no./total no.(%)	67/511(13.1)	65/473(13.7)	62/479(12.9)	58/434(13.4)
Bronchopulmonary dysplasia§-no./total no.(%)	223/569(39.2)	219/539(40.6)	193/511(37.8)	187/479(39)
IVH grade 3-4/PVL-no./total no.(%)	111/642(17.3)	87/628(13.9)	70/510(13.7)	46/478(9.6)*
NEC-stage ≥2 -no./total no.(%)	83/654(12.7)	63/636(9.9)	56/511(11)	30/479(6.3)***
Late onset sepsis/meningitis-no./total no.(%)	224/634(35.3)	230/624(36.9)	167/511(32.1)	154/479(32)
Postnatal steroids-no./total no.(%)	47/649(7.2)	83/631(13.2)****	34/508(6.7)	55/476(11.4)**
Died before discharge-no./total no.(%)	109/663(16.4)	128/653(19.6)		

†Not available for trial cohort at time of discharge

*p<0.05, **p<0.02,***p<0.01 ****p<0.001

*Results presented as number/total number (%); All values adjusted for stratification factors (study center and gestational-age group) and familial clustering.

Table 2: SUPPORT Death and NDI Outcomes at 18-22 Months Corrected Age*

	CPAP	SURFACTANT	aRR	p
a. **Entire cohort:CPAP vs. Surfactant**				
Death before 18-22 mo CA-no./total no.(%)	118/643(18.4)	140/638(22)	0.83(0.67,1.04)	0.1
Outcome determined for death or NDI	621/663(93.7)	613/653(93.9)	1(0.97,1.03)	0.83
Death or NDI	173/621(27.9)	183/613(29.9)	0.93(0.78,1.1)	0.39
NDI	56/503(11.1)	43/473(8.9)	1.16(0.79,1.71)	0.44
BSID-III cognitive composite score < 70	36/502(7.2)	36/472(7.6)	0.95(0.61,1.5)	0.84
Gross motor function level ≥ 2	26/511(5.1)	23/479(4.8)	0,98(0.57,1.69)	0.95
Moderate/severe cerebral palsy	21/511(4.1)	19/479(4)	0.93(0.51,1.72)	0.82
Blindness, bilateral	4/511*0.8)	7/479(1.5)	0.53(0.16,1.78)	0.31
Hearing impairment	17/511(3.3)	7/479(1.5)	2.8(1.1-6.9)	0.06

	CPAP	SURFACTANT	aRR	p
b. <u>24 0/7-25 6/7 weeks Gestational Age</u>				
Death before 18-22 mo CA-no./total no.(%)	73/276(26.4)	97/273(35.5)	0.74(0.57,0.96)	0.02
Death/NDI determined-no./total no.(%)	272/285(95.4)	265/280(94.6)	1.01(0.97,1.05)	0.68
NDI or death-no./total no.(%)	109/272(40.1)	118/265(44.5)	0.9 (0.74,1.09)	0.27
NDI-no./total no.(%)	36/199(18.1)	21/168(12.5)	1.37(0.83,2.27)	0.22
BSID-III cognitive score < 70-no./total no.(%)	23/198(11.6)	16/167(9.6)	1.16(0.64,2.12)	0.62
Gross motor function level ≥ 2-no./total no.(%)	17/201(8.5)	9/1712(5.2)	1.52(0.7,3.29)	0.29
Moderate/severe cerebral palsy-no./total no.(%)	14/201(7.0)	8/172(4.7)	1.32(0.57,3.04)	0.51
Blindness, bilateral -no./total no.(%)	2/201(1.0)	2/172(1.2)	0.86(0.12,6.02)	0.88
Hearing impairment-no./total no.(%)	11/201(5.5)	3/172(1.7)	3.24(0.9,11.71)	0.07

	CPAP	SURFACTANT	aRR*	p
c. <u>26 0/7-27 6/7 weeks Gestational Age</u>				
Death before 18-22 mo CA-no./total no.(%)	45/366(12.3)	43/365(11.8)	1.05(0.71,1.55)	0.82
Death/NDI determined-no./total no.(%)	349/378(92.3)	348/373(93.3)	0.99(0.95,1.03)	0.57
NDI or death-no./total no.(%)	64/349(18.3)	65/348(18.7)	0.99(0.72,1.35)	0.93
NDI-no./total no.(%)	19/304(6.3)	22/305(7.2)	0.93(0.5,1.72)	0.81
BSID-III cognitive score < 70-no./total no.(%)	13/304(4.3)	20/305(6.6)	0.74(0.36,1.51)	0.41
Gross motor function level ≥ 2-no./total no.(%)	9/310(2.9)	14/307(4.6)	0.61(0.27,1.4)	0.24
Moderate/severe cerebral palsy-no./total no.(%)	7/310(2.3)	11/307(3.6)	0.62(0.24,1.58)	0.31
Blindness, bilateral-no./total no.(%)	2/310(0.6)	5/307(1.6)	0.39(0.08,1.99)	0.26
Hearing impairment-no./total no.(%)	6/310(1.9)	4/307(1.3)	1.53(0.44,5.26)	0.5

Relative risk adjusted for stratification factors (study center and gestational-age group) and familial clustering (except for blindness due to small N)

Table 4: CPAP vs Surfactant: Medical Outcomes for entire cohort and both gestational age strata

	CPAP	SURF	RR	p
a. **Entire cohort: CPAP vs. Surfactant**				
Respiratory Medications–no./total no.(%)				
Bronchodilators–no./total no.(%)	176/507(34.7)	168/474(35.4)	0.95(0.81,1.14)	0.66
Diuretics–no./total no.(%)	15/507(3)	14/474(3)	0.99(0.49,1.98)	0.97
Steroids–no./total no.(%)	115/507(22.7)	88/474(18.6)	1.21(0.94,1.55)	0.14
Anticonvulsants–no./total no.(%)	14/510(2.7)	10/479(2.1)	1.29(0.59,2.82)	0.52
Readmission Any–no./total no.(%)	228/510(44.7)	221/479(46.1)	0.99(0.86,1.13)	0.84
For respiratory problem–no./total no.(%)	118/502(23.5)	119/471(25.3)	0.96(0.77,1.2)	0.71
Any surgery–no./total no.(%)	239/508(47)	212/479(44.3)	1.06(0.92,1.21)	0.41
Eye surgery–no./total no.(%)	50/508(9.8)	48/478(10)	0.96(0.66,1.38)	0.82

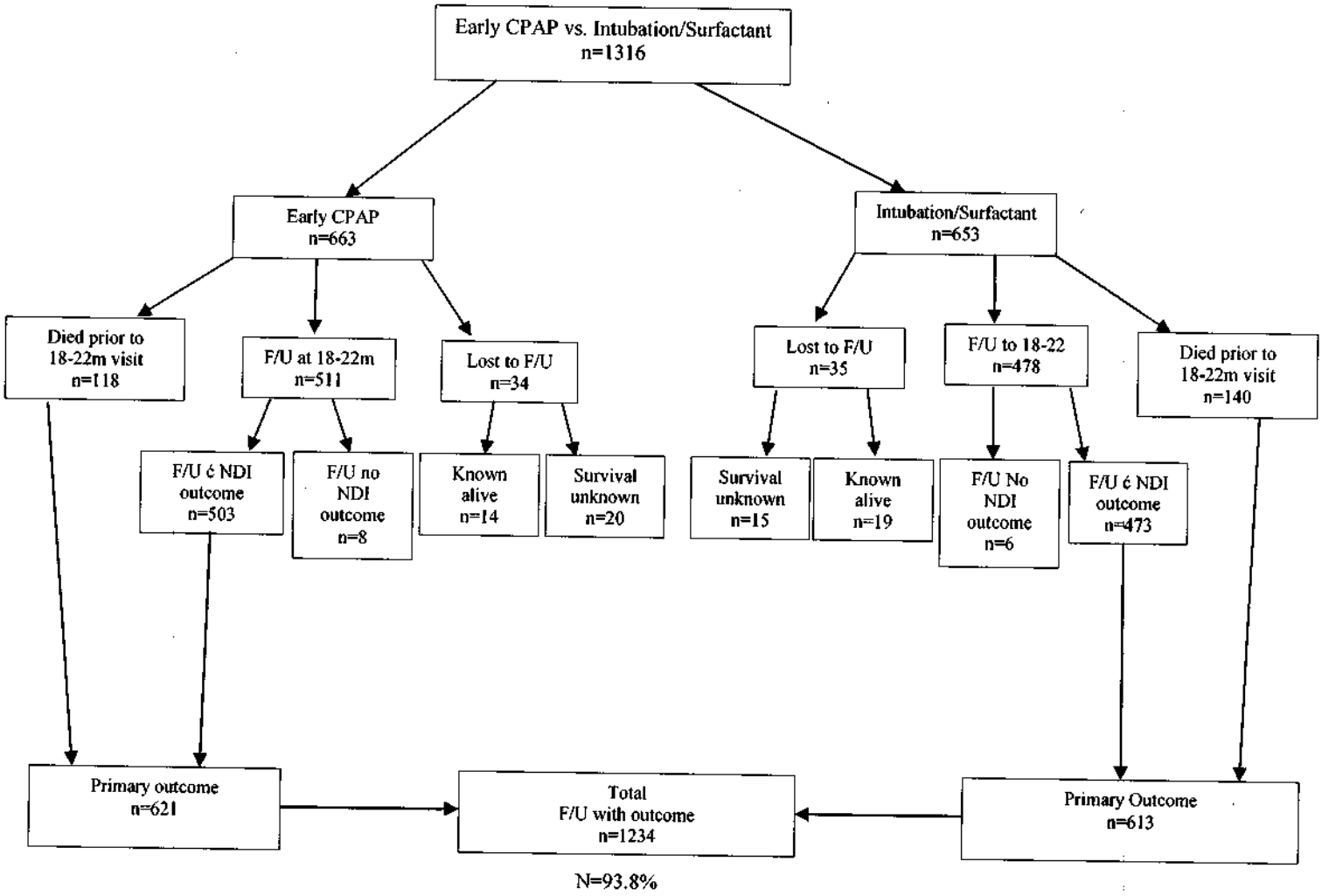
b. <u>24 0/7-25 6/7 weeks Gestational Age</u>

Respiratory Medications–no./total no.(%)				
Bronchodilators–no./total no.(%)	85/199(42.7)	65/171(38)	1.12(0.87,1.44)	0.38
Diuretics–no./total no.(%)	10/199(5)	10/171(5.8)	0.89(0.39,2.02)	0.77
Steroids–no./total no.(%)	58/199(28.1)	38/171(22.2)	1.37(0.96,1.97)	0.08
Anticonvulsants–no./total no.(%)	10/201(5)	2/172(1.2)	4.49(0.98,20.53)	0.05
Readmission Any–no./total no.(%)	102/201(50.7)	95/172(55.2)	0.96(0.79,1.16)	0.67
For respiratory problem–no./total no.(%)	49/167(24.9)	48/169(28.4)	0.95(0.67,1.35)	0.79
Any surgery–no./total no.(%)	102/200(51)	103/172(59.9)	0.87(0.72,1.05)	0.14
Eye surgery–no./total no.(%)	27/200(13.5)	42/171(24.6)	0.56(0.36,0.86)	0.009

c. 26 0/7-27 6/7 weeks Gestational Age

Respiratory Medications–no./total no.(%)				
Bronchodilators–no./total no.(%)	91/308(29.5)	103/303(34)	0.85(0.67,1.08)	0.20
Diuretics–no./total no.(%)	5/308(1.6)	4/303(1.3)	1.25(0.33,4.64)	0.74
Steroids–no./total no.(%)	57/308(18.5)	50/303(34)	0.85(0.67,1.08)	0.20
Anticonvulsants–no./total no.(%)	4/309(1.3)	8/307(2.6)	0.48(0.15,1.56)	0.22
Readmission Any–no./total no.(%)	126/309(40.8)	126/307(41)	1.01(0.83,1.22)	0.94
For respiratory problem–no./total no.(%)	69/305(22.6)	71/302(23.5)	0.96(0.72,1.28)	0.79
Any surgery–no./total no.(%)	137/308(44.5)	109/307(35.5)	1.25(1.03,1.5 1)	0.02
Eye surgery–no./total no.(%)	23/308(7.5)	6/307(2)	3.95(1.63,9.56)	0.002

Figure: Patient Flow Diagram: CPAP vs. Surfactant



Early CPAP versus Surfactant in Extremely Preterm Infants: Neurodevelopmental Outcomes in Early Childhood

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ABSTRACT

BACKGROUND

The recent randomized, multicenter SUPPORT trial demonstrated that initial treatment with early, non-invasive CPAP is an alternative to early surfactant administration after intubation and is associated with similar rates of death or BPD in infants born at 24 to 28 weeks gestation. We hypothesized that, compared to treatment with surfactant administration after intubation, treatment with early CPAP would decrease the composite outcome of mortality or neurodevelopmental impairment.

METHODS

We followed 1108 infants, 24 0/7 to 27 6/7 weeks gestation, who had been randomized in the SUPPORT trial to receive either early CPAP with limited ventilation or intubation with surfactant administration within one hour after birth. A standardized neurodevelopmental assessment was performed at 18-22 months corrected age. The primary composite outcome was death or neurodevelopmental impairment (NDI) which was defined as having any of the following: cognitive score < 70, Gross Motor Function Classification score of ≥ 2, moderate/severe cerebral palsy, bilateral blindness or permanent hearing impairment.

RESULTS

Death or NDI was determined for 1234/1316 (93.8%) of infants enrolled in SUPPORT and 93.5% (**990/1058**) of known survivors were evaluated at 18-22 months corrected age. Death or NDI occurred in 27.9% (173/621) of the CPAP group and in 29.9% (183/613) of the Surfactant group (p=0.39). Rates of death (CPAP-18.4 -vs. Surf-21.9%, p=0.10), NDI alone (CPAP-11.1 vs. Surf-8.9%, p=0.32), cognitive score < 70 (CPAP-7.2 vs. Surf-7.6%, p=0.84), moderate/severe cerebral palsy (CPAP-4.1 vs. Surf-4.0%, p=0.82) and blindness (CPAP-0.8 vs. Surf-1.5%, p=0.31), were similar in both treatment arms. In the most immature stratum (24 0/7-25-6/7 weeks gestation) there were fewer deaths [CPAP-26.4% (73/277) vs. Surf-35.5% (97/273), p=0.022].

CONCLUSION

We found no significant differences in the in the composite outcome of death or NDI at 18-22 months corrected age between extremely premature infants who were randomized to receive either early CPAP with a limited ventilation strategy if needed or early intubation with surfactant administration followed by conventional ventilation.

BACKGROUND

Extremely premature infants are at high risk for death or neurodevelopmental impairment- in early childhood. (ref) The risk of impairment is increases with decreasing gestational age, severity of illness and a a consequence of neonatal complications including- IVH/PVL, symptomatic PDA, NEC, CLD/BPD- and severe ROP. (REF) Although surfactant administration decreases both death and BPD, subsequent RCTs of -respiratory interventions including HFPV, HFJT, iNO have failed to consistently decrease mortality, IVH/PVL, NEC, or CLD/BPD.(REF)

The recent, multicenter, randomized, controlled (SUPPORT) trial demonstrated that treatment with non-invasive CPAP shortly after birth is an alternative to surfactant administration after intubation and is associated with similar rates of death or BPD in extremely premature infants born at 24 0/7 to 27 6/7 weeks gestation (REF Finer). Early CPAP was associated with less frequent need for postnatal steroids, shorter duration of mechanical ventilation, and similar rates of air leak and IVH compared with surfactant, all factors associated with adverse ND outcome in ELBW/ELGA infants. In addition, mortality was lower in the most immature, 24-25 week gestation stratum.

The Surfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT) in extremely low birth weight (ELBW) infants was in initially designed and powered to evaluate early childhood neurodevelopmental outcome of enrolled infants. We hypothesized that compared to treatment with surfactant administration after intubation, treatment with early, non-invasive CPAP and a limited ventilation strategy would result in decreased mortality or neurodevelopmental impairment at 18-22 months corrected age.

METHODS

Study Design

1316 extremely preterm infants (24 weeks 0 days to 27 weeks 6 days) born between February 2005 and February 2009 at 20 centers in the United States participating in the Neonatal Research Network (NRN) of the Eunice Kennedy Shriver National Institute of Child Health and Human Development were enrolled immediately following delivery in the prospective, randomized, controlled SUPPORT trial. Permuted block randomization was used, with stratification according to center and gestational age (24 weeks 0 days to 25 weeks 6 days or 26 weeks 0 days to 27 weeks 6 days). The infants were randomly assigned before birth to receive either CPAP immediately following delivery and a limited ventilation strategy if subsequent intubation was required or intubation with surfactant administration within an

hour after birth. Using a 2-by-2 factorial design, participants were also randomly assigned to a target range of oxygen saturation of 85% to 89% (lower oxygen saturation group) or 91 to 95% (higher oxygenation group). Procedures for enrollment, intervention, and data collection have been previously reported. (REF Finer) . The study was approved by the institutional review board at each participating site and RTI international which is the independent data coordinating center for the Neonatal Research Network. Written informed consent was obtained from the parent or guardian of each child before delivery.

Comment [yes 1]: We can reverse the order of CPAP and saturation ranges for our papers.

Assessments

All infants who survived to 36 weeks corrected age were eligible to participate in the prospective NRN follow-up cohort of the SUPPORT trial. A comprehensive neurodevelopmental assessment was performed at 18-22 months corrected age for prematurity by neurologic examiners and neurodevelopmental testers who were unaware of the treatment assignments and were trained annually for reliability of assessments during a 2-day workshop. Developmental function was assessed using the Bayley Scales of Infant and Toddler Development, 3rd ed (BSID-III). (REF) Cognitive Composite Scores are reported as a standardized score with a mean of 100 and a standard deviation of 15. The modified Gross Motor Function Classification System (GMFCS) describes the gross motor performance and has a range from 0 (normal) to 5 (most impaired). (REF) Examiners also recorded the presence of cerebral palsy defined as a nonprogressive disorder of the central nervous system and characterized by abnormal muscle tone in at least one arm or leg associated with abnormal control of movement or posture with delayed attainment of motor milestones.(REF Amiel-Tison) Cerebral palsy was classified depending on severity into mild (GMFCS $\leq$1), moderate (GMFCS 2 or 3) or severe (GMFCS $\geq$ 4). Hearing and visual impairment were determined based on parental history and examination.

Certified research nurses collected demographic and neonatal outcome data using standardized definitions recorded in the trial's manual of operations. Data collection included gestational age, birthweight, gender, multiple gestation, race/ethnicity, , ROP status, BPD status, history of medical or surgical NEC, history of late onset sepsis, use of postnatal steroids, rehospitalizations, interim medical history, surgeries, insurance status, marital status, maternal education, household income, language spoken at home, whether living with biological parents, Socioeconomic data was updated during the 18-24 month visit and if not available, data during the neonatal period was used.

Outcome

The primary neurodevelopmental outcome was the composite of death or neurodevelopmental impairment at 18 to 22 months corrected age. This composite outcome was selected because infants who died before 18 months could not be classified as having neurodevelopmental impairment. Neurodevelopmental impairment was defined as having any of the following: BSID III cognitive composite score less than 70, GMFCS $\geq$ 2, presence of moderate or severe cerebral palsy, permanent hearing loss that does not permit the child to

Comment [yes 2]: This remains a question but let's leave as is for now

understand directions of the examiner and communicate despite amplification with hearing aids or cochlear implants, or bilateral visual impairment (vision < 20/200).

Statistical Analysis

The sample size calculations were based on NRN data from the year 2000 which showed the rate of death or neurodevelopmental impairment at 18-22 months corrected age to be 61%. The sample size was increased by a factor of 1.12 to allow for infants in multiple births to be randomly assigned together to the same treatment arm and was further enlarged by an additional 17% to allow for loss to follow-up after discharge. The target sample was 1310 infants. Details regarding sample size calculations for the SUPPORT trial have been previously reported (REF Finer).

Data was entered in standard forms and was transmitted to RTI International, the data center for the NRN, which stored, managed and analyzed the data for this study. All analyses were performed according to the intention-to-treat principle. The denominator that was used to calculate the rate of each outcome was the number of infants for whom that outcome was known. The primary analyses focused on the percentage of infants in each group for whom the primary outcome of death or NDI at 18-22 months corrected age could be assigned. Analysis of this and all other categorical outcomes was performed with the use of robust Poisson regression in a generalized-estimating-equation model to obtain adjusted relative risks with 95% confidence intervals. Continuous outcomes were analyzed with the use of mixed-effects linear models to obtain adjusted means and standard errors.

Comment [yes 3]: This is all directly from Abhik

In the analysis of all outcomes, the results were adjusted, as prespecified, for gestational-age strata, center, and familial clustering. Two-sided P values of less than 0.05 were considered to indicate statistical significance, and no adjustments have been made for multiple comparisons. For the ____ planned analyses of secondary outcomes according to treatment, we would expect no more than _____tests to have p values of less than 0.05 on the basis of chance alone. Subgroup analyses were conducted within prespecified gestational-age strata for ____ predefined outcomes. Although these tests have not been adjusted for multiple comparisons, we would expect no more than _____ tests per stratum to have p values of less than 0.05 on the basis of chance alone.

Comment [adk]: This is lifted straight from the NEJM paper because we used the same approach here as well.

RESULTS

All survivors at 36 weeks post-conceptual age (N=1108/1316) were enrolled at discharge in the prospective SUPPORT follow-up cohort. (See Figure ~~1~~) Fifty children were known to have died after 36 weeks adjusted age and before 18-22 months. Sixty-eight children (6.1%) were lost to follow-up; the survival status of 35/68 of these children was unknown. A neurodevelopmental assessment at 18-22 months corrected age was performed for 990/**1058 (93.6%)** children known to be alive during the assessment interval. Of those who were seen for their 18-22 mo

Comment [y5]: This # will change with new data)

evaluation exam, NDI was determined for 976 children; 14 children were seen but had an incomplete evaluation that precluded assigning a NDI status. Ultimately, the pre-specified outcome, death or NDI, was determined for 93.8% (1234/1316) of the eligible cohort. There was no difference in the FUP rate between the CPAP and Surfactant arms (93.4 vs 93.4%) of the trial.

Compared with mothers of the 990 children who had a neurodevelopmental assessment at 18-22 months, mothers of 68 children lost to follow-up were less likely to be married (31 vs 47%, p=0.01), and more likely to have public insurance (69 vs 52%, p=0.008). No other demographic variables or neonatal characteristics were significantly different between the groups.

Demographics and neonatal characteristics:

Trial and Follow-up Cohorts: (See Table 1) Compared to the Surfactant arm, infants in the in the CPAP arm of the trial cohort were less likely to be SGA (5.6 vs 9%, unadjusted p=0.016) and less likely to have been exposed to postnatal steroids (7.2 vs 13.2 %, unadjusted p=0.0005). There was a trend towards fewer deaths before 18-22 months corrected age in the CPAP arm (18.5 vs. 22.2%, adjusted p=0.1). This difference reached significance in the lower 24 0/7 to 25 6/7 weeks gestation stratum (26.4 vs. 35.7%, unadjusted p=0.02), but not in the higher gestational age stratum 12.4 vs. 12%). The 24 0/7 to 25 6/7 weeks gestation stratum of the CPAP arm also had less ROP compared to the Surfactant arm (22.2 vs. 31.6%, unadjusted p=0.042) whereas the reverse occurred in the 26 0/7 to 27 6/7 weeks gestation stratum (7.3 vs. 10.2%, unadjusted p=0.044). Thirty-four percent of infants in the CPAP arm were intubated in the delivery room and 67% ultimately received surfactant and ventilation. Almost all mothers (97%) in both arms received antenatal steroids.

In the follow-up cohort there were no significant differences between the CPAP and Surfactant trial arms in the incidence of death before discharge, SGA status, sepsis, ROP in survivors, or LOS. BW, GA, gender, race/ethnicity, multiple birth, mode of delivery, insurance status, maternal education, English as the primary language, household income were also similar in the both groups. Compared to the Surfactant arm, infants in the in the CPAP arm were more likely to be have Grade 3-4 IVH or cystic PVL (13.7 vs 9.6%, unadjusted p=0.05) and more likely to have modified Bell's Stage ≥ 2, medical or surgical NEC (11 vs 6.3%, unadjusted p=0.009). Infants in the CPAP arm were less likely to have been exposed to postnatal steroids (6.7 vs 11.4%, unadjusted p=0.01.)

Primary neurodevelopmental outcome: (See Table 2) The mean corrected age at neurodevelopmental assessment was similar for both treatment arms (CPAP 19.9 ± 2.4 mo vs. Surf 20.1 ± 2.7 mo, p=0.31). There were no significant differences in the composite outcome of *death or NDI* at 18-22 month corrected age between the CPAP and surfactant arms in the entire cohort (27.9 vs. 29.9%) or for the either of the two gestational age strata (40.1 vs. 44.5%

for 24 0/7-25 6/7 weeks gestation; 18.3 vs. 18.7% for 26 0/7 to 27 6/7 weeks gestation). For the entire cohort there was there were no significant difference between the CPAP and Surfactant arms in the incidence of *NDI* (10.9 vs. 9.1%, adjusted p=0.44) or in either of the two gestational age strata (18.1 vs. 12.5, p=0.21 for 24 0/7-25 6/7 weeks gestation; 6.3 vs. 7.2%, p=0.81 for 26 0/7 to 27 6/7 weeks gestation).

Components of NDI: (See Table 2) The incidence of cognitive impairment (BSID-III cognitive composite score < 70) (7.2% vs. 7.6%), gross motor function level ≥ 2 (5.1 vs. 4.8%), moderate/severe CP (4.1 vs. 4.0%), or blindness (0.8 vs. 1.5%) were similar in both the CPAP and Surfactant treatment groups. Although the incidences of NDI, cognitive impairment, moderate to severe cerebral palsy and blindness were higher in the lower gestational age compared to the higher gestational age group, there were no significant differences between the trial arms in either group. Overall 24 infants had permanent hearing impairment, 13 of whom had bilateral hearing aids. There was a trend toward an increased incidence of hearing impairment in the early CPAP treatment arm compared to the surfactant treatment arm (3.3 vs. 1.5%, adjusted p=.06). Compared to the surfactant treatment arm, the incidence of hearing impairment in the CPAP arm was higher in the 24-25 weeks gestation stratum of CPAP arm (5.5 vs.1.7%, adjusted p=.07) but not in the 26-27 weeks stratum (1.9 vs. 1.3%, p=0.50). There was no association between hearing impairment and severe IVH/PVL or NEC, which had a higher incidence in the CPAP arm.

Comment [y6]: Marie: Is this true for both higher and lower GA strata? Is there any interaction for hearing impairmenrt between the CPAP/Surf and high/low oxygen saturation groups).

There were no significant differences in the risk of death or individual NDI composite outcomes between the CPAP and Surfactant arms for the entire cohort. (Table 3) However, in the lower gestational age stratum there was a significantly higher risk of death or bilateral blindness in the Surfactant arm and a trend towards lower risk in the CPAP treatment arm for death or cognitive composite score < 70 and death or moderate to severe cerebral palsy.

Sixty percent of all children (CPAP -59.7% and Surfactant 59.6%) had normal neuromotor, normal neurosensory and normal developmental (i.e. BSID-III cognitive composite score > 85) evaluations. Infants in the 26-27 week gestational age stratum were more likely to be normal (CPAP 67.5% and -Surfactant 65.2%) than those in the 24-25 weeks gestational age stratum(CPAP 47.7% and Surfactant 49.4%).

Other neurodevelopmental outcomes (Appendix) Mean BSID-III composite *cognitive scores* were similar in both CPAP and Surfactant arms for the entire FUP cohort (91.0 ± 0.74 vs. 90.0 ± 0.75) as well as for the 24 0/7 to 25 6/7 week (89.0 ± 1.1 vs. 88.1 ± 1.7) and 26 0/7 to 27 6/7 week (93.0 ± 0.9 vs. 93.0.6 ± 0.9) gestational age strata. Median BSID-III composite scores were virtually identical to the mean composite scores for all of the above groups.

Other outcomes: (Table 4) Overall readmission rates (CPAP 44.7% vs. Surfactant 46%) and readmission rates for respiratory problems (CPAP 23.5% vs. Surfactant 25.3%) were similar in

both treatment arms. There were no significant differences in bronchodilator (CPAP 34.7% v.s Surfactant 35.4%), steroid (CPAP 22.7% vs. Surfactant 18.6%), or diuretic (CPAP 3% vs. Surfactant 3%)use after discharge. There was a similar rate of surgery in both groups (CPAP 47% vs. Surfactant 44.3%).

DISCUSSION:

We report the neurodevelopmental outcome in early childhood at 18-22 months gestational age for extremely premature children enrolled in the SUPPORT trial which compared the use of early CPAP and a limited ventilator strategy with intubation and surfactant administration in the delivery room followed by conventional ventilation in extremely premature infants born between 24 0/7 to 26 6/7 weeks gestation.(REF)

There was no significant difference in the primary, pre-specified composite outcome of death or NDI at 18-22 months corrected age between those extremely premature infants treated with early CPAP vs. those treated early intubation and surfactant administration. Neither were there differences between the CPAP and Surfactant arms in the post-hoc stratified analyses of individual outcomes including NDI, severe mental impairment (cognitive score < 70), moderate/severe CP, moderate/severe motor impairment (GMFSC ≥2), bilateral blindness, or in mean composite cognitive, language or motor BSID-III scores. The was a trend towards a higher rate of hearing impairment in the CPAP compared to the Surfactant treated arm, particularly in the lower gestational age stratum. However, the number of affected children was small and this finding needs to be further explored by other large RCT comparing these alternative treatments.

As reported in previous studies, compared to the more mature infants (26 to 27 weeks gestation), the most immature infants (24 to 25 weeks gestation) in both CPAP and Surfactant arms were at substantially higher risk for all adverse neurodevelopmental outcomes in early childhood including death before 18-22 months, severe cognitive impairment, abnormal gross motor function, moderate/severe cerebral palsy and hearing impairment. (REF)

Bronchopulmonary dysplasia is associated with adverse neurodevelopmental outcome. (REF) Although infants in the CPAP arm had significantly fewer days of ventilation and less often received postnatal steroids compared to the surfactant treated arm, the incidence of BPD and need for supplemental oxygen was similar in both groups before discharge as was the use of respiratory medications and readmission for respiratory problems after discharge.

The strengths of this study include the large number of extremely premature, 24-27 weeks gestation, infants enrolled in this national, multicenter trial; sufficient power to detect a clinically significant difference in the pre-specified neurodevelopmental outcome; the very high percentage of participants who were followed and evaluated in early childhood; and the comprehensive and standardized neurodevelopmental evaluation performed. One third of

infants in the CPAP arm were intubated in the delivery room and two thirds subsequently required surfactant treatment and ventilation which may have blunted any difference in neurodevelopmental outcomes between the two groups. The generalizability of this study may be somewhat limited by the need for antenatal consent which resulted in a trial cohort with higher socioeconomic status than the entire eligible cohort (Ref WR).

In summary, we found no significant differences in the incidence death or NDI, or in any of the individual components of NDI at 18-22 months corrected age between extremely premature infants who were randomized to either early CPAP with a limited ventilation strategy or early intubation with surfactant administration followed by conventional ventilation. Early CPAP is an effective management strategy for the extremely premature infant and is associated with increased survival without increasing neurodevelopmental impairment in the most immature infants.

Acknowledgements

The National Institutes of Health, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), and the National Heart, Lung, and Blood Institute (NHLBI) provided grant support for the Neonatal Research Network's SUPPORT Trial.

Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Drs. Abhik Das (DCC Principal Investigator) and Marie Gantz (DCC Statistician) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study. The following investigators, in addition to those listed as authors, participated in this study:

NRN Steering Committee Chairs: Alan H. Jobe, MD PhD, University of Cincinnati (2003-2006); Michael S. Caplan, MD, University of Chicago, Pritzker School of Medicine (2006-2011).

Alpert Medical School of Brown University and Women & Infants Hospital of Rhode Island (U10 HD27904) – William Oh, MD; Angelita M. Hensman, RN BSN; Bonnie E. Stephens, MD; Barbara Alksninis, PNP; Dawn Andrews, RN; Kristen Angela, RN; Susan Barnett, RRT; Bill Cashore, MD; Melinda Caskey, MD; Kim Francis, RN; Dan Gingras, RRT; Regina A. Gargus, MD FAAP; Katharine Johnson, MD; Shabnam Lainwala, MD; Theresa M. Leach, MEd CAES; Martha R. Leonard, BA BS; Sarah Lillie, RRT; Kalida Mehta; James R. Moore, MD; Lucy Noel; Suzy Ventura; Rachel V. Walden; Victoria E. Watson, MS CAS.

Case Western Reserve University, Rainbow Babies & Children's Hospital (U10 HD21364, M01 RR80) – Avroy A. Fanaroff, MD; Bonnie S. Siner, RN; Arlene Zadell RN; Julie DiFiore, BS; Monika Bhola, MD; Harriet G. Friedman, MA; Gulgun Yalcinkaya, MD.

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Duke University School of Medicine, University Hospital, Alamance Regional Medical Center, and Durham Regional Hospital (U10 HD40492, M01 RR30) – Ronald N. Goldberg, MD; C. Michael Cotten, MD MHS; Patricia Ashley, MD; Kathy J. Auten, MSHS; Kimberley A. Fisher, PhD FNP-BC IBCLC; Katherine A. Foy, RN; Sharon F. Freedman, MD; Kathryn E. Gustafson, PhD; Melody B. Lohmeyer, RN MSN; William F. Malcolm, MD; David K. Wallace, MD MPH.

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Eunice Kennedy Shriver National Institute of Child Health and Human Development – Stephanie Wilson Archer, MA.

Indiana University, University Hospital, Methodist Hospital, Riley Hospital for Children, and Wishard Health Services (U10 HD27856, M01 RR750) – Brenda B. Poindexter, MD MS; James A. Lemons, MD; Leslie D. Wilson, BSN CCRC; Faithe Hamer, BS; Ann B. Cook, MS; Dianne E. Herron, RN; Carolyn Lytle, MD MPH; Heike M. Minnich, PsyD HSPP.

National Heart, Lung, and Blood Institute – Mary Anne Berberich, PhD; Carol J. Blaisdell, MD; Dorothy B. Gail, PhD; James P. Kiley, PhD.

RTI International (U10 HD36790) – W. Kenneth Poole, PhD; Jamie E. Newman, PhD MPH; Betty K. Hastings; Jeanette O'Donnell Auman, BS; Carolyn Petrie Huitema, MS; James W. Pickett II, BS; Dennis Wallace, PhD; Kristin M. Zaterka-Baxter, RN BSN.

Stanford University and Lucile Packard Children's Hospital (U10 HD27880, UL1 RR25744, M01 RR70) – Krisa P. Van Meurs, MD; David K. Stevenson, MD; M. Bethany Ball, BS CCRC; Barbara Bentley, PsychD MSEd; Elizabeth F. Bruno, PhD; Alexis S. Davis, MD MS; Maria Elena DeAnda, PhD; Anne M. DeBattista, RN, PNP; Jean G. Kohn, MD MPH; Melinda S. Proud, RCP; Renee P. Pyle, PhD; Nicholas H. St. John, PhD; Hali E. Weiss, MD.

Tufts Medical Center, Floating Hospital for Children (U10 HD53119, M01 RR54) – Ivan D. Frantz III, MD; John M. Fiascone, MD; Anne Furey, MPH; Brenda L. MacKinnon, RNC; Ellen Nylen, RN BSN; Ana Brussa, MS OTR/L; Cecelia Sibley, PT MHA.

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University of Iowa Children's Hospital (U10 HD53109, UL1 RR24979, M01 RR59) – Edward F. Bell, MD; John A. Widness, MD; Jonathan M. Klein, MD; Tarah T. Colaizy, MD MPH; Karen J. Johnson, RN BSN; Diane L. Eastman, RN CPNP MA.

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University of New Mexico Health Sciences Center (U10 HD53089, M01 RR997) – Kristi L. Watterberg, MD; Robin K. Ohls, MD; Julie Rohr, MSN RNC CNS; Conra Backstrom Lacy, RN; Jean Lowe, PhD; Rebecca Montman, BSN.

University of Rochester Medical Center, Golisano Children's Hospital (U10 HD40521, M01 RR44) – Nirupama Laroia, MD; Dale L. Phelps, MD; Gary David Markowitz, MD; Linda J. Reubens, RN CCRC; Diane Hust, MS RN CS; Lisa Augostino; Julie Babish Johnson, MSW; Erica Burnell, RN; Harris Gelbard, MD PhD; Rosemary L. Jensen; Emily Kushner, MA; Joan Merzbach, LMSW; Jonathan Mink, MD PhD; Carlos Torres, MD; David Wang, MD; Kelley Yost, PhD.

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University of Utah Medical Center, Intermountain Medical Center, LDS Hospital, and Primary Children's Medical Center (U10 HD53124, M01 RR64) – Shawna Baker, RN; Karie Bird, RN; Jill Burnett, RN; Laura Cole, RN; Karen A. Osborne, RN BSN CCRC; Cynthia Spencer, RNC; Mike Steffens, PhD; Kimberlee Weaver-Lewis, RN BSN; Karen Zanetti, RN.

Wake Forest University, Baptist Medical Center, Brenner Children's Hospital, and Forsyth Medical Center (U10 HD40498, M01 RR7122) – Robert G. Dillard, MD; Lisa K. Washburn, MD; Nancy J. Peters, RN CCRP; Barbara G. Jackson, RN BSN; Korinne Chiu, MA; Deborah Evans Allred, MA LPA; Donald J. Goldstein, PhD; Raquel Halfond, MA; Carroll Peterson, MA; Ellen L. Waldrep, MS; Cherrie D. Welch, MD MPH; Melissa Whalen Morris, MA; Gail Wiley Hounshell, PhD.

Wayne State University, Hutzel Women's Hospital, and Children's Hospital of Michigan (U10 HD21385) – Seetha Shankaran, MD; Beena G. Sood, MD MS; Rebecca Bara, RN BSN; Elizabeth Billian, RN MBA; Laura A. Goldston, MA; Mary Johnson, RN BSN.

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Data and Safety Monitoring Committee – Gordon Avery, MD, chair, Children's National Medical Center; Christine A. Gleason, MD, chair, University of Washington; Marilee C. Allen, MD, Johns Hopkins University School of Medicine; Shrikant I. Bangdiwala, PhD, University of North Carolina; Carol J. Blaisdell, MD, National Heart, Lung, and Blood Institute; Robert J. Boyle, MD, University of Virginia Health System; Traci Clemons, PhD, The EMMES Corporation; Mary E. D'Alton, MD, Columbia University; Abhik Das (ex officio), PhD, RTI International; Dorothy B. Gail, PhD, National Heart, Lung, and Blood Institute; Carl Hunt, MD, National Heart, Lung, and Blood Institute; Martin Keszler, MD, Georgetown University Hospital; W. Kenneth Poole (ex officio), PhD, RTI International; Carol K. Redmond, ScD, University of Pittsburg; Michael G. Ross, MD, MPH; UCLA School of Medicine and Public Health; Merran A. Thomson, MD, Hammersmith Hospital, UK; Steven J. Weiner, MS, The George Washington University; Marian Willinger (ex officio), PhD, Eunice Kennedy Shriver National Institute of Child Health and Human Development.

Retinopathy of Prematurity Adjudication Committee - Gary David Markowitz, MD, University of Rochester; Amy K. Hutchinson, MD, Emory University; David K. Wallace, MD, MPH, Duke University; Sharon F. Freedman, MD, Duke University.

Figure 1: Patient Flow diagram-CPAP vs. Surfactant

Table 1: Demographic and neonatal characteristics of trial and FUP cohorts-Early CPAP vs. Surfactant treatment arms

Table 2: Pre-specified outcomes and components of NDI for entire cohort and by gestational age strata for Early CPAP vs. Surfactant treatment arms

Table 3: Death and components of NDI for entire cohort and by gestational age strata for Early CPAP vs. Surfactant treatment arms

Table 4: Developmental outcome for entire cohort and by gestational age strata for Early CPAP vs. Surfactant treatment arms

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Beau Batton"; "Phelps, Dale"; "Bell, Edward (Pediatrics)"; "Michael Cotten"; "Myriam Peralta, M.D."; "Vaucher, Yvonne"; "Susan Hintz"; "Navarrete, Cristina"; "Erika Fernandez"; "Shankaran, Seetha"; "James Wynn, M.D."; "William MD Oh (woh@wihri.org)"; "Kennedy, Kathleen A"; "Natarajan, Girija"; "alaptook@WIHRI.org"; "Pappas, Athina"; "yohr"
Cc: "mcw3@cwru.edu"; "D"Angio, Carl"; "Ron, MD Goldberg (goldb008@mc.duke.edu)"; "Wally Carlo (wacarlo@uab.edu)"; "Finer, Neil"; "vanmeurs@leland.stanford.edu"; "Duara, Shahnaz"; "Das, Abhik"; "Wallace, Dennis"; Archer, Stephanie (NIH/NICHD) [E]; "Zaterka-Baxter, Kristin"; "Cunningham, Meg"; "Gabrio, Jenna"; "Newman, Jamie"
Subject: PAS Deadlines
Date: Tuesday, September 27, 2011 11:26:00 AM
Attachments: Submitted_Abstracts2012 8.31.2011.xlsx
Deadlines.doc

Please note—I have included you on this email as you have a PAS abstract (s) listed on the spreadsheet.

September 30, 2011 – Initial abstract draft due to subcommittee. This need not contain final data analyses results.

October 17, 2011 – Final abstract due to subcommittee. Approvals for abstracts must be obtained in advance of NICHD Clearance

Let me know if there are any questions.

Thanks
Rose

NRN PAS Abstracts 2012

Subcommittee	Type (Pilot, Main, Secondary, or Analysis)	Status	Study Investigator	Title
Early BP	0. Pilot	7. PAS Abstract	Batton B; Walsh MC	Early BP Time-Limited Observational Study
Inositol	0. Pilot	7. PAS Abstract	Phelps DL	Inositol Phase 2: Multi-dose Pilot (INS-2)
Vitamin E	0. Pilot	7. PAS Abstract	Bell EF	Vitamin E pilot
Genomics	1. Main	7. PAS Abstract	Cotten CM	Retrospective DNA Repository
SUPPORT	1. Main	7. PAS Abstract	Peralta-Carcelen M; Carlo WA	SUPPORT FU Oxygen Saturations
SUPPORT	1. Main	7. PAS Abstract	Vaucher Y; Finer NN	SUPPORT FU CPAP
SUPPORT	2. Secondary	7. PAS Abstract	Hintz SR	SUPPORT MRI - MRI findings
SUPPORT	2. Secondary	7. PAS Abstract	Navarrete C; Duara S	SUPPORT Growth
Term Hypotension	2. Secondary	7. PAS Abstract	Fernandez E	Term Hypotension secondary analyses
GDB	3. Analysis	7. PAS Abstract	Boghossian NS; Bell EF; Das A; Stoll BJ; Walsh MC; Carlo WA; Laptook AR; Sánchez PJ; Shankaran S; Van Meurs KP; Colaizy TT; Ball MB; Hale EC; Newman NS; Higgins RD	Prenatal growth failure: when is it significant for the early preterm infant?
GDB	3. Analysis	7. PAS Abstract	Kelleher J; Salas AA; Bhat R; Ambalavanan N; Carlo WA	Spontaneous Intestinal Perforation Associated with Prophylactic Indomethacin and Concurrent Enteral Nutrition in Extremely Low Birth Weight Newborns
GDB	3. Analysis	7. PAS Abstract	Shankaran S; Pappas A; Bajaj M; Natarajan G; Davis A; Hintz SR; Adams-Chapman I; Higgins RD; Das A; and the GDB Subcommittee	Management of Post-hemorrhagic Ventricular Dilatation (PHVD): Impact of Early vs. Later Intervention
GDB	3. Analysis	7. PAS Abstract	Wynn JL; Hansen NI; Cotten CM; Goldberg RN; Benjamin Jr DK; Stoll BJ	Risk of secondary infection in preterm neonates after early sepsis
PCV-7	3. Analysis	7. PAS Abstract	Wynn JL; Lei L; Cotten CM; Goldberg RN; D'Angio CT	The effect of sepsis on subsequent PCV-7 vaccine responses in very low birth weight infants
Phototherapy	3. Analysis	7. PAS Abstract	Oh W	Bilirubin and ABR

SUPPORT	3. Analysis	7. PAS Abstract	Kennedy KA; Phelps DL	Retinopathy of Prematurity (ROP) Natural History Study Secondary Study for SUPPORT Trial
Whole body hypothermia	3. Analysis	7. PAS Abstract	Natarajan et al	Apgar scores and outcome
Whole-body Hypothermia Extended FU	3. Analysis	7. PAS Abstract	Laptook AR	Elevated Temperatures among Infants with HIE who are Assessed for Outcome at 6-7 Years
Whole-body Hypothermia Extended FU	3. Analysis	7. PAS Abstract	Pappas A	Predictive Validity of 18 Month Assessments for Cognitive, Language, Executive Function and School Age Performance in Children with HIE
Whole-body Hypothermia Extended FU	3. Analysis	7. PAS Abstract	Vohr BR	Growth parameters at 6-7 yrs
Preemie aEEG	0. Pilot	7b. On Hold	Davis AS	Preemie aEEG pilot
SUPPORT	2. Secondary	7b. On Hold	Stevens T	SUPPORT Pulmonary Outcomes
GDB	3. Analysis	7b. On Hold	LeVan J; Wyckoff M; Sánchez PJ; Heyne RJ; Ahn C; Jaleel M; Brion LP; Finer NN; Carlo WA; Walsh MC; Rich W; Gantz MG; Laptook AR; Yoder BA; Faix RG; Das A; Poole WK; Ambalavanan N; Schibler K; Donovan E; Newman N; Frantz III ID; Buchter S; Morris BH; Laroia N; Poindexter BB; Cotten CM; Van Meurs KP; Sood BG; Duara S; O'Shea TM; Bell EF; Bhandari V; Watterberg KL; Stoll BJ; Higgins RD	Changes in Therapy and Outcomes Associated with The SUPPORT Trial
GDB	3. Analysis	Rejected	Salas AA; Peralta-Carcelen M; Ambalavanan N; Carlo WA	Effect of post-discharge environment on mental development of extremely low birth weight infants
GDB	3. Analysis	Rejected	Szyld EG; Carlo WA; Ambalavanan N; Berazategui JP; Aguilar AM; and the GDB Subcommittee	Risk factors for advanced neonatal resuscitation in the delivery room in VLBW infants
Phototherapy	3. Analysis	Rejected	Salas AA; Ambalavanan N; Bhat R; Carlo WA; Tyson JE; and the Phototherapy Subcommittee	Serum bilirubin concentrations and neurodevelopmental impairment in ELBW infants

			PAS Abstracts			
Center	Includes FU?	Statistician	Protocol Subcomm. Decision (Approved, Revise, Rejected)	Abstract Subcomm. Decision (Approved, Revise, Rejected)	PAS Decision (Accepted, Rejected)	Presented at PAS
Case	No	Lei Li	—	—		
Rochester	Yes	Tracey Nolan/Rick Williams	—	—		
Iowa	Yes	Nellie Hansen	—	—		
Duke	Yes	Grier Page	—	—		
Alabama	Yes	Marie Gantz	—	—		
UCSD	Yes	Marie Gantz	—	—		
Stanford	Yes	Lisa Wrage	—	—		
Miami	Yes	Lisa Wrage	—	—		
UNM	No	Doug Kendrick	—	—		
Iowa	No		GDB: Accept with revisions	Major revision - Withdrawn by investigators		
Alabama	Yes		GDB: Revise FU: Revise	Major revision		
Wayne	Yes		GDB: Revise FU: Revise	Accept with revisions		
Duke	Yes	Nellie Hansen	GDB: Accept FU: Accept	Accept		
Duke	No	Lei Li	Accept	Accept		
Brown	Yes		Photother.: Accept	Accept with revisions		

Houston	Yes	Lisa Wrage	SUPPORT: Accept	Accept		
Wayne	Yes		Accept	Accept		
Brown	Yes	Scott McDonald	Extended FU: Accept	Accept		
Wayne	Yes	Scott McDonald	Extended FU: Accept	Accept		
Brown	Yes	Scott McDonald	Extended FU: Accept	Accept		
Stanford	No	Marie Gantz				
Rochester	Yes		—	—		
Dallas	Yes	Marie Gantz	GDB: Defer for a year	Accept, but defer pending more data availability		
Alabama	Yes	—	GDB: Reject FU: Reject	Reject	—	—
Alabama	No	—	GDB: Reject	Reject	—	—
Alabama	Yes	—	Photother.: Rejected FU: Rejected	Reject	—	—

Comments	Last Update Received
Early Bird Submission	
Early Bird Submission	
Early Bird Submission	
3/4/11 Proposed for PAS 2012 Early Bird Submission Analysis already started	

PAS Abstract Subcommittee defers to Extended Hypothermia FU Subcommittee for priority	
PAS Abstract Subcommittee defers to Extended Hypothermia FU Subcommittee for priority	
PAS Abstract Subcommittee defers to Extended Hypothermia FU Subcommittee for priority	
PAS Abstract Subcommittee defers to Extended Hypothermia FU Subcommittee for priority	
8/30/11 Still completing aEEG readings	8/30/11
8/30/11 Data still needs cleaning and edits completed	8/30/11
Early Bird Submission Defer pending more data availability	
Early Bird Submission	
Early Bird Submission	

Pediatric Academic Societies Meeting Deadlines for 2012

PLEASE NOTE – prior to writing your proposal, please visit the website publications link (https://neonatal.rti.org/pdf/Publications.pdf) to insure that there is not overlap with previous abstracts/publications.
The predefined Primary and secondary studies will have the priority according to our policies and procedures:

1. Primary protocols
2. Secondary protocols
   For primary and secondary protocols, please contact the statistician as soon as your data are available; there is no need to wait for the deadlines listed below. If you do wait, there may be delays in getting your output from the DCC.*
3. Generic Database annual report
4. Secondary analyses of primary protocol data
5. Secondary analyses of GDB/FU data

May 6, 2011 – early bird deadline for protocol submission. If submitted by the early bird deadline, there is an improved chance for resubmission if protocol is not deemed acceptable on the first review.

June 10, 2011 – last day for protocol submission to go to the appropriate protocol subcommittee(s) – site PI approves abstract submission

****PLEASE NOTE – If you have an outstanding manuscript on the publications spreadsheet that has not been submitted for review by the publications subcommittee, you will not be allowed to submit a new proposal.****

July 15, 2011 – Review by relevant subcommittee and SPR abstract committee.

August 1, 2011 - Once an abstract is accepted to move forward, the first author should contact the RTI statistician as soon as possible and no later than August 1, 2011.

September 30, 2011 – Initial abstract draft due to subcommittee. This need not contain final data analyses results.

October 17, 2011 – Final abstract due to subcommittee. Approvals for abstracts must be obtained in advance of NICHD Clearance

Early November – Final abstracts to NICHD for clearance
Mid-November– PAS deadline
April 28- May 1, 2012 -PAS meeting –Boston, MA
Certainly proposals and protocols are encouraged prior to these dates.

For the months of October and November, SPR abstract analyses will take priority over pre-existing analyses (for example, manuscripts, pending presentations for other meetings, and so forth). If it is anticipated that an analysis for work other than SPR 2012 will need to occur during this time period, please speak to Drs. Das and Higgins prior to September 1, 2011.

From: Vaucher, Yvonne
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT CPAP Hot Topics CPAP slides.pptx
Date: Tuesday, September 27, 2011 9:20:25 AM

OK. Thanks.

Yvonne

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]
Sent: Tuesday, September 27, 2011 6:00 AM
To: Vaucher, Yvonne; Finer, Neil
Cc: 'Wally Carlo, M.D.'; Myriam Peralta, M.D.
Subject: SUPPORT CPAP Hot Topics CPAP slides.pptx

Yvonne – I changed the last few slides to make one slide for the results and conclusions.

In the interest of time and ample input, I will send this version to the SC and FU PI's for input and tell them to get back to you by Thursday as I believe the slides are due Oct 1, correct?

Also – Myriam – can you send me your slides??
Thanks
Rose

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Vaucher, Yvonne"
Subject: RE: SUPPORT CPAP Hot Topics CPAP slides.pptx
Date: Tuesday, September 27, 2011 9:21:00 AM

I sent it so you may get comments back. I don't anticipate too many but have given folks a chance to express their views!!
Thanks for all the hard work and effort!!
Rose

Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network
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301-496-3790 (FAX)
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-----Original Message-----
From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]
Sent: Tuesday, September 27, 2011 9:20 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT CPAP Hot Topics CPAP slides.pptx

OK. Thanks.

Yvonne

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]
Sent: Tuesday, September 27, 2011 6:00 AM
To: Vaucher, Yvonne; Finer, Neil
Cc: 'Wally Carlo, M.D.'; Myriam Peralta, M.D.
Subject: SUPPORT CPAP Hot Topics CPAP slides.pptx

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In the interest of time and ample input, I will send this version to the SC and FU PI's for input and tell them to get back to you by Thursday as I believe the slides are due Oct 1, correct?

Also – Myriam – can you send me your slides??
Thanks
Rose

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: SUPPORT CPAP Draft
Date: Tuesday, September 27, 2011 9:07:00 AM

I had included Roger Soll instead of Roger Faix!! I called Roger and left him a message to delete

Thanks
Rose

Rosemary D. Higgins, MD

Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network

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From: Archer, Stephanie (NIH/NICHD) [E]
Sent: Tuesday, September 27, 2011 9:07 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Message Recall Failure: SUPPORT CPAP Draft

Your message

To: 'Finer, Neil'; 'Wally Carlo, M.D.'; 'kurt.schibler@cchmc.org'; 'mcw3@cwru.edu'; 'Soll, Roger F.'; 'Laptook, Abbot'; 'Bradley Yoder'; 'Das, Abhik'; 'Gantz, Marie';

'Nancy Newman'; 'Rich, Wade'; 'Myriam Peralta, M.D.'

Cc: Archer, Stephanie (NIH/NICHD) [E]

Subject: SUPPORT CPAP Draft

Sent: 9/27/2011 9:02 AM

cannot be recalled on 9/27/2011 9:07 AM.

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Pablo.Sanchez@UTSouthwestern.edu"
Subject: Re: Safe and Effective Oxygenation in ELBW Infants-June 2011 (2).ppt
Date: Tuesday, September 27, 2011 5:56:22 AM

Can I please get your budget vote? Those with pending protocols want their results.
Thanks
Rose

From: Pablo Sanchez <Pablo.Sanchez@UTSouthwestern.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tue Sep 27 01:19:14 2011
Subject: RE: Safe and Effective Oxygenation in ELBW Infants-June 2011 (2).ppt

yes--pablo

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]
Sent: Monday, September 26, 2011 2:51 PM
To: (suhas.kallapur@cchmc.org); Abbot Laptook (alaptook@wihri.org); Abhik Das (adas@rti.org); Ambal (ambal@uab.edu); Anna Maria Hibbs (AnnaMaria.hibbs@cwru.edu); barbara_stoll@oz.ped.emory.edu; bpoindex@iupui.edu; carl_dangio@urmc.rochester.edu; Carlton, David P; cotte010@mc.duke.edu; dstevenson@stanford.edu; dwallace@rti.org; Ed Bell (edward-bell@uiowa.edu); goldb008@mc.duke.edu; Greg Sokol (gsokol@iupui.edu); Haresh Kirpalani (KIRPALANIH@email.chop.edu); John Barks; Jon.E.Tyson@uth.tmc.edu; Kennedy, Kathleen A; Krisa Van Meurs (vanmeurs@stanford.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); Kurt Schibler [kurt.schibler@cchmc.org]; Luc Brion; Martin Keszler (mkeszler@wihri.org); mcw3@po.cwru.edu; Meena Garg (mgarg@mednet.ucla.edu); Nelin, Leif; Pablo Sanchez; Polin, Richard; Robin Ohls (rohls@salud.unm.edu); ronnie_guillet@urmc.rochester.edu; Satyan Lakshminrusimha; Schmidt, Barbara (Neonatology); Seetha Shankaran ; Sood, Beena [bsood@med.wayne.edu]; Truog, William (MD); Uday Devaskar (UDEVASKAR@MEDNET.UCLA.EDU); Wally Carlo (wacarlo@uab.edu)
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: Safe and Effective Oxygenation in ELBW Infants-June 2011 (2).ppt

HI,
Dr. Eduardo Bancalari has asked that we share a prior SUPPORT presentation with him so that he can prepare his Hot Topics talk "Oxygen targets: can they be achieved?" Dr. Bancalari will acknowledge the network.
Wally has sent a recent talk that is suitable.
Please send me a yes./No vote by Sept. 30 to share with Eduardo
Just a reminder, Miami did enroll in the SUPPORT Trial as part of their network involvement.

Thanks
Rose

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: Fw: Safe and Effective Oxygenation in ELBW Infants-June 2011 (2).ppt
Date: Monday, September 26, 2011 9:21:23 PM

From: Wally Carlo, M.D. <WCarlo@peds.uab.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Archer, Stephanie (NIH/NICHD) [E]
Sent: Mon Sep 26 20:57:27 2011
Subject: RE: Safe and Effective Oxygenation in ELBW Infants-June 2011 (2).ppt

yes

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Mon 9/26/2011 2:51 PM
To: (suhas.kallapur@cchmc.org); Abbot Laptook (alaptook@wihri.org); Abhik Das (adas@rti.org); Ambal (ambal@uab.edu); Anna Maria Hibbs (AnnaMaria.hibbs@cwru.edu); barbara_stoll@oz.ped.emory.edu; bpoindex@iupui.edu; carl_dangio@urmc.rochester.edu; Carlton, David P; cotte010@mc.duke.edu; dstevenson@stanford.edu; dwallace@rti.org; Ed Bell (edward-bell@uiowa.edu); goldb008@mc.duke.edu; Greg Sokol (gsokol@iupui.edu); Haresh Kirpalani (KIRPALANIH@email.chop.edu); John Barks; Jon.E.Tyson@uth.tmc.edu; Kennedy, Kathleen A; Krisa Van Meurs (vanmeurs@stanford.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); Kurt Schibler [kurt.schibler@cchmc.org]; Luc Brion (luc.brion@utsouthwestern.edu); Martin Keszler (mkeszler@wihri.org); mcw3@po.cwru.edu; Meena Garg (mgarg@mednet.ucla.edu); Nelin, Leif; Pablo.Sanchez@UTSouthwestern.edu; Polin, Richard; Robin Ohls (rohls@salud.unm.edu); ronnie_guillet@urmc.rochester.edu; Satyan Lakshminrusimha; Schmidt, Barbara (Neonatology); Seetha Shankaran ; Sood, Beena [bsood@med.wayne.edu]; Truog, William (MD); Uday Devaskar (UDEVASKAR@MEDNET.UCLA.EDU); Wally Carlo (wacarlo@uab.edu)
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Subject: Safe and Effective Oxygenation in ELBW Infants-June 2011 (2).ppt

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Just a reminder, Miami did enroll in the SUPPORT Trial as part of their network involvement.

Thanks

Rose

From: Vaucher, Yvonne
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Gantz, Marie
Subject: FW: SUPPORT CPAP Draft
Date: Monday, September 26, 2011 8:52:39 PM
Attachments: AppendixA_BSIDIIIabcCompositeCogLangMotorScoresMean less than70_85_CPAP09222011.docx
Table1_DemoNeoCharacteristicsCPAP09222011.docx
Table2_abcNDIOutcomesCPAP09222011.docx
Table3_abcDeathNDIComponentsGACompCPAP09222011.docx
Table4_abcMedicalrOutcomesCPAP09222011.docx
Figure ConsortCPAP09262011.doc
Vaucher SUPPORT FU CPAP PAPERwithoutTables9262011_YEVver3.5 SUPPORTSubCommittee.docx

Rose,
Here is the most recent draft. I could not attach the Tables properly. Will try to do that tomorrow.

Marie, please review consort diagram to be sure the numbers are correct. Also the bolded numbers in the paper. Thanks.

I have left the percentages in the paper so the reader can see them while reading without referring to the tables but they can be removed or stay depending upon what is included in the final tables. Tables can be combined or deleted (Tables 3 &/or 4) and the relevant data included in the text instead. I have included the GA strata in the Tables for Subcommittee review as the strata are very different. Again we don't need to put them in the final paper or they could be another Appendix.

Yvonne

Yvonne E. Vaucher, M.D., M.P.H.
Division of Neonatal/Perinatal Medicine
Clinical Professor of Pediatrics
UCSD School of Medicine

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FAX: 619-543-3812

BSID-III at 18-22 months Corrected Age

a. Entire cohort:CPAP vs. Surfactant

	CPAP	SURF	RR**	p
Cognitive Composite score (N=974,mean±SEM)	91±0.74	90±0.75	0.92(-0.94, 2.79)	0.33
Language composite score (N=960,mean±SEM)	86±0.87	86±0.88	0.57 (-1.63, 2.77)	0.61
Composite motor score (N=277,mean±SEM)	88±1.45	88±1.37	0.72(-3.14, 4.58	0.7
Cognitive Composite score < 70*	36/502(7.2)	36/472(7.6)	0.95(0.61, 1.5)	0.84
Language composite score <70*	73/479(14.7)	81/463(17.5)	0.83 (0.62, 1.12)	0.23
Composite motor score < 70*	16/135(11.9)	18/142(12.7)	0.92(0.51, 1.66)	0.77
Cognitive Composite score < 85*	111/502(22.1)	26/472(26.7)	0.82(0.66, 1.02)	0.08
Language composite score <85*	214/497(43.1)	214/463(46.2)	0.91 (0.79, 1.06)	0.23
Composite motor score < 85*	41/135(30.4)	45/142(31.7)	0.88 (0.63, 1.25)	0.48

b. <u>24 0/7-25 6/7 weeks Gestational Age</u>

Cognitive Composite score (N=352,mean±SEM)	89±0.1.09	88±1,17	1.06(-1./96 4.08)	0.49
Language composite score (N=361,mean±SEM)	84±1.28	83±1.38	1.47 (-2.09, 5.02)	0.42
Composite motor score (N=106,mean±SEM)	88±1.45	88±1.37	0.72(-3.14, 4.58	0.7
Cognitive Composite score < 70*	23/198(11.6)	16/167(9.6)	1.16(0.64, 2.12)	0.62
Language composite score <70*	44/196(22.4)	37/165(22.4)	1.01 (0.68, 1.49)	0.97
Composite motor score < 70*	12/53(22.6)	11/53(20.8)	1.09(0.53, 2.22)	0.82
Cognitive Composite score < 85*	57/198(28.8)	55/167(32.9)	0.9(0.66, 1.22)	0.5
Language composite score <85*	97/196(49.5)	92/165(55.8)	0.9 (0.73, 1.1)	0.3
Composite motor score < 85*	27/53(50.9)	25/53(47.2)	1.04 (0.69, 1.585)	0.84

c. <u>26 0/7-27 6/7 weeks Gestational Age</u>

Cognitive Composite score (N=609,mean±SEM)	93±0.91	93±0.88	0.84(-1.53, 3.21)	0.49
Language composite score (N=599,mean±SEM)	88±1.07	88±1.04	0.02 (-2.77, 2.81)	0.99
Composite motor score (N=171,mean±SEM)	93±1.83	92±1.70	1.19(-3.72, 6.11)	0.62
Cognitive Composite score < 70*	13/304(4.3)	20/305(6.6)	0.74(0.36, 1.51)	0.42
Language composite score <70*	29/301(9.6)	44/298(14.8)	0.67 (0.43, 1.06)	0.08
Composite motor score < 70*	4/82(4.9)	20/89(22.5)	0.68(0.36, 1.28)	0.46
Cognitive Composite score < 85*	54/304(17.8)	71/305(23.3)	0.75(0.55, 1.03)	0.08
Language composite score <85*	117/301(38.9)	122/298(40.9)	0.93 (0.75, 1.14)	0.48
Composite motor score < 85*	14/82(17.1)	20/89(22.5)	0.68 (0.36, 1.26)	0.23

* -no./total no.(%)

** Adjusted difference in means(95% CI)

Table 1: Demographics and Characteristics of Trial Cohort and Follow-up Cohorts

	Trial Cohort		Follow-up Cohort	
	CPAP	SURFACTANT	CPAP	SURFACTANT
	N=663	N=653	N=511	N=479
Birth weight (grams, Mean ± SD)	835±188	825±198	849±186	852±193
Gestational age (weeks, Mean ± SD)	26.2±1.1	26.2±1.1	26.3±1.1	26.3±1.1
Small for gestational age < 10-no./total no.(%)	37/663(5.6)	59/653(9)**	23/511(4.5)	32(479(6.7)
Male-no./total no.(%)	342/663(51.6)	370/653(56.7)	256/511(50.1)	266/479(55.5)
Race				
Non-Hispanic White-no./total no.(%)	250/663(39.1	271/653(41.5)	196/511(38.4)	200/479(41.8)
Non-Hispanic Black-no./total no.(%)	254/663(38.3)	235/653(36)	200/511(39.1)	177/479(37)
Hispanic-no./total no.(%)	138/663(20.8)	121/653(18.5)	98/511(19.2)	85/479(17.7)
Other or unknown-no./total no.(%)	21/663(3.2)	26/653(4)	17/511(3.3)	17/479(3.5)
Multiples-no./total no.(%)	178/663(26.8)	159/653(24.3)	138/511(27)	114/470(23.8)
Antenatal steroids(any)-no./total no.(%)	642/663(96.8)	623/652(95.6)	493/511(96.5)	456/479(95.2)
Cesarean section-no./total no.(%)	449/663(67.7)	434/653(66.5)	352/511(68.9)	315/479(65.8)
Public health insurance only-no./total no.(%)	351/661(53.1)	353/649(54.4)	262/511(51.3)	257/479(53.7)

Mother married-no./total no.(%)	305/662(46.1)	287/651(44.1)	244/511(47.7)	221/479(46.1)
With both biological parents-no./total no.(%)	365/539(67.7)	353/516(68.4)	348/510(68.2)	329/479(68.7)
Maternal education < 12-no./total no.(%)	161/616(26.1)	152/590(25.8)	128/506(25.3)	116/469(24.7)
Income < $30,000/year†-no./total no.(%)	270/514(52.5)	268/488(54.9)	260/493(52.7)	251/461(54.4)
English as primary language-no./total no.(%)	427/511(83.6)	403/478(84.3)	426/510(83.5)	403/478(84.3)
Severe ROP-no./total no.(%)	67/511(13.1)	65/473(13.7)	62/479(12.9)	58/434(13.4)
Bronchopulmonary dysplasia§-no./total no.(%)	223/569(39.2)	219/539(40.6)	193/511(37.8)	187/479(39)
IVH grade 3-4/PVL-no./total no.(%)	111/642(17.3)	87/628(13.9)	70/510(13.7)	46/478(9.6)*
NEC-stage ≥2 -no./total no.(%)	83/654(12.7)	63/636(9.9)	56/511(11)	30/479(6.3)***
Late onset sepsis/meningitis-no./total no.(%)	224/634(35.3)	230/624(36.9)	167/511(32.1)	154/479(32)
Postnatal steroids-no./total no.(%)	47/649(7.2)	83/631(13.2)****	34/508(6.7)	55/476(11.4)**
Died before discharge-no./total no.(%)	109/663(16.4)	128/653(19.6)		

†Not available for trial cohort at time of discharge

*p<0.05, **p<0.02,***p<0.01 ****p<0.001

*Results presented as number/total number (%); All values adjusted for stratification factors (study center and gestational-age group) and familial clustering.

Table 2: SUPPORT Death and NDI Outcomes at 18-22 Months Corrected Age*

	CPAP	SURFACTANT	aRR	p
a. Entire cohort:CPAP vs. Surfactant				
Death before 18-22 mo CA-no./total no.(%)	118/643(18.4)	140/638(22)	0.83(0.67,1.04)	0.1
Outcome determined for death or NDI	621/663(93.7)	613/653(93.9)	1(0.97,1.03)	0.83
Death or NDI	173/621(27.9)	183/613(29.9)	0.93(0.78,1.1)	0.39
NDI	56/503(11.1)	43/473(8.9)	1.16(0.79,1.71)	0.44
BSID-III cognitive composite score < 70	36/502(7.2)	36/472(7.6)	0.95(0.61,1.5)	0.84
Gross motor function level ≥ 2	26/511(5.1)	23/479(4.8)	0,98(0.57,1.69)	0.95
Moderate/severe cerebral palsy	21/511(4.1)	19/479(4)	0.93(0.51,1.72)	0.82
Blindness, bilateral	4/511*0.8)	7/479(1.5)	0.53(0.16,1.78)	0.31
Hearing impairment	17/511(3.3)	7/479(1.5)	2.8(1.1-6.9)	0.06

	CPAP	SURFACTANT	aRR	p
b. <u>24 0/7-25 6/7 weeks Gestational Age</u>				
Death before 18-22 mo CA-no./total no.(%)	73/276(26.4)	97/273(35.5)	0.74(0.57,0.96)	0.02
Death/NDI determined-no./total no.(%)	272/285(95.4)	265/280(94.6)	1.01(0.97,1.05)	0.68
NDI or death-no./total no.(%)	109/272(40.1)	118/265(44.5)	0.9 (0.74,1.09)	0.27
NDI-no./total no.(%)	36/199(18.1)	21/168(12.5)	1.37(0.83,2.27)	0.22
BSID-III cognitive score < 70-no./total no.(%)	23/198(11.6)	16/167(9.6)	1.16(0.64,2.12)	0.62
Gross motor function level ≥ 2-no./total no.(%)	17/201(8.5)	9/1712(5.2)	1.52(0.7,3.29)	0.29
Moderate/severe cerebral palsy-no./total no.(%)	14/201(7.0)	8/172(4.7)	1.32(0.57,3.04)	0.51
Blindness, bilateral -no./total no.(%)	2/201(1.0)	2/172(1.2)	0.86(0.12,6.02)	0.88
Hearing impairment-no./total no.(%)	11/201(5.5)	3/172(1.7)	3.24(0.9,11.71)	0.07

	CPAP	SURFACTANT	aRR*	p
c. <u>26 0/7-27 6/7 weeks Gestational Age</u>				
Death before 18-22 mo CA-no./total no.(%)	45/366(12.3)	43/365(11.8)	1.05(0.71,1.55)	0.82
Death/NDI determined-no./total no.(%)	349/378(92.3)	348/373(93.3)	0.99(0.95,1.03)	0.57
NDI or death-no./total no.(%)	64/349(18.3)	65/348(18.7)	0.99(0.72,1.35)	0.93
NDI-no./total no.(%)	19/304(6.3)	22/305(7.2)	0.93(0.5,1.72)	0.81
BSID-III cognitive score < 70-no./total no.(%)	13/304(4.3)	20/305(6.6)	0.74(0.36,1.51)	0.41
Gross motor function level ≥ 2-no./total no.(%)	9/310(2.9)	14/307(4.6)	0.61(0.27,1.4)	0.24
Moderate/severe cerebral palsy-no./total no.(%)	7/310(2.3)	11/307(3.6)	0.62(0.24,1.58)	0.31
Blindness, bilateral-no./total no.(%)	2/310(0.6)	5/307(1.6)	0.39(0.08,1.99)	0.26
Hearing impairment-no./total no.(%)	6/310(1.9)	4/307(1.3)	1.53(0.44,5.26)	0.5

Relative risk adjusted for stratification factors (study center and gestational-age group) and familial clustering (except for blindness due to small N)

Table 3: CPAP vs. Surfactant- Death and Components of NDI for entire cohort and gestational age strata

a. Entire cohort: CPAP vs. Surfactant

Death or cognitive composite<70-no./total no.(%)	154/620(24.8)	176/612(28.8)	0.86(0.72,1.03)	0.11
Death or GMF level ≥2-no./total no.(%)	144/629(22.9)	163/619(26.3)	0.87(0.72,1.05)	0.16
Death or moderate/severe CP-no./total no.(%)	139/629(22.1)	159/619(25.7)	0.86(0.71,1.05)	0.14
Death or blind in both eyes-no./total no.(%)	122/629(19.4)	147/619(23.7)	0.82(0.67,1.02)	0.07
Death or hearing impairment-no./total no.(%)	135/629(21.5)	147/619(23.8)	0.9(0.74,1.11)	0.33

b. 24 0/7-25 6/7 weeks Gestational Age

Death or cognitive composite<70-no./total no.(%)	96/271(35.4)	113/264(42.8)	0.83(0.67,1.02)	0.08
Death or GMF level ≥2-no./total no.(%)	90/274(32.8)	106/269(39.4)	0.84(0.67,1.04)	0.12
Death or moderate/severe CP-no./total no.(%)	87/274(31.8)	105/269(39)	0.82(0.65,1.02)	0.08

Death or blind in both eyes-no./total no.(%)	75/274(27.4)	99/269(36.8)	0.75(0.58,0.96)	0.03
Death or hearing impairment-no./total no.(%)	84/274(30.7)	100/269(37.2)	0.83(0.65,1.05)	0.12

c. **26 0/7-27 6/7 weeks Gestational Age**

Death or cognitive composite<70-no./total no.(%)	58/349(16.6)	63/348(18.1)	0.93(0.67,1.29)	0.67
Death or GMF level ≥2-no./total no.(%)	54/355(15.2)	57/350(16.3)	0.94(0.67,1.33)	0.74
Death or moderate/severe CP-no./total no.(%)	52/355(14.6)	54/350(25.7)	0.96(0.68,1.36)	0.82
Death or blind in both eyes-no./total no.(%)	47/355(13.2)	48/350(13.7)	0.97(0.67,1.42)	0.89
Death or hearing impairment-no./total no.(%)	51/355(14.4)	47/350(13.4)	1.07(0.74,1.55)	0.71

Table 4: CPAP vs Surfactant: Medical Outcomes for entire cohort and both gestational age strata

	CPAP	SURF	RR	p
a. <u>Entire cohort: CPAP vs. Surfactant</u>				
Respiratory Medications–no./total no.(%)				
Bronchodilators–no./total no.(%)	176/507(34.7)	168/474(35.4)	0.95(0.81,1.14)	0.66
Diuretics–no./total no.(%)	15/507(3)	14/474(3)	0.99(0.49,1.98)	0.97
Steroids–no./total no.(%)	115/507(22.7)	88/474(18.6)	1.21(0.94,1.55)	0.14
Anticonvulsants–no./total no.(%)	14/510(2.7)	10/479(2.1)	1.29(0.59,2.82)	0.52
Readmission Any–no./total no.(%)	228/510(44.7)	221/479(46.1)	0.99(0.86,1.13)	0.84
For respiratory problem–no./total no.(%)	118/502(23.5)	119/471(25.3)	0.96(0.77,1.2)	0.71
Any surgery–no./total no.(%)	239/508(47)	212/479(44.3)	1.06(0.92,1.21)	0.41
Eye surgery–no./total no.(%)	50/508(9.8)	48/478(10)	0.96(0.66,1.38)	0.82

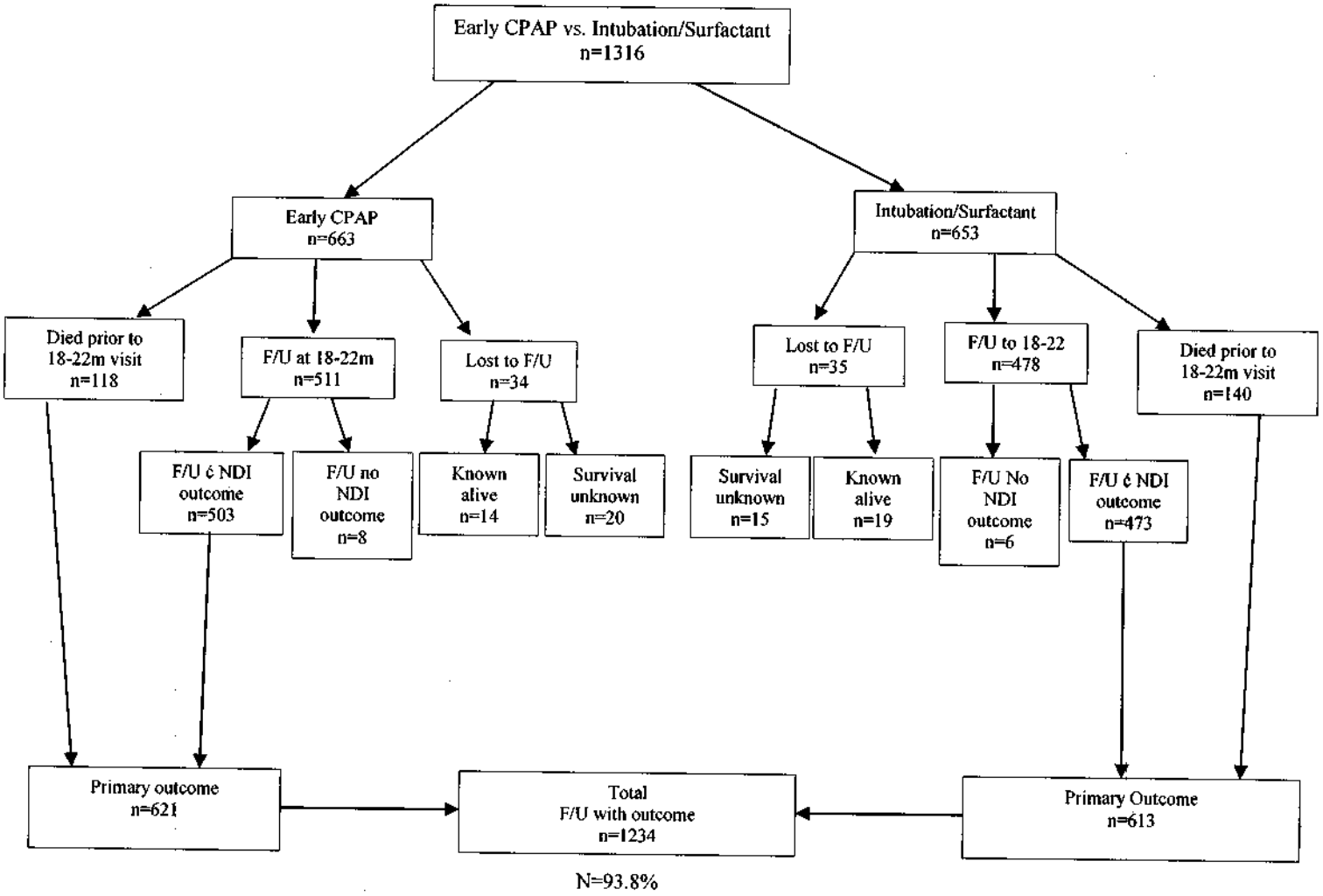
b. <u>24 0/7-25 6/7 weeks Gestational Age</u>

Respiratory Medications–no./total no.(%)				
Bronchodilators–no./total no.(%)	85/199(42.7)	65/171(38)	1.12(0.87,1.44)	0.38
Diuretics–no./total no.(%)	10/199(5)	10/171(5.8)	0.89(0.39,2.02)	0.77
Steroids–no./total no.(%)	58/199(28.1)	38/171(22.2)	1.37(0.96,1.97)	0.08
Anticonvulsants–no./total no.(%)	10/201(5)	2/172(1.2)	4.49(0.98,20.53)	0.05
Readmission Any–no./total no.(%)	102/201(50.7)	95/172(55.2)	0.96(0.79,1.16)	0.67
For respiratory problem–no./total no.(%)	49/167(24.9)	48/169(28.4)	0.95(0.67,1.35)	0.79
Any surgery–no./total no.(%)	102/200(51)	103/172(59.9)	0.87(0.72,1.05)	0.14
Eye surgery–no./total no.(%)	27/200(13.5)	42/171(24.6)	0.56(0.36,0.86)	0.009

c. **26 0/7-27 6/7 weeks Gestational Age**

Respiratory Medications–no./total no.(%)				
Bronchodilators–no./total no.(%)	91/308(29.5)	103/303(34)	0.85(0.67,1.08)	0.20
Diuretics–no./total no.(%)	5/308(1.6)	4/303(1.3)	1.25(0.33,4.64)	0.74
Steroids–no./total no.(%)	57/308(18.5)	50/303(34)	0.85(0.67,1.08)	0.20
Anticonvulsants–no./total no.(%)	4/309(1.3)	8/307(2.6)	0.48(0.15,1.56)	0.22
Readmission Any–no./total no.(%)	126/309(40.8)	126/307(41)	1.01(0.83,1.22)	0.94
For respiratory problem–no./total no.(%)	69/305(22.6)	71/302(23.5)	0.96(0.72,1.28)	0.79
Any surgery–no./total no.(%)	137/308(44.5)	109/307(35.5)	1.25(1.03,1.5 1)	0.02
Eye surgery–no./total no.(%)	23/308(7.5)	6/307(2)	3.95(1.63,9.56)	0.002

Figure: Patient Flow Diagram: CPAP vs. Surfactant



Early CPAP versus Surfactant in Extremely Preterm Infants: Neurodevelopmental Outcomes in Early Childhood

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ABSTRACT

BACKGROUND

The recent randomized, multicenter SUPPORT trial demonstrated that initial treatment with early, non-invasive CPAP is an alternative to early surfactant administration after intubation and is associated with similar rates of death or BPD in infants born at 24 to 28 weeks gestation. We hypothesized that, compared to treatment with surfactant administration after intubation, treatment with early CPAP would decrease the composite outcome of mortality or neurodevelopmental impairment.

METHODS

We followed 1108 infants, 24 0/7 to 27 6/7 weeks gestation, who had been randomized in the SUPPORT trial to receive either early CPAP with limited ventilation or intubation with surfactant administration within one hour after birth. A standardized neurodevelopmental assessment was performed at 18-22 months corrected age. The primary composite outcome was death or neurodevelopmental impairment (NDI) which was defined as having any of the following: cognitive score < 70, Gross Motor Function Classification score of ≥ 2, moderate/severe cerebral palsy, bilateral blindness or permanent hearing impairment.

RESULTS

Death or NDI was determined for 1234/1316 (93.8%) of infants enrolled in SUPPORT and 93.5% (**990/1058**) of known survivors were evaluated at 18-22 months corrected age. Death or NDI occurred in 27.9% (173/621) of the CPAP group and in 29.9% (183/613) of the Surfactant group (p=0.39). Rates of death (CPAP-18.4 -vs. Surf-21.9%, p=0.10), NDI alone (CPAP-11.1 vs. Surf-8.9%, p=0.32), cognitive score < 70 (CPAP-7.2 vs. Surf-7.6%, p=0.84), moderate/severe cerebral palsy (CPAP-4.1 vs. Surf-4.0%, p=0.82) and blindness (CPAP-0.8 vs. Surf-1.5%, p=0.31), were similar in both treatment arms. In the most immature stratum (24 0/7-25-6/7 weeks gestation) there were fewer deaths [CPAP-26.4% (73/277) vs. Surf-35.5% (97/273), p=0.022].

CONCLUSION

We found no significant differences in the in the composite outcome of death or NDI at 18-22 months corrected age between extremely premature infants who were randomized to receive either early CPAP with a limited ventilation strategy if needed or early intubation with surfactant administration followed by conventional ventilation.

BACKGROUND

Extremely premature infants are at high risk for death or neurodevelopmental impairment- in early childhood. (ref) The risk of impairment is increases with decreasing gestational age, severity of illness and a a consequence of neonatal complications including- IVH/PVL, symptomatic PDA, NEC, CLD/BPD- and severe ROP. (REF) Although surfactant administration decreases both death and BPD, subsequent RCTs of -respiratory interventions including HFPV, HFJT, iNO have failed to consistently decrease mortality, IVH/PVL, NEC, or CLD/BPD.(REF)

The recent, multicenter, randomized, controlled (SUPPORT) trial demonstrated that treatment with non-invasive CPAP shortly after birth is an alternative to surfactant administration after intubation and is associated with similar rates of death or BPD in extremely premature infants born at 24 0/7 to 27 6/7 weeks gestation (REF Finer). Early CPAP was associated with less frequent need for postnatal steroids, shorter duration of mechanical ventilation, and similar rates of air leak and IVH compared with surfactant, all factors associated with adverse ND outcome in ELBW/ELGA infants. In addition, mortality was lower in the most immature, 24-25 week gestation stratum.

The Surfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT) in extremely low birth weight (ELBW) infants was in initially designed and powered to evaluate early childhood neurodevelopmental outcome of enrolled infants. We hypothesized that compared to treatment with surfactant administration after intubation, treatment with early, non-invasive CPAP and a limited ventilation strategy would result in decreased mortality or neurodevelopmental impairment at 18-22 months corrected age.

METHODS

Study Design

1316 extremely preterm infants (24 weeks 0 days to 27 weeks 6 days) born between February 2005 and February 2009 at 20 centers in the United States participating in the Neonatal Research Network (NRN) of the Eunice Kennedy Shriver National Institute of Child Health and Human Development were enrolled immediately following delivery in the prospective, randomized, controlled SUPPORT trial. Permuted block randomization was used, with stratification according to center and gestational age (24 weeks 0 days to 25 weeks 6 days or 26 weeks 0 days to 27 weeks 6 days). The infants were randomly assigned before birth to receive either CPAP immediately following delivery and a limited ventilation strategy if subsequent intubation was required or intubation with surfactant administration within an

hour after birth. Using a 2-by-2 factorial design, participants were also randomly assigned to a target range of oxygen saturation of 85% to 89% (lower oxygen saturation group) or 91 to 95% (higher oxygenation group). Procedures for enrollment, intervention, and data collection have been previously reported. (REF Finer) . The study was approved by the institutional review board at each participating site and RTI international which is the independent data coordinating center for the Neonatal Research Network. Written informed consent was obtained from the parent or guardian of each child before delivery.

Comment [yev 1]: We can reverse the order of CPAP and saturation ranges for our papers.

Assessments

All infants who survived to 36 weeks corrected age were eligible to participate in the prospective NRN follow-up cohort of the SUPPORT trial. A comprehensive neurodevelopmental assessment was performed at 18-22 months corrected age for prematurity by neurologic examiners and neurodevelopmental testers who were unaware of the treatment assignments and were trained annually for reliability of assessments during a 2-day workshop. Developmental function was assessed using the Bayley Scales of Infant and Toddler Development, 3rd ed (BSID-III). (REF) Cognitive Composite Scores are reported as a standardized score with a mean of 100 and a standard deviation of 15. The modified Gross Motor Function Classification System (GMFCS) describes the gross motor performance and has a range from 0 (normal) to 5 (most impaired). (REF) Examiners also recorded the presence of cerebral palsy defined as a nonprogressive disorder of the central nervous system and characterized by abnormal muscle tone in at least one arm or leg associated with abnormal control of movement or posture with delayed attainment of motor milestones.(REF Amiel-Tison) Cerebral palsy was classified depending on severity into mild (GMFCS $\leq$1), moderate (GMFCS 2 or 3) or severe (GMFCS $\geq$ 4). Hearing and visual impairment were determined based on parental history and examination.

Certified research nurses collected demographic and neonatal outcome data using standardized definitions recorded in the trial's manual of operations. Data collection included gestational age, birthweight, gender, multiple gestation, race/ethnicity, , ROP status, BPD status, history of medical or surgical NEC, history of late onset sepsis, use of postnatal steroids, rehospitalizations, interim medical history, surgeries, insurance status, marital status, maternal education, household income, language spoken at home, whether living with biological parents, Socioeconomic data was updated during the 18-24 month visit and if not available, data during the neonatal period was used.

Outcome

The primary neurodevelopmental outcome was the composite of death or neurodevelopmental impairment at 18 to 22 months corrected age. This composite outcome was selected because infants who died before 18 months could not be classified as having neurodevelopmental impairment. Neurodevelopmental impairment was defined as having any of the following: BSID III cognitive composite score less than 70, GMFCS $\geq$ 2, presence of moderate or severe cerebral palsy, permanent hearing loss that does not permit the child to

Comment [yev 2]: This remains a question but let's leave as is for now

understand directions of the examiner and communicate despite amplification with hearing aids or cochlear implants, or bilateral visual impairment (vision < 20/200).

Statistical Analysis

The sample size calculations were based on NRN data from the year 2000 which showed the rate of death or neurodevelopmental impairment at 18-22 months corrected age to be 61%. The sample size was increased by a factor of 1.12 to allow for infants in multiple births to be randomly assigned together to the same treatment arm and was further enlarged by an additional 17% to allow for loss to follow-up after discharge. The target sample was 1310 infants. Details regarding sample size calculations for the SUPPORT trial have been previously reported (REF Finer).

Data was entered in standard forms and was transmitted to RTI International, the data center for the NRN, which stored, managed and analyzed the data for this study. All analyses were performed according to the intention-to-treat principle. The denominator that was used to calculate the rate of each outcome was the number of infants for whom that outcome was known. The primary analyses focused on the percentage of infants in each group for whom the primary outcome of death or NDI at 18-22 months corrected age could be assigned. Analysis of this and all other categorical outcomes was performed with the use of robust Poisson regression in a generalized-estimating-equation model to obtain adjusted relative risks with 95% confidence intervals. Continuous outcomes were analyzed with the use of mixed-effects linear models to obtain adjusted means and standard errors.

Comment [yes 3]: This is all directly from Abhik

In the analysis of all outcomes, the results were adjusted, as prespecified, for gestational-age strata, center, and familial clustering. Two-sided P values of less than 0.05 were considered to indicate statistical significance, and no adjustments have been made for multiple comparisons. For the ____ planned analyses of secondary outcomes according to treatment, we would expect no more than _____tests to have p values of less than 0.05 on the basis of chance alone. Subgroup analyses were conducted within prespecified gestational-age strata for ____ predefined outcomes. Although these tests have not been adjusted for multiple comparisons, we would expect no more than _____ tests per stratum to have p values of less than 0.05 on the basis of chance alone.

Comment [ad4]: This is lifted straight from the NEJM paper because we used the same approach here as well.

RESULTS

All survivors at 36 weeks post-conceptual age (N=1108/1316) were enrolled at discharge in the prospective SUPPORT follow-up cohort. (See Figure ~~1~~) Fifty children were known to have died after 36 weeks adjusted age and before 18-22 months. Sixty-eight children (6.1%) were lost to follow-up; the survival status of 35/68 of these children was unknown. A neurodevelopmental assessment at 18-22 months corrected age was performed for 990/**1058 (93.6%)** children known to be alive during the assessment interval. Of those who were seen for their 18-22 mo

Comment [y5]: This # will change with new data

evaluation exam, NDI was determined for 976 children; 14 children were seen but had an incomplete evaluation that precluded assigning a NDI status. Ultimately, the pre-specified outcome, death or NDI, was determined for 93.8% (1234/1316) of the eligible cohort. There was no difference in the FUP rate between the CPAP and Surfactant arms (93.4 vs 93.4%) of the trial.

Compared with mothers of the 990 children who had a neurodevelopmental assessment at 18-22 months, mothers of 68 children lost to follow-up were less likely to be married (31 vs 47%, p=0.01), and more likely to have public insurance (69 vs 52%, p=0.008). No other demographic variables or neonatal characteristics were significantly different between the groups.

Demographics and neonatal characteristics:

Trial and Follow-up Cohorts: (See Table 1) Compared to the Surfactant arm, infants in the in the CPAP arm of the trial cohort were less likely to be SGA (5.6 vs 9%, unadjusted p=0.016) and less likely to have been exposed to postnatal steroids (7.2 vs 13.2 %, unadjusted p=0.0005). There was a trend towards fewer deaths before 18-22 months corrected age in the CPAP arm (18.5 vs. 22.2%, adjusted p=0.1). This difference reached significance in the lower 24 0/7 to 25 6/7 weeks gestation stratum (26.4 vs. 35.7%, unadjusted p=0.02), but not in the higher gestational age stratum 12.4 vs. 12%). The 24 0/7 to 25 6/7 weeks gestation stratum of the CPAP arm also had less ROP compared to the Surfactant arm (22.2 vs. 31.6%, unadjusted p=0.042) whereas the reverse occurred in the 26 0/7 to 27 6/7 weeks gestation stratum (7.3 vs. 10.2%, unadjusted p=0.044). Thirty-four percent of infants in the CPAP arm were intubated in the delivery room and 67% ultimately received surfactant and ventilation. Almost all mothers (97%) in both arms received antenatal steroids.

In the follow-up cohort there were no significant differences between the CPAP and Surfactant trial arms in the incidence of death before discharge, SGA status, sepsis, ROP in survivors, or LOS. BW, GA, gender, race/ethnicity, multiple birth, mode of delivery, insurance status, maternal education, English as the primary language, household income were also similar in the both groups. Compared to the Surfactant arm, infants in the in the CPAP arm were more likely to be have Grade 3-4 IVH or cystic PVL (13.7 vs 9.6%, unadjusted p=0.05) and more likely to have modified Bell's Stage ≥ 2, medical or surgical NEC (11 vs 6.3%, unadjusted p=0.009). Infants in the CPAP arm were less likely to have been exposed to postnatal steroids (6.7 vs 11.4%, unadjusted p=0.01.)

Primary neurodevelopmental outcome: (See Table 2) The mean corrected age at neurodevelopmental assessment was similar for both treatment arms (CPAP 19.9 ± 2.4 mo vs. Surf 20.1 ± 2.7 mo, p=0.31). There were no significant differences in the composite outcome of *death or NDI* at 18-22 month corrected age between the CPAP and surfactant arms in the entire cohort (27.9 vs. 29.9%) or for the either of the two gestational age strata (40.1 vs. 44.5%

for 24 0/7-25 6/7 weeks gestation; 18.3 vs. 18.7% for 26 0/7 to 27 6/7 weeks gestation). For the entire cohort there was there were no significant difference between the CPAP and Surfactant arms in the incidence of *NDI* (10.9 vs. 9.1%, adjusted p=0.44) or in either of the two gestational age strata (18.1 vs. 12.5, p=0.21 for 24 0/7-25 6/7 weeks gestation; 6.3 vs. 7.2%, p=0.81 for 26 0/7 to 27 6/7 weeks gestation).

Components of NDI: (See Table 2) The incidence of cognitive impairment (BSID-III cognitive composite score < 70) (7.2% vs. 7.6%), gross motor function level ≥ 2 (5.1 vs. 4.8%), moderate/severe CP (4.1 vs. 4.0%), or blindness (0.8 vs. 1.5%) were similar in both the CPAP and Surfactant treatment groups. Although the incidences of NDI, cognitive impairment, moderate to severe cerebral palsy and blindness were higher in the lower gestational age compared to the higher gestational age group, there were no significant differences between the trial arms in either group. Overall 24 infants had permanent hearing impairment, 13 of whom had bilateral hearing aids. There was a trend toward an increased incidence of hearing impairment in the early CPAP treatment arm compared to the surfactant treatment arm (3.3 vs. 1.5%, adjusted p=.06). Compared to the surfactant treatment arm, the incidence of hearing impairment in the CPAP arm was higher in the 24-25 weeks gestation stratum of CPAP arm (5.5 vs.1.7%, adjusted p=.07) but not in the 26-27 weeks stratum (1.9 vs. 1.3%, p=0.50). There was no association between hearing impairment and severe IVH/PVL or NEC, which had a higher incidence in the CPAP arm.

Comment [y6]: Marie: Is this true for both higher and lower GA strata? Is there any interaction for hearing impairment between the CPAP/Surf and high/low oxygen saturation groups).

There were no significant differences in the risk of death or individual NDI composite outcomes between the CPAP and Surfactant arms for the entire cohort. (Table 3) However, in the lower gestational age stratum there was a significantly higher risk of death or bilateral blindness in the Surfactant arm and a trend towards lower risk in the CPAP treatment arm for death or cognitive composite score < 70 and death or moderate to severe cerebral palsy.

Sixty percent of all children (CPAP -59.7% and Surfactant 59.6%) had normal neuromotor, normal neurosensory and normal developmental (i.e. BSID-III cognitive composite score > 85) evaluations. Infants in the 26-27 week gestational age stratum were more likely to be normal (CPAP 67.5% and -Surfactant 65.2%) than those in the 24-25 weeks gestational age stratum(CPAP 47.7% and Surfactant 49.4%).

Other neurodevelopmental outcomes (Appendix) Mean BSID-III composite *cognitive scores* were similar in both CPAP and Surfactant arms for the entire FUP cohort (91.0 ± 0.74 vs. 90.0 ± 0.75) as well as for the 24 0/7 to 25 6/7 week (89.0 ± 1.1 vs. 88.1 ± 1.7) and 26 0/7 to 27 6/7 week (93.0 ± 0.9 vs. 93.0.6 ± 0.9) gestational age strata. Median BSID-III composite scores were virtually identical to the mean composite scores for all of the above groups.

Other outcomes: (Table 4) Overall readmission rates (CPAP 44.7% vs. Surfactant 46%) and readmission rates for respiratory problems (CPAP 23.5% vs. Surfactant 25.3%) were similar in

both treatment arms. There were no significant differences in bronchodilator (CPAP 34.7% v.s Surfactant 35.4%), steroid (CPAP 22.7% vs. Surfactant 18.6%), or diuretic (CPAP 3% vs. Surfactant 3%)use after discharge. There was a similar rate of surgery in both groups (CPAP 47% vs. Surfactant 44.3%).

DISCUSSION:

We report the neurodevelopmental outcome in early childhood at 18-22 months gestational age for extremely premature children enrolled in the SUPPORT trial which compared the use of early CPAP and a limited ventilator strategy with intubation and surfactant administration in the delivery room followed by conventional ventilation in extremely premature infants born between 24 0/7 to 26 6/7 weeks gestation.(REF)

There was no significant difference in the primary, pre-specified composite outcome of death or NDI at 18-22 months corrected age between those extremely premature infants treated with early CPAP vs. those treated early intubation and surfactant administration. Neither were there differences between the CPAP and Surfactant arms in the post-hoc stratified analyses of individual outcomes including NDI, severe mental impairment (cognitive score < 70), moderate/severe CP, moderate/severe motor impairment (GMFSC ≥2), bilateral blindness, or in mean composite cognitive, language or motor BSID-III scores. The was a trend towards a higher rate of hearing impairment in the CPAP compared to the Surfactant treated arm, particularly in the lower gestational age stratum. However, the number of affected children was small and this finding needs to be further explored by other large RCT comparing these alternative treatments.

As reported in previous studies, compared to the more mature infants (26 to 27 weeks gestation), the most immature infants (24 to 25 weeks gestation) in both CPAP and Surfactant arms were at substantially higher risk for all adverse neurodevelopmental outcomes in early childhood including death before 18-22 months, severe cognitive impairment, abnormal gross motor function, moderate/severe cerebral palsy and hearing impairment. (REF)

Bronchopulmonary dysplasia is associated with adverse neurodevelopmental outcome. (REF) Although infants in the CPAP arm had significantly fewer days of ventilation and less often received postnatal steroids compared to the surfactant treated arm, the incidence of BPD and need for supplemental oxygen was similar in both groups before discharge as was the use of respiratory medications and readmission for respiratory problems after discharge.

The strengths of this study include the large number of extremely premature, 24-27 weeks gestation, infants enrolled in this national, multicenter trial; sufficient power to detect a clinically significant difference in the pre-specified neurodevelopmental outcome; the very high percentage of participants who were followed and evaluated in early childhood; and the comprehensive and standardized neurodevelopmental evaluation performed. One third of

infants in the CPAP arm were intubated in the delivery room and two thirds subsequently required surfactant treatment and ventilation which may have blunted any difference in neurodevelopmental outcomes between the two groups. The generalizability of this study may be somewhat limited by the need for antenatal consent which resulted in a trial cohort with higher socioeconomic status than the entire eligible cohort (Ref WR).

In summary, we found no significant differences in the incidence death or NDI, or in any of the individual components of NDI at 18-22 months corrected age between extremely premature infants who were randomized to either early CPAP with a limited ventilation strategy or early intubation with surfactant administration followed by conventional ventilation. Early CPAP is an effective management strategy for the extremely premature infant and is associated with increased survival without increasing neurodevelopmental impairment in the most immature infants.

Acknowledgements

The National Institutes of Health, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), and the National Heart, Lung, and Blood Institute (NHLBI) provided grant support for the Neonatal Research Network's SUPPORT Trial.

Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Drs. Abhik Das (DCC Principal Investigator) and Marie Gantz (DCC Statistician) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study. The following investigators, in addition to those listed as authors, participated in this study:

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Emory University, Children's Healthcare of Atlanta, Grady Memorial Hospital, and Emory Crawford Long Hospital (U10 HD27851, RR25008, M01 RR39) – Barbara J. Stoll, MD; Susie Buchter, MD; Anthony J. Piazza, MD; David P. Carlton, MD; Linda Black, MD; Ann M. Blackwelder, RNC BS MS; Sheena Carter, PhD; Elisabeth Dinkins, PNP; Sobha Fritz, PhD; Ellen C. Hale, RN BS CCRC; Amy K. Hutchinson, MD; Maureen Mulligan LaRossa, RN; Gloria V. Smikle, PNP MSN.

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National Heart, Lung, and Blood Institute – Mary Anne Berberich, PhD; Carol J. Blaisdell, MD; Dorothy B. Gail, PhD; James P. Kiley, PhD.

RTI International (U10 HD36790) – W. Kenneth Poole, PhD; Jamie E. Newman, PhD MPH; Betty K. Hastings; Jeanette O'Donnell Auman, BS; Carolyn Petrie Huitema, MS; James W. Pickett II, BS; Dennis Wallace, PhD; Kristin M. Zaterka-Baxter, RN BSN.

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University of Alabama at Birmingham Health System and Children's Hospital of Alabama (U10 HD34216, M01 RR32) – Namasivayam Ambalavanan, MD; Monica V. Collins, RN BSN MaEd; Shirley S. Cosby, RN BSN. Vivien A. Phillips, RN BSN; Kirstin J. Bailey, PhD; Fred J. Biasini, PhD; Maria Hopkins, PhD; Kristen C. Johnston, MSN CRNP; Sara Krzywanski, MS; Kathleen G. Nelson, MD; Cryshelle S. Patterson, PhD; Richard V. Rector, PhD; Leslie Rodriguez, PhD; Amanda Soong, MD; Sally Whitley, MA OTR-L FAOTA; Sheree York, PT DPT MS PCS.

University of California – San Diego Medical Center and Sharp Mary Birch Hospital for Women (U10 HD40461) – Maynard R. Rasmussen, MD; Paul R. Wozniak, MD; Kathy Arnell, RNC; Rene Renee Bridge, RN; Clarence Demetrio, RN; Martha G. Fuller, RN MSN;

University of Iowa Children's Hospital (U10 HD53109, UL1 RR24979, M01 RR59) – Edward F. Bell, MD; John A. Widness, MD; Jonathan M. Klein, MD; Tarah T. Colaizy, MD MPH; Karen J. Johnson, RN BSN; Diane L. Eastman, RN CPNP MA.

University of Miami, Holtz Children's Hospital (U10 HD21397, M01 RR16587) – Shahnaz Duara, MD; Ruth Everett-Thomas, RN MSN; Maria Calejo, MEd; Alexis N. Diaz, BA; Silvia M. Frade Eguaras, BA; Andrea Garcia, MA; Kasey Hamlin-Smith, PhD; Michelle Harwood Berkowits, PhD; Sylvia Hiriart-Fajardo, MD; Elaine O. Mathews, RN; Helina Pierre, BA; Arielle Riguard, MD; Alexandra Stroerger, BA.

University of New Mexico Health Sciences Center (U10 HD53089, M01 RR997) – Kristi L. Watterberg, MD; Robin K. Ohls, MD; Julie Rohr, MSN RNC CNS; Conta Backstrom Lacy, RN; Jean Lowe, PhD; Rebecca Montman, BSN.

University of Rochester Medical Center, Golisano Children's Hospital (U10 HD40521, M01 RR44) – Nirupama Laroia, MD; Dale L. Phelps, MD; Gary David Markowitz, MD; Linda J. Reubens, RN CCRC; Diane Hust, MS RN CS; Lisa Augostino; Julie Babish Johnson, MSW; Erica Burnell, RN; Harris Gelbard, MD PhD; Rosemary L. Jensen; Emily Kushner, MA; Joan Merzbach, LMSW; Jonathan Mink, MD PhD; Carlos Torres, MD; David Wang, MD; Kelley Yost, PhD.

University of Texas Southwestern Medical Center at Dallas, Parkland Health & Hospital System, and Children's Medical Center Dallas (U10 HD40689, M01 RR633) – Pablo J. Sánchez, MD; Charles R. Rosenfeld, MD; Walid A. Salhab, MD; Sally S. Adams, MS RN CPNP; James Allen, RRT; Laura Grau, RN; Alicia Guzman; Gaynelle Hensley, RN; Elizabeth T. Heyne, PsyD PA-C; Melissa H. Lepps, RN; Linda A. Madden, RN CPNP; Melissa Martin, RN; Nancy A. Miller, RN; Janet S. Morgan, RN; Araceli Solis, RRT; Lizette E. Torres, RN; Catherine Twell Boatman, MS CIMI; Diana M Vasil, RNC-NIC; Kerry Wilder, RN.

University of Texas Health Science Center at Houston Medical School and Children's Memorial Hermann Hospital (U10 HD21373) – Kathleen A. Kennedy, MD MPH; Jon E. Tyson, MD MPH; Nora I. Alaniz, BS; Patricia Evans, MD; Beverly Foley Harris, RN BSN; Charles Green, PhD; Margarita Jiminez, MD MPH; Anna E. Lis, RN BSN; Sarah Martin, RN BSN; Georgia E. McDavid, RN; Brenda H. Morris, MD; Margaret L. Poundstone, RN BSN; Stacy Reddoch, BA; Saba Siddiki, MD; Patti L. Pierce Tate, RCP; Laura L. Whitely, MD; Sharon L. Wright, MT (ASCP).

University of Utah Medical Center, Intermountain Medical Center, LDS Hospital, and Primary Children's Medical Center (U10 HD53124, M01 RR64) – Shawna Baker, RN; Karie Bird, RN; Jill Burnett, RN; Laura Cole, RN; Karen A. Osborne, RN BSN CCRC; Cynthia Spencer, RNC; Mike Steffens, PhD; Kimberlee Weaver-Lewis, RN BSN; Karen Zanetti, RN.

Wake Forest University, Baptist Medical Center, Brenner Children's Hospital, and Forsyth Medical Center (U10 HD40498, M01 RR7122)– Robert G. Dillard, MD; Lisa K. Washburn, MD; Nancy J. Peters, RN CCRP; Barbara G. Jackson, RN BSN; Korinne Chiu, MA; Deborah Evans Allred, MA LPA; Donald J. Goldstein, PhD; Raquel Halfond, MA; Carroll Peterson, MA; Ellen L. Waldrep, MS; Cherrie D. Welch, MD MPH; Melissa Whalen Morris, MA; Gail Wiley Hounshell, PhD.

Wayne State University, Hutzel Women's Hospital, and Children's Hospital of Michigan (U10 HD21385) – Seetha Shankaran, MD; Beena G. Sood, MD MS; Rebecca Bara, RN BSN; Elizabeth Billian, RN MBA; Laura A. Goldston, MA; Mary Johnson, RN BSN.

Yale University, Yale-New Haven Children's Hospital, and Bridgeport Hospital (U10 HD27871, UL1 RR24139, MO1 RR125) – Vineet Bhandari, MD DM; Harris C. Jacobs, MD; Pat Cervone, RN; Patricia Gettner, RN; Monica Konstantino, RN BSN; JoAnn Poulsen, RN; Janet Taft, RN BSN; Christine G. Butler, MD; Nancy Close, PhD; Walter Gilliam, PhD; Sheila Greisman, RN; Elaine Romano, MSN; Joanne Williams, RN BSN.

Data and Safety Monitoring Committee – Gordon Avery, MD, chair, Children's National Medical Center; Christine A. Gleason, MD, chair, University of Washington; Marilee C. Allen, MD, Johns Hopkins University School of Medicine; Shrikant I. Bangdiwala, PhD, University of North Carolina; Carol J. Blaisdell, MD, National Heart, Lung, and Blood Institute; Robert J. Boyle, MD, University of Virginia Health System; Traci Clemons, PhD, The EMMES Corporation; Mary E. D'Alton, MD, Columbia University; Abhik Das (ex officio), PhD, RTI International; Dorothy B. Gail, PhD, National Heart, Lung, and Blood Institute; Carl Hunt, MD, National Heart, Lung, and Blood Institute; Martin Keszler, MD, Georgetown University Hospital; W. Kenneth Poole (ex officio), PhD, RTI International; Carol K. Redmond, ScD, University of Pittsburg; Michael G. Ross, MD, MPH; UCLA School of Medicine and Public Health; Merran A. Thomson, MD, Hammersmith Hospital, UK; Steven J. Weiner, MS, The George Washington University; Marian Willinger (ex officio), PhD, Eunice Kennedy Shriver National Institute of Child Health and Human Development.

Retinopathy of Prematurity Adjudication Committee - Gary David Markowitz, MD, University of Rochester; Amy K. Hutchinson, MD, Emory University; David K. Wallace, MD, MPH, Duke University; Sharon F. Freedman, MD, Duke University.

Figure 1: Patient Flow diagram-CPAP vs. Surfactant

Table 1: Demographic and neonatal characteristics of trial and FUP cohorts-Early CPAP vs. Surfactant treatment arms

Table 2: Pre-specified outcomes and components of NDI for entire cohort and by gestational age strata for Early CPAP vs. Surfactant treatment arms

Table 3: Death and components of NDI for entire cohort and by gestational age strata for Early CPAP vs. Surfactant treatment arms

Table 4: Developmental outcome for entire cohort and by gestational age strata for Early CPAP vs. Surfactant treatment arms

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: Fw: Safe and Effective Oxygenation in ELBW Infants-June 2011 (2).ppt
Date: Monday, September 26, 2011 8:37:51 PM

From: Kennedy, Kathleen A <Kathleen.A.Kennedy@uth.tmc.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Mon Sep 26 19:18:21 2011
Subject: RE: Safe and Effective Oxygenation in ELBW Infants-June 2011 (2).ppt

Yes

Kathleen A. Kennedy, MD, MPH
Richard W. Mithoff Professor of Pediatrics
Director, MS in Clinical Research Degree Program
UT-Houston Medical School
6431 Fannin, Suite 2.106
Houston, TX 77030
713 500-6708

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, September 26, 2011 2:52 PM
To: (suhas.kallapur@cchmc.org); Abbot Laptook (alaptook@wihri.org); Abhik Das (adas@rti.org); Ambal (ambal@uab.edu); Anna Maria Hibbs (AnnaMaria.hibbs@cwru.edu); barbara_stoll@oz.ped.emory.edu; bpoindex@iupui.edu; carl_dangio@urmc.rochester.edu; Carlton, David P; cotte010@mc.duke.edu; dstevenson@stanford.edu; dwallace@rti.org; Ed Bell (edward-bell@uiowa.edu); goldb008@mc.duke.edu; Greg Sokol (gsokol@iupui.edu); Haresh Kirpalani (KIRPALANIH@email.chop.edu); John Barks; Tyson, Jon E; Kennedy, Kathleen A; Krisa Van Meurs (vanmeurs@stanford.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); Kurt Schibler [kurt.schibler@cchmc.org]; Luc Brion (luc.brion@utsouthwestern.edu); Martin Keszler (mkeszler@wihri.org); mcw3@po.cwru.edu; Meena Garg (mgarg@mednet.ucla.edu); Nelin, Leif; Pablo.Sanchez@UTSouthwestern.edu; Polin, Richard; Robin Ohls (rohls@salud.unm.edu); ronnie_guillet@urmc.rochester.edu; Satyan Lakshminrusimha; Schmidt, Barbara (Neonatology); Seetha Shankaran; Sood, Beena [bsood@med.wayne.edu]; Truog, William (MD); Uday Devaskar (UDEVASKAR@MEDNET.UCLA.EDU); Wally Carlo (wacarlo@uab.edu)
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Wally has sent a recent talk that is suitable.
Please send me a yes./No vote by Sept. 30 to share with Eduardo
Just a reminder, Miami did enroll in the SUPPORT Trial as part of their network involvement.

Thanks
Rose

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: Fw: Safe and Effective Oxygenation in ELBW Infants-June 2011 (2).ppt
Date: Monday, September 26, 2011 8:37:29 PM

From: Ronald Goldberg, M.D. <ronald.goldberg@duke.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Mon Sep 26 20:22:15 2011
Subject: Re: Safe and Effective Oxygenation in ELBW Infants-June 2011 (2).ppt

Yes from Duke

From: NIH <higginsr@mail.nih.gov>
Date: Mon, 26 Sep 2011 15:51:52 -0400
To: "(suhas.kallapur@cchmc.org)" <suhas.kallapur@cchmc.org>, Abbot Laptook <alaptook@wihri.org>, "Abhik Das (adas@rti.org)" <adas@rti.org>, "Ambal (ambal@uab.edu)" <ambal@uab.edu>, "Anna Maria Hibbs (AnnaMaria.hibbs@cwru.edu)" <AnnaMaria.hibbs@cwru.edu>, Barbara Stoll <barbara_stoll@oz.ped.emory.edu>, Brenda Poindexter <bpoindex@iupui.edu>, "carl_dangio@urmc.rochester.edu" <carl_dangio@urmc.rochester.edu>, "Carlton, David P" <dpcarlt@emory.edu>, "cotte010@mc.duke.edu" <cotte010@mc.duke.edu>, David Stevenson <dstevenson@stanford.edu>, "dwallace@rti.org" <dwallace@rti.org>, Edward Bell <edward-bell@uiowa.edu>, "goldb008@mc.duke.edu" <goldb008@mc.duke.edu>, "Greg Sokol (gsokol@iupui.edu)" <gsokol@iupui.edu>, "Kirpalani, Haresh" <KIRPALANIH@email.chop.edu>, John Barks <jbarks@med.umich.edu>, Jon Tyson <Jon.E.Tyson@uth.tmc.edu>, Kathleen Kennedy <Kathleen.A.Kennedy@uth.tmc.edu>, Krisa Meurs <vanmeurs@stanford.edu>, Kristi Watterberg <KWatterberg@salud.unm.edu>, Kurt Schibler <kurt.schibler@cchmc.org>, "Luc Brion (luc.brion@utsouthwestern.edu)" <luc.brion@utsouthwestern.edu>, "Martin Keszler (mkeszler@wihri.org)" <mkeszler@wihri.org>, Michelle Walsh <mcw3@po.cwru.edu>, "Meena Garg (mgarg@mednet.ucla.edu)" <mgarg@mednet.ucla.edu>, "Nelin, Leif" <Leif.Nelin@nationwidechildrens.org>, Pablo Sanchez <Pablo.Sanchez@utsouthwestern.edu>, "Polin, Richard" <rap32@mail.cumc.columbia.edu>, "Robin Ohls (rohls@salud.unm.edu)" <rohls@salud.unm.edu>, Ronnie Guillet <Ronnie_Guillet@URMC.Rochester.edu>, Satyan Lakshminrusimha <slakshmi@buffalo.edu>, Barbara Schmidt <barbara.schmidt@uphs.upenn.edu>, Seetha Shankaran <sshankar@med.wayne.edu>, Beena Sood <bsood@med.wayne.edu>, William Truog <wtruog@cmh.edu>, "Uday Devaskar (UDEVASKAR@MEDNET.UCLA.EDU)" <UDEVASKAR@mednet.ucla.edu>, "Wally Carlo (wacarlo@uab.edu)" <wacarlo@uab.edu>
Cc: NIH/NICHD <archerst@mail.nih.gov>
Subject: Safe and Effective Oxygenation in ELBW Infants-June 2011 (2).ppt

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From: Kennedy, Kathleen A
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Safe and Effective Oxygenation in ELBW Infants-June 2011 (2).ppt
Date: Monday, September 26, 2011 7:18:26 PM

Yes

Kathleen A. Kennedy, MD, MPH
Richard W. Mithoff Professor of Pediatrics
Director, MS in Clinical Research Degree Program
UT-Houston Medical School
6431 Fannin, Suite 2.106
Houston, TX 77030
713 500-6708

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To: (suhas.kallapur@cchmc.org); Abbot Laptook (alaptook@wihri.org); Abhik Das (adas@rti.org); Ambal (ambal@uab.edu); Anna Maria Hibbs (AnnaMaria.hibbs@cwru.edu); barbara_stoll@oz.ped.emory.edu; bpoindex@iupui.edu; carl_dangio@urmc.rochester.edu; Carlton, David P; cotte010@mc.duke.edu; dstevenson@stanford.edu; dwallace@rti.org; Ed Bell (edward-bell@uiowa.edu); goldb008@mc.duke.edu; Greg Sokol (gsokol@iupui.edu); Haresh Kirpalani (KIRPALANIH@email.chop.edu); John Barks; Tyson, Jon E; Kennedy, Kathleen A; Krisa Van Meurs (vanmeurs@stanford.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); Kurt Schibler [kurt.schibler@cchmc.org]; Luc Brion (luc.brion@utsouthwestern.edu); Martin Keszler (mkeszler@wihri.org); mcw3@po.cwru.edu; Meena Garg (mgarg@mednet.ucla.edu); Nelin, Leif; Pablo.Sanchez@UTSouthwestern.edu; Polin, Richard; Robin Ohls (rohls@salud.unm.edu); ronnie_guillet@urmc.rochester.edu; Satyan Lakshminrusimha; Schmidt, Barbara (Neonatology); Seetha Shankaran; Sood, Beena [bsood@med.wayne.edu]; Truog, William (MD); Uday Devaskar (UDEVASKAR@MEDNET.UCLA.EDU); Wally Carlo (wacarlo@uab.edu)
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To: Archer, Stephanie (NIH/NICHD) [E]
Subject: Fw: Safe and Effective Oxygenation in ELBW Infants-June 2011 (2).ppt
Date: Monday, September 26, 2011 6:13:39 PM

From: Laptook, Abbot <ALaptook@WIHRI.org>
To: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Mon Sep 26 18:13:14 2011
Subject: RE: Safe and Effective Oxygenation in ELBW Infants-June 2011 (2).ppt

Yes, AL

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, September 26, 2011 3:52 PM
To: (suhas.kallapur@cchmc.org); Laptook, Abbot; Abhik Das (adas@rti.org); Ambal (ambal@uab.edu); Anna Maria Hibbs (AnnaMaria.hibbs@cwru.edu); barbara_stoll@oz.ped.emory.edu; bpoindex@iupui.edu; carl_dangio@urmc.rochester.edu; Carlton, David P; cotte010@mc.duke.edu; dstevenson@stanford.edu; dwallace@rti.org; Ed Bell (edward-bell@uiowa.edu); goldb008@mc.duke.edu; Greg Sokol (gsokol@iupui.edu); Haresh Kirpalani (KIRPALANIH@email.chop.edu); John Barks; Jon.E.Tyson@uth.tmc.edu; Kennedy, Kathleen A; Krisa Van Meurs (vanmeurs@stanford.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); Kurt Schibler [kurt.schibler@cchmc.org]; Luc Brion (luc.brion@utsouthwestern.edu); Keszler, Martin; mcw3@po.cwru.edu; Meena Garg (mgarg@mednet.ucla.edu); Nelin, Leif; Pablo.Sanchez@UTSouthwestern.edu; Polin, Richard; Robin Ohls (rohls@salud.unm.edu); ronnie_guillet@urmc.rochester.edu; Satyan Lakshminrusimha; Schmidt, Barbara (Neonatology); Seetha Shankaran ; Sood, Beena [bsood@med.wayne.edu]; Truog, William (MD); Uday Devaskar (UDEVASKAR@MEDNET.UCLA.EDU); Wally Carlo (wacarlo@uab.edu)
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Thanks
Rose

From: Barbara Stoll
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: Safe and Effective Oxygenation in ELBW Infants-June 2011 (2).ppt
Date: Monday, September 26, 2011 3:53:43 PM

YES

Barbara J. Stoll, MD
George W. Brumley, Jr., Professor and Chair
Department of Pediatrics, Emory University School of Medicine
President and CEO, Emory-Children's Center
SVP and Chief Academic Officer, Children's Healthcare of Atlanta
2015 Uppergate Dr
Atlanta GA 30022
Office: 404-727-2456 Fax: 404-727-5737
barbara_stoll@oz.ped.emory.edu

From: Vaucher, Yvonne
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Gantz, Marie
Subject: Hot Topic slides Introduction, Objective and Methods for Syllabus
Date: Monday, September 26, 2011 5:32:48 PM
Attachments: SUPPORT CPAP Hot TopicsNRNYEV_09262011.pptx

Rose,

Here are the few slides for the Hot Topics syllabus..Introduction through methods.
I assume the syllabus doesn't need the conflict of interest slide but I would like to add the acknowledgements and as I recall there is a standard slide for this.

Marie, did I phrase the analyses correctly?

Yvonne

Yvonne E. Vaucher, M.D., M.P.H.
Division of Neonatal/Perinatal Medicine
Clinical Professor of Pediatrics
UCSD School of Medicine

tele: 619-543-3759
FAX: 619-543-3812

SUPPORT Trial
Early CPAP vs. Surfactant
Neurodevelopmental Outcome

Yvonne E. Vaucher, MD, MPH

Myriam Peralta-Carcelen, MD, MPH

Neil Finer, M.D.

Wally Carlo, M.D.

NICHD Neonatal Research Network Follow-up PIs

Introduction

- Extremely premature infants have high rates of disability including cognitive impairment, neurosensory deficits and cerebral palsy.

- Neonatal complications (e.g., IVH, PVL, NEC, PDA, ROP, BPD) each contribute independently to the adverse neurodevelopmental outcomes of extremely premature infants

- The goals of neonatal interventions are to increase survival, decrease the risk of acute and chronic complications and reduce the risk of adverse neurodevelopmental outcomes

Respiratory Interventions

- Surfactant treatment has been shown to reduce the rates of both death and CLD/BPD

- Various respiratory interventions have been compared with conventional ventilation with the hope of further reducing mortality and the rate of chronic lung disease (BPD) without increasing risk of other adverse complications (e.g., IVH, PVL, PDA, ROP).

- Multiple RCTs have not demonstrated consistent superiority of any intervention (e.g. HFOV, HFJV, iNO) over conventional ventilation in terms of neurodevelopmental outcomes

SUPPORT Trial

- The SUPPORT trial recently demonstrated that early CPAP application in the delivery room is an alternative to immediate intubation and surfactant administration.

- After adjustment for gestational age, center, multiple birth there was no difference in the **composite primary outcome of death or BPD** at 36 weeks post-conceptual age (PCA).

SUPPORT Study Group. NEJM 2010; 362:1970-9

SUPPORT Trial

- Infants treated with CPAP had significantly
  - fewer days of mechanical ventilation (25% vs. 28%, p=0.03)
  - increased survival without need for HFOV or CV at 7 days (55% vs.49%, p=0.01)
  - less need for postnatal steroids (7% vs. 13%, p,0.001)

- Infants treated with CPAP showed a trend towards decreased death by 36 wks PCA (14.2 vs. 17.5%, p=0.09)

SUPPORT Study Group. NEJM 2010; 362:1970-9

Objective

- This study compares the neurodevelopmental outcome at 18-22 months corrected age for infants enrolled in in the CPAP treatment arm versus the Surfactant treatment arm of the SUPPORT trial.

- The hypothesis of this study was that compared to immediate intubation and surfactant administration, early CPAP would decrease the **composite outcome of mortality or neurodevelopmental impairment**.

Methods: SUPPORT RCT

- Extremely preterm infants enrolled were eligible if estimated gestation was between 24 and 28 weeks by best obstetrical estimate, free of malformation, decision made for full resuscitation, consent obtained before delivery
- Inborn at one of the 20 US centers participating in the NICHD Neonatal Research Network
- Infants were randomized to either early CPAP application (CPAP) or intubation with surfactant administration (SURF)
- Randomization was stratified by center and gestational age group (24 0/7 to 25 6/7 and 26 0/6 to 27 6/7 weeks)
- Limited ventilation was used if needed subsequently in the CPAP arm; conventional ventilation strategies were used in the surfactant treatment arm

Methods (cont'd)

- Approved by the IRB of each participating institution and RTI International
- Using a 2X2 factorial design infants were also randomly assigned to lower (85-89%) vs. higher (91-95%) target ranges of oxygen saturation
- Sample size: based on NRN neurodevelopmental outcome data (yr 2000); powered to detect a outcome difference of 10%

Neurodevelopmental Follow-up

- Survivors were enrolled in the NRN follow-up cohort at 36 weeks post-conceptual age

- Comprehensive, standardized physical, neurologic (Amiel-Tison) and developmental (BSID-III) evaluations performed at 18-22 months corrected age by annually certified examiners

Primary composite outcome:

Death or neurodevelopmental impairment (NDI)

Neurodevelopmental Impairment (NDI): Components

- NDI defined as having at least one of the following:
  - Cognitive composite score < 70 (BSID-III)
  - Gross Motor Function Classification Score ≥ 2
  - Moderate/severe cerebral palsy (CP)
  - Blind in both eyes (vision < 20/200)
  - Permanent hearing impairment with or without amplification

Methods: Data collection and analyses

- Demographic and neonatal outcome data were collected and entered in standardized forms which were transmitted to, stored and analyzed by Research Triangle Institute International

- Analyses:
  - Intention to treat
  - Results adjusted for gestational age, center, familial clustering
  - Adjusted relative risks and 95% CI for categorical and continuous variables estimated using Poisson regression and mixed linear models
  - 2-sided $p < 0.05$ statistically significant

Results

Conclusion

No Conflict of Interest Slide

Acknowledgements

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: Fw: Safe and Effective Oxygenation in ELBW Infants-June 2011 (2).ppt
Date: Monday, September 26, 2011 5:11:44 PM

From: Tyson, Jon E <Jon.E.Tyson@uth.tmc.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Mon Sep 26 17:05:43 2011
Subject: RE: Safe and Effective Oxygenation in ELBW Infants-June 2011 (2).ppt

Sounds good to me, though I of course defer to Kathleen as the PI here.

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, September 26, 2011 2:52 PM
To: (suhas.kallapur@cchmc.org); Abbot Laptook (alaptook@wihri.org); Abhik Das (adas@rti.org); Ambal (ambal@uab.edu); Anna Maria Hibbs (AnnaMaria.hibbs@cwru.edu); barbara_stoll@oz.ped.emory.edu; bpoindex@iupui.edu; carl_dangio@urmc.rochester.edu; Carlton, David P; cotte010@mc.duke.edu; dstevenson@stanford.edu; dwallace@rti.org; Ed Bell (edward-bell@uiowa.edu); goldb008@mc.duke.edu; Greg Sokol (gsokol@iupui.edu); Haresh Kirpalani (KIRPALANIH@email.chop.edu); John Barks; Tyson, Jon E; Kennedy, Kathleen A; Krisa Van Meurs (vanmeurs@stanford.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); Kurt Schibler [kurt.schibler@cchmc.org]; Luc Brion (luc.brion@utsouthwestern.edu); Martin Keszler (mkeszler@wihri.org); mcw3@po.cwru.edu; Meena Garg (mgarg@mednet.ucla.edu); Nelin, Leif; Pablo.Sanchez@UTSouthwestern.edu; Polin, Richard; Robin Ohls (rohls@salud.unm.edu); ronnie_guillet@urmc.rochester.edu; Satyan Lakshminrusimha; Schmidt, Barbara (Neonatology); Seetha Shankaran; Sood, Beena [bsood@med.wayne.edu]; Truog, William (MD); Uday Devaskar (UDEVASKAR@MEDNET.UCLA.EDU); Wally Carlo (wacarlo@uab.edu)
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Thanks
Rose

From: Vaucher, Yvonne
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Manuscripts and Hot TOpics presentations for SC
Date: Monday, September 26, 2011 4:53:20 PM

Will send today.

Yvonne

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, September 26, 2011 1:47 PM
To: Vaucher, Yvonne; Myriam Peralta, M.D.
Cc: Finer, Neil; 'Wally Carlo, M.D.'
Subject: Manuscripts and Hot TOpics presentations for SC
Importance: High

Hi,

Can each of you send me your SUPPORT manuscript drafts as well as the slides for Hot Topics? **The Hot Topics Slides need to be approved by the steering committee prior to submission as they will appear in print form.** My understanding is that the slides are due at the end of the week.

Thanks

Rose

Rosemary D. Higgins, MD
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301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: Safe and Effective Oxygenation in ELBW Infants-June 2011 (2).ppt
Date: Monday, September 26, 2011 4:36:00 PM

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higginsr@mail.nih.gov

From: Kurt Schibler [mailto:kurt.schibler@chmcc.org]
Sent: Monday, September 26, 2011 4:35 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: Safe and Effective Oxygenation in ELBW Infants-June 2011 (2).ppt

Hi Rose, Yes, Thanks, Kurt

On 9/26/11 3:51 PM, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> wrote:

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To: Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: Safe and Effective Oxygenation in ELBW Infants-June 2011 (2).ppt
Date: Monday, September 26, 2011 4:33:00 PM

(b)(5) for this one and the ambal presentation sent earlier

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From: Archer, Stephanie (NIH/NICHD) [E]
Sent: Monday, September 26, 2011 4:33 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Safe and Effective Oxygenation in ELBW Infants-June 2011 (2).ppt

You?

Stephanie Wilson Archer
The Eunice Kennedy Shriver
National Institute of Child Health and Human Development
Pregnancy & Perinatology Branch
6100 Executive Boulevard, Room 4B03
Rockville, MD 20852

Tel. 301-496-0430
Fax 301-496-3790
archerst@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Monday, September 26, 2011 4:31 PM
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: Safe and Effective Oxygenation in ELBW Infants-June 2011 (2).ppt

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higginsr@mail.nih.gov

From: Das, Abhik [mailto:adas@rti.org]
Sent: Monday, September 26, 2011 4:30 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Safe and Effective Oxygenation in ELBW Infants-June 2011 (2).ppt

Yes

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, September 26, 2011 3:52 PM
To: (suhas.kallapur@cchmc.org); Abbot Laptook (alaptook@wihri.org); Das, Abhik; Ambal (ambal@uab.edu); Anna Maria Hibbs (AnnaMaria.hibbs@cwru.edu); [SCRN] Stoll, Barbara; bpoindex@iupui.edu; carl_dangio@urmc.rochester.edu; Carlton, David P; cotte010@mc.duke.edu; dstevenson@stanford.edu; Wallace, Dennis; Ed Bell (edward-bell@uiowa.edu); goldb008@mc.duke.edu; Greg Sokol (gsokol@iupui.edu); Haresh Kirpalani (KIRPALANIH@email.chop.edu); John Barks; Jon.E.Tyson@uth.tmc.edu; Kennedy, Kathleen A; Krisa Van Meurs (vanmeurs@stanford.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); Kurt Schibler [kurt.schibler@cchmc.org]; Luc Brion (luc.brion@utsouthwestern.edu); Martin Keszler (mkeszler@wihri.org); mcw3@po.cwru.edu; Meena Garg (mgarg@mednet.ucla.edu); Nelin, Leif; Pablo.Sanchez@UTSouthwestern.edu; Polin, Richard; Robin Ohls (rohls@salud.unm.edu); ronnie_guillet@urmc.rochester.edu; Satyan Lakshminrusimha; Schmidt, Barbara (Neonatology); Seetha Shankaran ; Sood, Beena [bsood@med.wayne.edu]; Truog, William (MD); Uday Devaskar (UDEVASKAR@MEDNET.UCLA.EDU); Wally Carlo (wacarlo@uab.edu)
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To: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: Safe and Effective Oxygenation in ELBW Infants-June 2011 (2).ppt
Date: Monday, September 26, 2011 4:14:00 PM

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higginsr@mail.nih.gov

From: Krisa Van Meurs [mailto:vanmeurs@stanford.edu]
Sent: Monday, September 26, 2011 4:06 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: Safe and Effective Oxygenation in ELBW Infants-June 2011 (2).ppt

Yes.

Krisa

Sent from my iPhone

On Sep 26, 2011, at 12:51 PM, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> wrote:

> HI,
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>
> <Safe and Effective Oxygenation in ELBW Infants-June 2011 (2).ppt>

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: Safe and Effective Oxygenation in ELBW Infants-June 2011 (2).ppt
Date: Monday, September 26, 2011 4:02:00 PM

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From: Ed Bell [mailto:edward-bell@uiowa.edu]
Sent: Monday, September 26, 2011 4:00 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: Safe and Effective Oxygenation in ELBW Infants-June 2011 (2).ppt

Yes

From: "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>
Date: Mon, 26 Sep 2011 15:51:52 -0400
To: (suhas.kallapur@cchmc.org)<suhas.kallapur@cchmc.org>; Abbot Laptook(alaptook@wihri.org)<alaptook@wihri.org>; Abhik Das (adas@rti.org) <adas@rti.org>; Ambal (ambal@uab.edu)<ambal@uab.edu>; Anna Maria Hibbs(AnnaMaria.hibbs@cwru.edu)<AnnaMaria.hibbs@cwru.edu>; barbara_stoll@oz.ped.emory.edu<barbara_stoll@oz.ped.emory.edu>; bpoindex@iupui.edu<bpoindex@iupui.edu>; carl_dangio@urmc.rochester.edu<carl_dangio@urmc.rochester.edu>; Carlton, David P<dpcarlt@emory.edu>; cotte010@mc.duke.edu<cotte010@mc.duke.edu>; dstevenson@stanford.edu<dstevenson@stanford.edu>; dwallace@rti.org<dwallace@rti.org>; Ed Bell(edward-bell@uiowa.edu)<edward-bell@uiowa.edu>; goldb008@mc.duke.edu<goldb008@mc.duke.edu>; Greg Sokol (gsokol@iupui.edu) <gsokol@iupui.edu>; Haresh Kirpalani (KIRPALANIH@email.chop.edu) <KIRPALANIH@email.chop.edu>; John Barks<jbarks@med.umich.edu>; Jon.E.Tyson@uth.tmc.edu<Jon.E.Tyson@uth.tmc.edu>; Kennedy, Kathleen A<Kathleen.A.Kennedy@uth.tmc.edu>; Krisa Van Meurs (vanmeurs@stanford.edu) <vanmeurs@stanford.edu>; Kristi Watterberg (kwatterberg@salud.unm.edu) <kwatterberg@salud.unm.edu>; Kurt Schibler [kurt.schibler@cchmc.org] <kurt.schibler@cchmc.org>; Luc Brion (luc.brion@utsouthwestern.edu) <luc.brion@utsouthwestern.edu>; Martin Keszler (mkeszler@wihri.org) <mkeszler@wihri.org>; mcw3@po.cwru.edu<mcw3@po.cwru.edu>; Meena Garg(mgarg@mednet.ucla.edu)<mgarg@mednet.ucla.edu>; Nelin,

Leif<Leif.Nelin@nationwidechildrens.org>;
Pablo.Sanchez@UTSouthwestern.edu<Pablo.Sanchez@utsouthwestern.edu>; Polin, Richard<rap32@mail.cumc.columbia.edu>; Robin Ohls (rohls@salud.unm.edu) <rohls@salud.unm.edu>;
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To: Archer, Stephanie (NIH/NICHD) [E]
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higginsr@mail.nih.gov

From: Poindexter, Brenda B [mailto:bpoindex@iupui.edu]
Sent: Monday, September 26, 2011 3:52 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Safe and Effective Oxygenation in ELBW Infants-June 2011 (2).ppt

yes

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, September 26, 2011 3:52 PM
To: (suhas.kallapur@cchmc.org); Abbot Laptook (alaptook@wihri.org); Abhik Das (adas@rti.org); Ambal (ambal@uab.edu); Anna Maria Hibbs (AnnaMaria.hibbs@cwru.edu); barbara_stoll@oz.ped.emory.edu; Poindexter, Brenda B; carl_dangio@urmc.rochester.edu; Carlton, David P; cotte010@mc.duke.edu; dstevenson@stanford.edu; dwallace@rti.org; Ed Bell (edward-bell@uiowa.edu); goldb008@mc.duke.edu; Sokol, Gregory M.; Haresh Kirpalani (KIRPALANIH@email.chop.edu); John Barks; Jon.E.Tyson@uth.tmc.edu; Kennedy, Kathleen A; Krisa Van Meurs (vanmeurs@stanford.edu); Kristi Watterberg (kwatterberg@salud.unm.edu); Kurt Schibler [kurt.schibler@cchmc.org]; Luc Brion (luc.brion@utsouthwestern.edu); Martin Keszler (mkeszler@wihri.org); mcw3@po.cwru.edu; Meena Garg (mgarg@mednet.ucla.edu); Nelin, Leif; Pablo.Sanchez@UTSouthwestern.edu; Polin, Richard; Robin Ohls (rohls@salud.unm.edu); ronnie_guillet@urmc.rochester.edu; Satyan Lakshminrusimha; Schmidt, Barbara (Neonatology); Seetha Shankaran ; Sood, Beena [bsood@med.wayne.edu]; Truog, William (MD); Uday Devaskar (UDEVASKAR@MEDNET.UCLA.EDU); Wally Carlo (wacarlo@uab.edu)
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Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: Safe and Effective Oxygenation in ELBW Infants-June 2011 (2).ppt
Date: Monday, September 26, 2011 3:51:00 PM
Attachments: Safe and Effective Oxygenation in ELBW Infants-June 2011 (2).ppt

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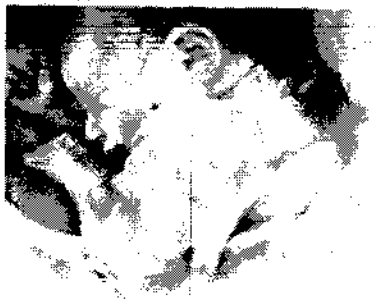


Safe and Effective Oxygenation in ELBW Infants

The SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network

UAB

National Heart Lung and Blood Institute

National Institutes of Health

Eunice Kennedy Shriver NICHD National Institute of Child Health & Human Development

Disclosure Statement

Dr. Carlo has documented that he has no relevant financial relationships to disclose or COIs to resolve

Dr. Carlo has documented that his presentation will not involve discussion of unapproved or off-label, experimental or investigational use

Objectives

1. Know the results of the SUPPORT RCT arm of lower versus high oxygen saturation targeting
2. Understand the limitations of using the results for changes in clinical practice
3. Be able to apply the results of this trial in your daily practice

Trial Design

Background

- No consensus on targets
- Published "acceptable" levels in neonates are 88-98%
- No standards for assessing "need" for oxygen supplementation in infants

What PaO_2 or SaO_2 should we target?

Does the oxygenation targeting matter?

Recent Trials of Oxygenation Targets

STOP-ROP Trial

BOOST Trial

SUPPORT Trial

SaO_2 Targets: STOP-ROP Trial

Methods

Design:	Multicenter RCT, not masked
Patient population:	649 preterm infants with prethreshold ROP
Treatment group:	O_2 sat 96-99% or 89-94%
Primary outcome:	Progression to threshold ROP in at least one eye

STOP-ROP Multicenter Study Group. Pediatrics 105:295, 2000

SaO_2 Targets: STOP-ROP Trial

	Sats 96 to 99%	Sats 89 to 94%	p value
Threshold ROP	41%	48%	<0.05
Pneumonia/BPD exacerbations	13%	8%	= 0.07
Prolonged hospitalization*	13%	7%	<0.05
Prolonged oxygen*	47%	37%	<0.05
Prolonged diuretics*	36%	24%	<0.05
Death	3%	2%	NS

* At 3 months corrected age

STOP-ROP Multicenter Study Group. Pediatrics 105:295, 2000

SaO_2 Targets: BOOST Trial

Methods

Design:	Multicenter RCT, double blind
Patient population:	358 infants born at < 30 weeks and oxygen dependent at 32 weeks
Treatment groups:	SaO_2 95-98% or 91-94%
Primary outcome:	Growth and neurodevelopment at 12 months corrected age

Askie et al. NEJM 349:959, 2003

SaO_2 Targets: BOOST Trial

	Sats 95-98%	Sats 91-94%	p value
Dev abnormality	23%	24%	NS
Weight < 10% tile	33%	37%	NS
Death	5%	3%	NS
O_2 at 36 w	64%	46%	<0.001
Home O_2	30%	17%	<0.001

Askie et al. NEJM 349:959, 2003

SaO_2 Targets: Retrospective Study

Methods

- Retrospective review
- Population study - All babies < 28 weeks in several referral units
- Data analyzed by SaO_2 targets

Tin et al. Arch Dis Child. 84:F106, 2001

SaO_2 Targets: Retrospective Study

Oxygen Saturation

Tin et al. Arch Dis Child. 84:F106, 2001

SaO_2 Targets: Expert Opinion

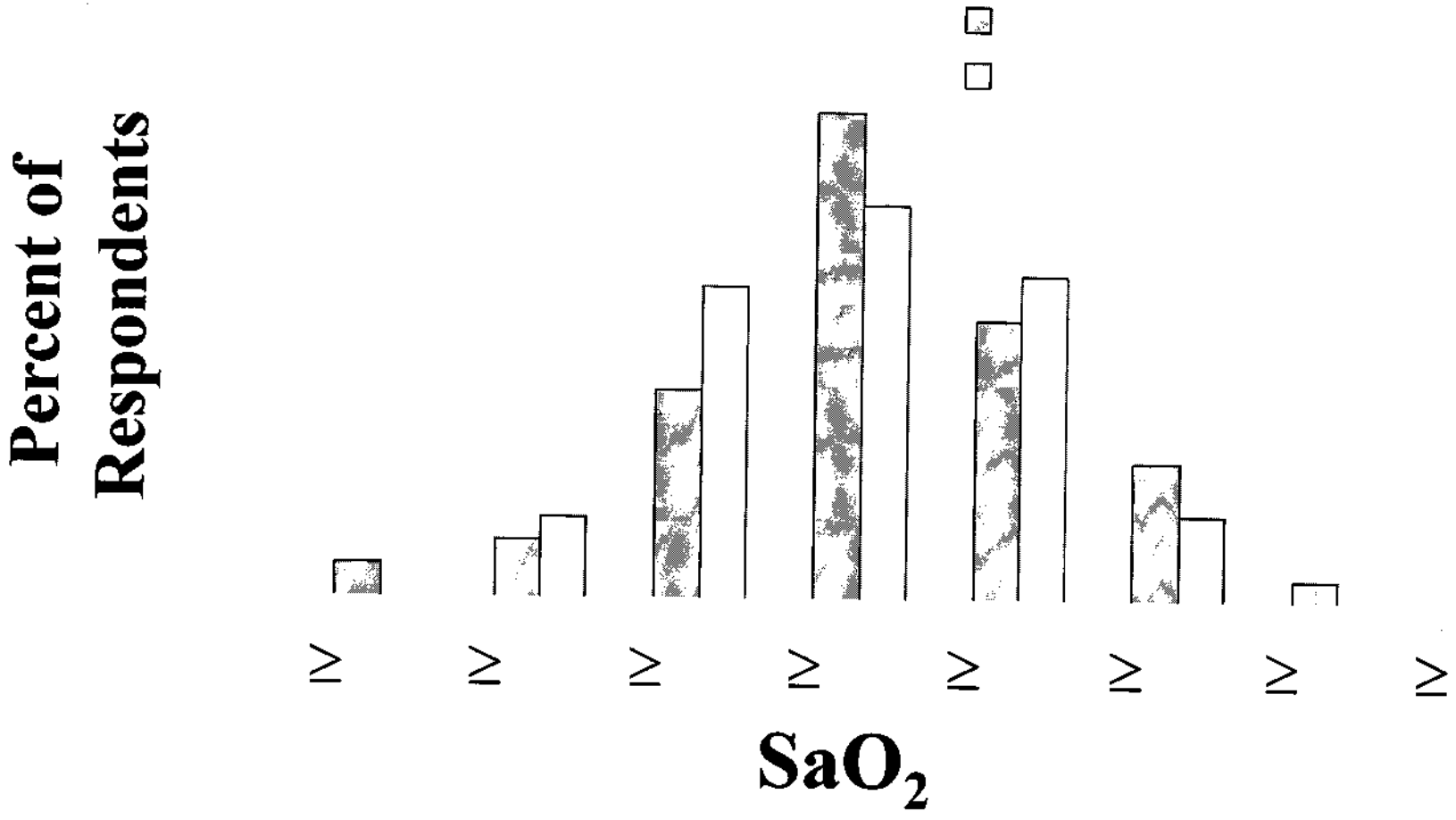
Methods

Design: Survey of VON Centers and ONTPD

Respondents: 181 (61%) VON Centers and 30 (42%) PD

Ellsbury et al. J Pediatr 140:247, 2002

SaO_2 Targets: Expert Opinion



Ellsbury et al. J Pediatr 140:247, 2002

Background - SUPPORT Oxygen Saturation Trial

- Retinopathy of prematurity (ROP) continues to be an important cause of blindness in preterm infants
- Recent observational data suggest that oxygen saturations in the lower limits of common clinical practice (83 or 85%) may reduce ROP but this has not been tested in RCTs
- Furthermore, in RCTs of oxygen supplementation to reduce ROP conducted in the 1950s, restriction of oxygen supplementation resulted in an increased mortality in infants in the lower oxygen group

Hypothesis

A lower O_2 saturation target range (85 to 89%)

compared to

a higher O_2 saturation target range (91 to 95%)

reduces

the incidence of the composite outcome of severe ROP or death

among

infants of 24 $^{0/7}$ to 27 $^{6/7}$ weeks gestational age

Method – Patients

- Inborn infants of 24 $^{0/7}$ to 27$^{6/7}$ weeks gestation for whom a decision had been made to provide full resuscitation were eligible
- Parental consent was obtained antenatally
- Enrollment was conducted from February 2005 to February 2009
- Randomization was stratified by center and by gestational age:
  - 24 and 25 weeks
  - 26 and 27 weeks

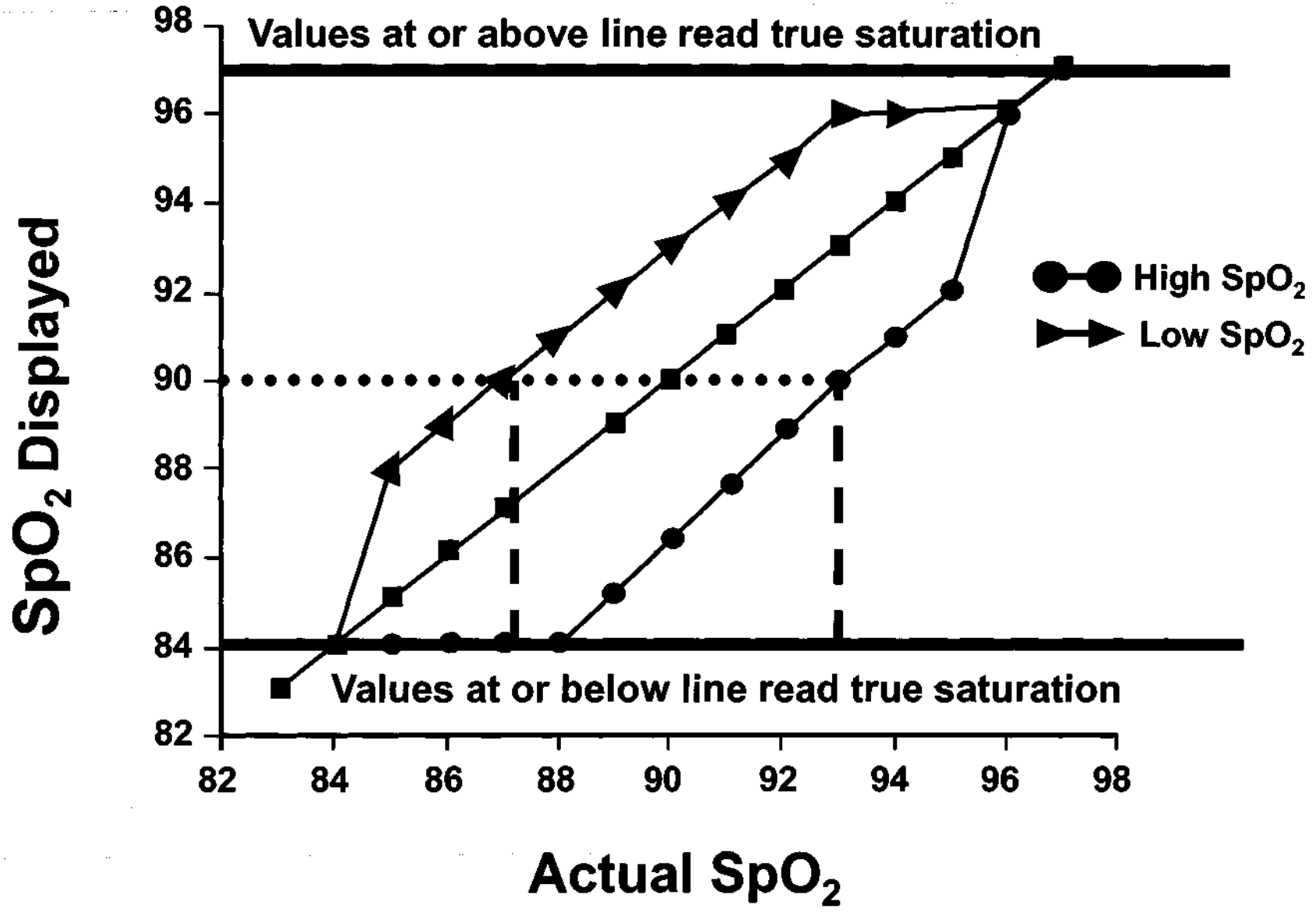
Methods – Intervention (1)

- Infants were randomized to:
  - lower saturation targeting (85 to 89%) or;
  - higher saturation targeting (91 to 95%)

- Oxygen saturations were monitored with electronically-altered Masimo Radical Pulse Oximeters

SpO_2 Group	Displayed	Actual Target	Alarm Values
Low SpO_2	88-92%	85-89%	<84 and >96%
High SpO_2	88-92%	91-95%	<84 and >96%

Actual vs Low and High Reading SpO_2



4-13845

Recent Trials of Oxygenation Targets

	Experimental	Control
SUPPORT	85-89%	91-95%
STOP-ROP	96-99%	89-94%
BOOST	95-98%	91-94%

Methods – Intervention (2)

- Oxygen saturation targeting from birth (< 2 hrs) to 36 weeks post-menstrual age or on room air and off the ventilator/CPAP for >72 hours, whichever occurred first
- Adjustments in supplemental oxygen to maintain the displayed saturation within the target range of 88 to 92% were performed by the clinical staff, not the researchers

Methods – Factorial Design

Infants were also randomized to CPAP started at birth or intubation with surfactant

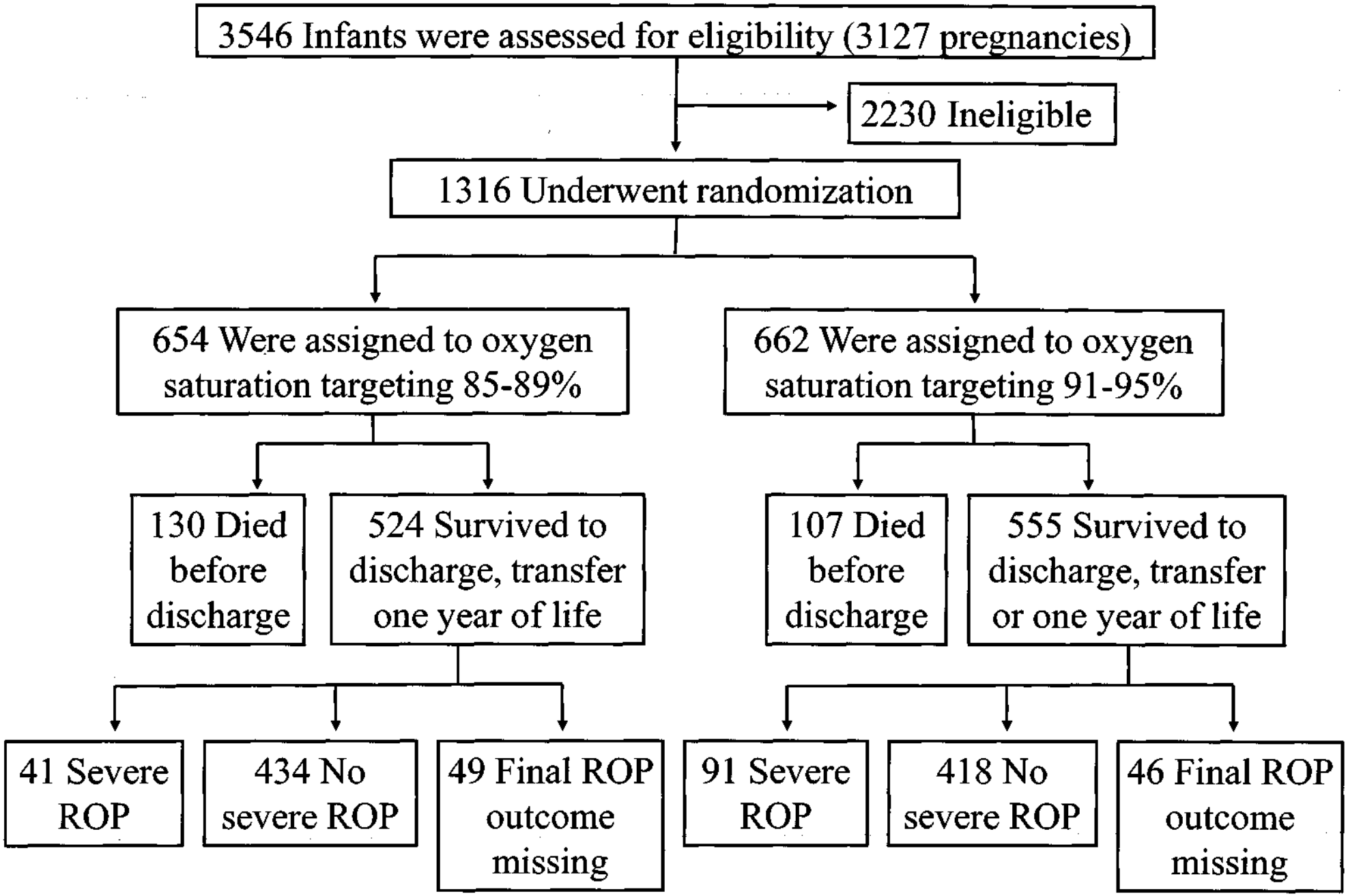
Methods – ROP Assessments

- Trained ophthalmologists followed the infants until the study endpoint of severe retinopathy *or* fully vascularized retinas *or* immature vessels in zone III for two consecutive exams in each eye were documented

- Severe retinopathy was defined as:
  - **threshold retinopathy** if any of the following were present:
    - In zone I: stage 3 ROP; plus disease with any stage of ROP or
    - In zone II: plus disease with stage 2 or 3 ROP or
  - If **ophthalmologic surgery** and/or **bevacizumab** ROP treatment was used

Methods – Sample Size Monitoring and Analysis

- Based on an absolute difference of 10% in the primary outcome, sample size was 1310
- An independent DSMC reviewed primary outcomes and adverse events at 25%, 50%, and 75% of outcome assessment
- The DSMC evaluated compliance with oxygen saturation targeting
- Adjustment was performed for pre-specified stratification (center and GA) and for familial clustering as multiple births were randomized to the same treatment arms

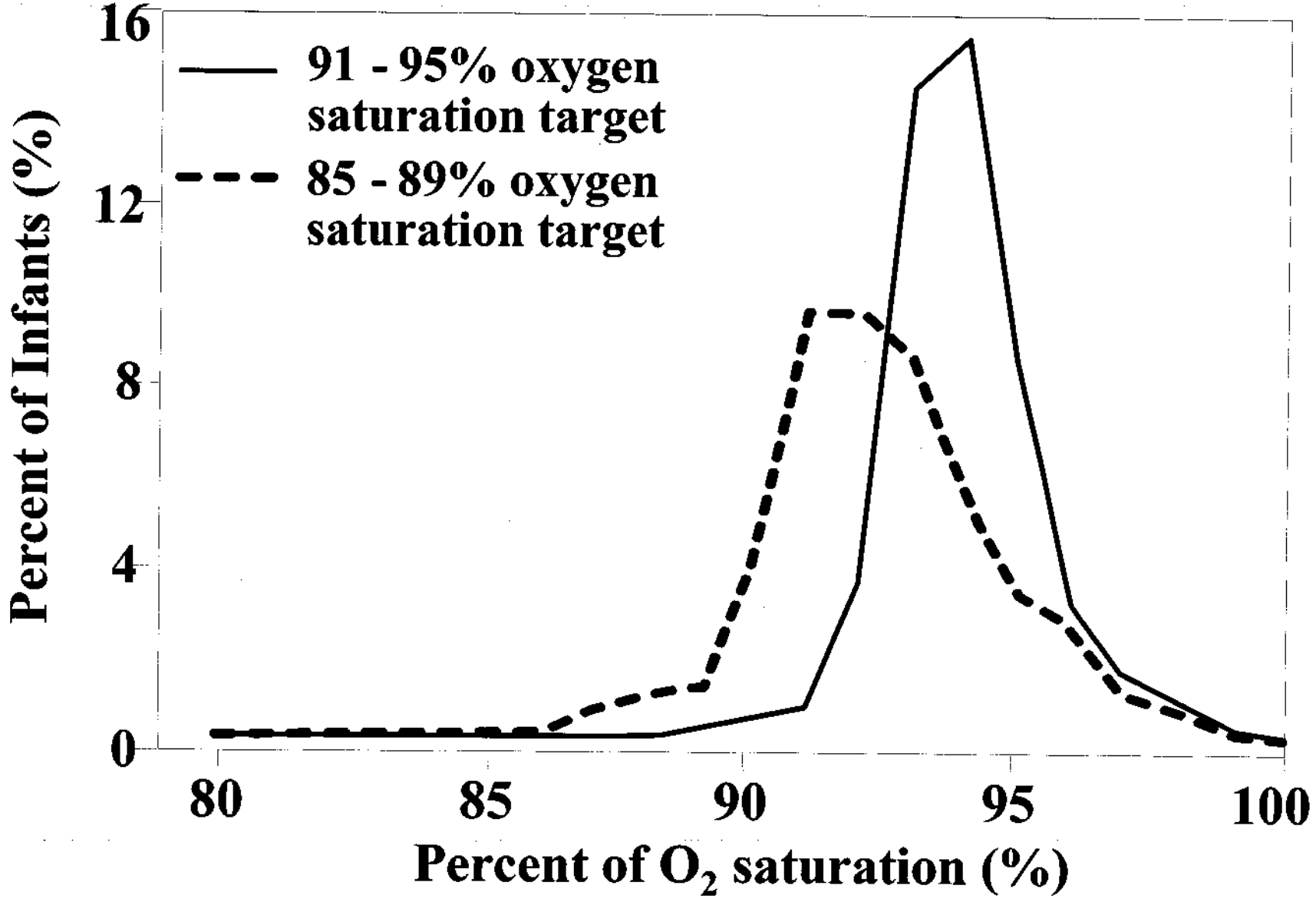


Results – Patient Population*

	Lower Saturation Group (N = 654)	Higher Saturation Group (N = 662)
Birth weight	836±193 grams	825±193 grams
Gestational age	26±1 weeks	26±1 weeks
Race, White/Black/Hispanic	37/39/20%	42/35/19%
Antenatal corticosteroids	96.8%	95.6%
Multiple births	24.6%	26.6%

*All p values >0.05

Actual Median Oxygen Saturation (%)



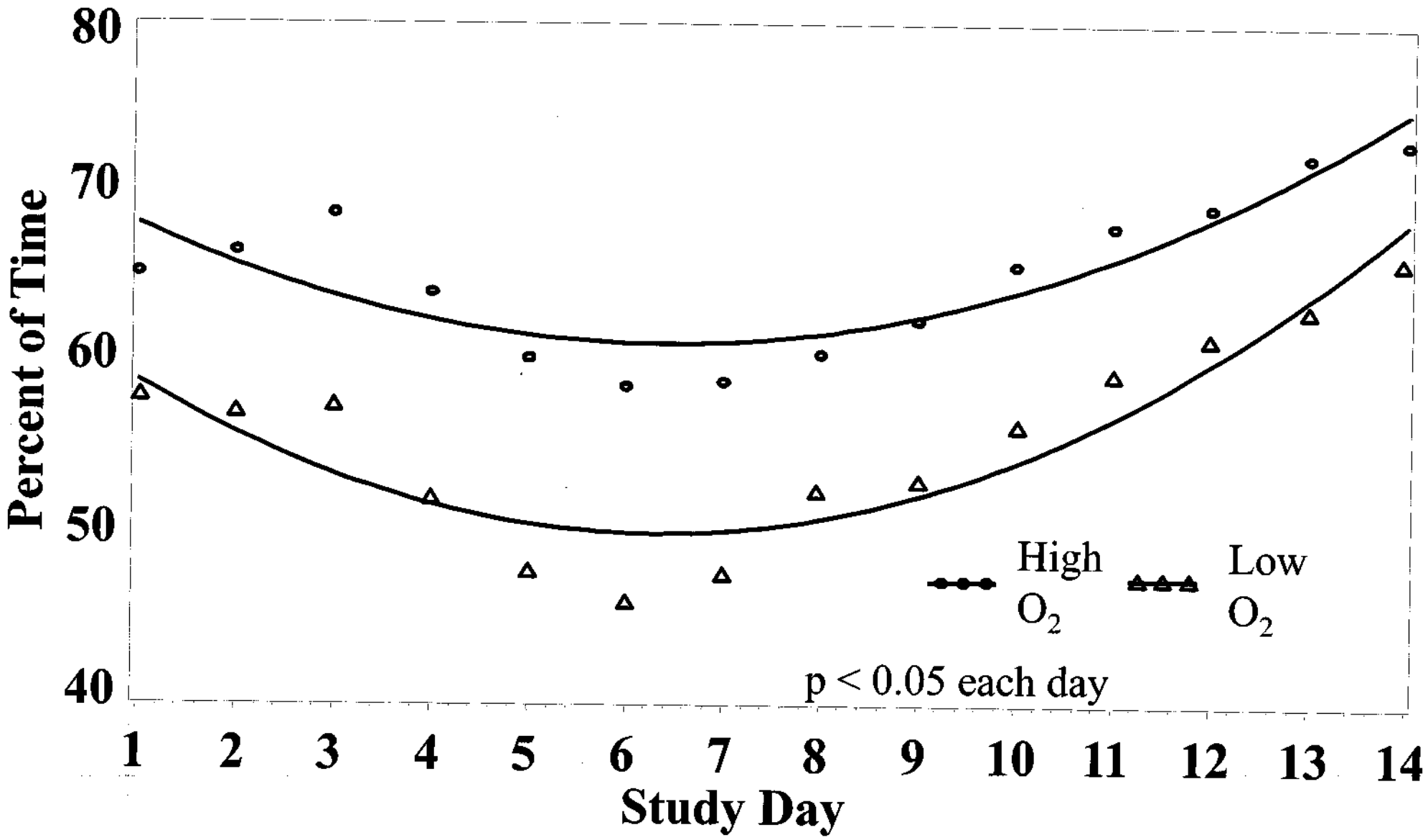
Mean Percent of Time Spent in SpO_2 Ranges While on Supplemental Oxygen

SpO_2 range	Lower Saturation Group Mean % of time in range (95% CI)	Higher Saturation Group Mean % of time in range (95% CI)	p value
>96%	20.1 (18.8, 21.3)	23.2 (22.0, 24.5)	0.001
<85%	7.3 (6.6, 8.1)	5.5 (4.8, 6.3)	0.001
<75%	4.5 (3.8, 5.2)	3.6 (2.9, 4.3)	0.049
<70%	2.5 (1.9, 3.1)	2.1 (1.5, 2.7)	0.409

Median Percent of Time Spent in SpO_2 Ranges While on Supplemental Oxygen

SpO_2 range	Lower Saturation Group Median % of time in range	Higher Saturation Group Median % of time in range	p value
>96%	16.0	19.6	<0.001
<85%	5.9	3.9	<0.001
<75%	3.3	2.1	<0.001
<70%	1.5	0.9	<0.001

Percent of Time on Oxygen by Day and Group



4-13856

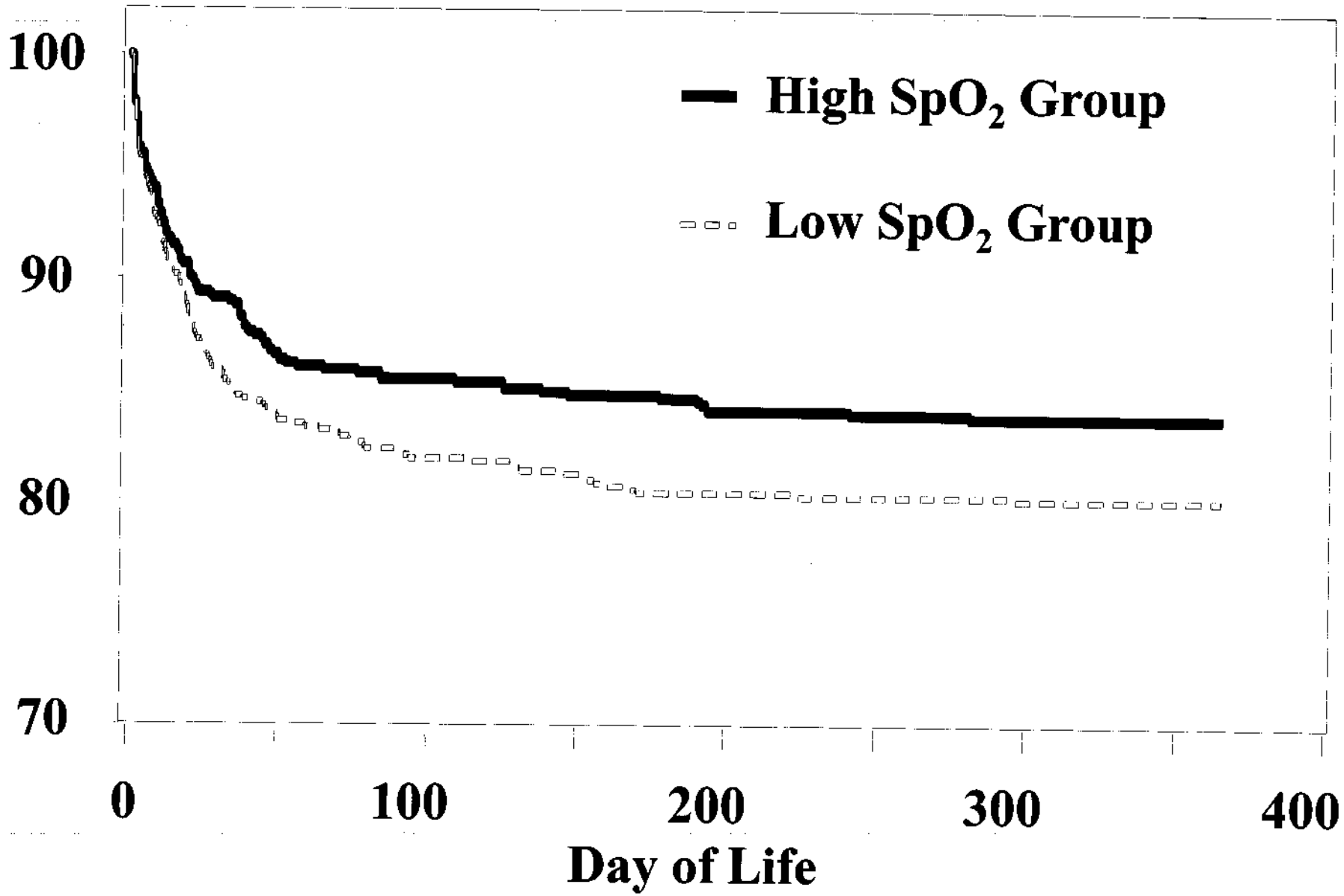
Results – Primary Outcome

	Lower Saturation Group N=654	Higher Saturation Group N=662	Adjusted Relative Risk (95% CI)	
Severe ROP/death	28.3%	32.1%	0.90 (0.76, 1.06)	
Severe ROP	8.6%	17.9%	0.52 (0.37, 0.73)	NNT=11
Death	19.9%	16.2%	1.27 (1.01, 1.60)	NNH=27

Results – ROP Adjudication Analysis

	Lower Saturation Group N=654	Higher Saturation Group N=662	Relative Risk for Low SpO_2 vs. High SpO_2 (95% CI)	
Severe ROP	8.6%	17.9%	0.52 (0.37, 0.73)	NNT=11
Severe ROP with adjudication (98.6%)	8.0%	16.6%	0.52 (0.37, 0.73)	NNT=12
Severe ROP with ROP if lost to F/U (100%)	10.1%	17.5%	0.62 (0.45, 0.84)	NNT=14

Survival Curve



Results – BPD and Other Pulmonary Outcomes

	Lower Saturation Group N=654	Higher Saturation Group N=662	Adjusted Relative Risk (95% CI)
BPD (O_2 use at 36 w)	37.6%	46.7%	0.82 (0.72, 0.93)
BPD (O_2 use) or death, 36 w	48.5%	54.2%	0.91 (0.83, 1.01)
BPD (phys), 36 w	38.0%	41.7%	0.92 (0.81, 1.05)
BPD (phys) or death, 36 w	48.8%	50.0%	0.99 (0.90, 1.10)
Pneumothorax	7.2%	6.5%	1.12 (0.74, 1.68)
Any air leaks (14 days)	7.8%	6.3%	1.23 (0.83, 1.83)
Postnatal steroids for BPD	9.6%	10.7%	0.91 (0.67, 1.24)

Results – PDA

	Lower Saturation Group N=654	Higher Saturation Group N=662	Adjusted Relative Risk (95% CI)
PDA	47.9%	50.0%	0.96 (0.86, 1.07)
Medical R_x for PDA	34.5%	36.1%	0.95 (0.82, 1.09)
Surgical R_x for PDA	11.4%	10.5%	1.09 (0.80, 1.48)

Results – Other Major Outcomes

	Lower Saturation Group N=654	Higher Saturation Group N=662	Adjusted Relative Risk (95% CI)
IVH, grade 3 or 4	13.2%	12.7%	1.06 (0.80, 1.40)
PVL	3.8%	4.7%	0.83 (0.49, 1.42)
NEC, stage ≥ 2	11.9%	10.8%	1.11 (0.82, 1.51)
Late onset sepsis	36.5%	35.6%	1.03 (0.89, 1.18)

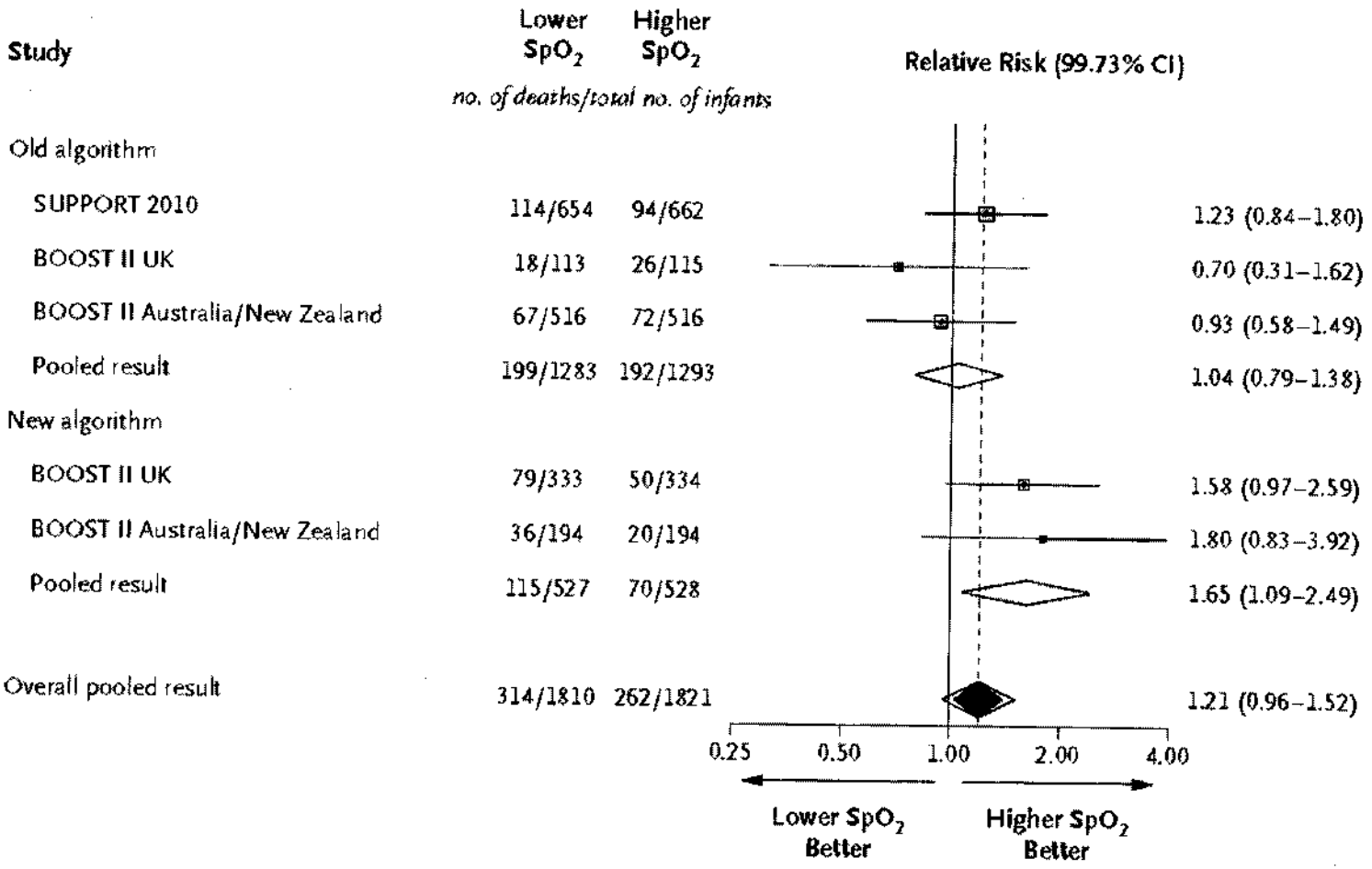
Summary

- O_2 saturation targeting in the range of 85-89% did not affect severe ROP/death
- O_2 saturation targeting in the range of 85-89% resulted in a significant reduction in severe ROP (17.9 to 8.6%, NNT = 11)
- However, mortality was significantly increased in the 85-89% target group (19.9 versus 16.2%, NNH = 27)

Conclusions

- Lower oxygen saturation targeting, as conducted in this trial, did not reduce severe ROP/death
- Lower oxygen saturation targeting, as conducted in this trial, decreased severe ROP
- However, there was a significant increase in mortality with low oxygen targeting
- Follow up of these infants and data from the similarly designed ongoing trials will be important

Survival to 36 Weeks in 3631 Infants in the SUPPORT and BOOST II Trials



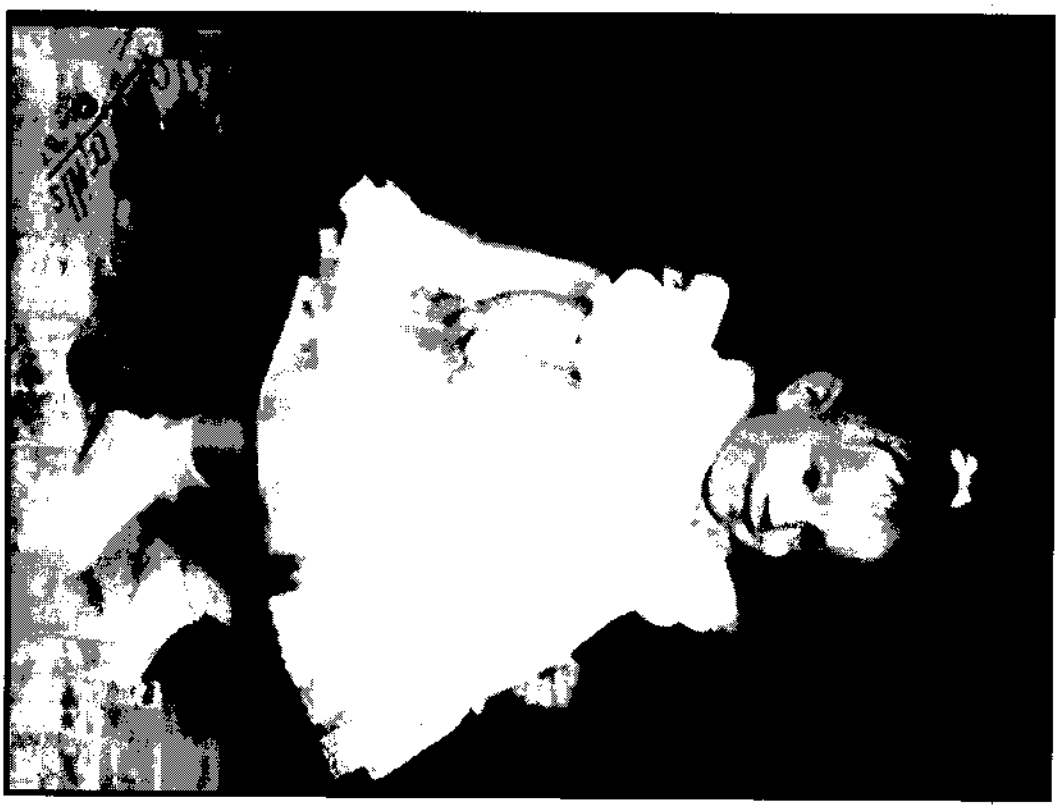
Stenson et al. N Engl J Med. 364:1680-2, 2011

Take Home Message

- Most current data suggest that oxygen saturation in the low 90s is sufficient to preterm infants
- Additional oxygen supplementation increases ROP and may worsen pulmonary outcomes
- Lower oxygen supplementation increases the risk for mortality
- Published studies indicate that rates of use of alarm limits and compliance with oxygen saturation targets can be improved

Consider Changes in Practice

- Develop guidelines and protocols to minimize hyperoxia
- Consider using the high saturation alarm at 95% if the baby is on oxygen supplementation and at 99% if the baby is on room air, but at risk for getting oxygen supplementation
- Target saturations 91-95%
- Exercise caution when targeting low saturations for presentation of ROP as mortality may increase



Trial Design

Thanks to the many infants, parents, and NICU staff

Thanks to the members of the Neonatal Research Network

NICHD Neonatal Research Network Centers (2005-2009)

- Brown University
- Case Western Reserve University
- Duke University
- Emory University
- Indiana University
- RTI International
- Stanford University
- Tufts Medical Center
- University of Alabama – Birmingham
- University of California – San Diego
- University of Cincinnati
- University of Iowa
- University of Miami
- University of New Mexico
- University of Rochester
- University of Texas, Southwestern – Dallas
- University of Texas – Houston
- University of Utah
- Wake Forest University
- Wayne State University
- Yale University

From: Walsh, Michele
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: ICMJE Disclosure Form Received for JAMA11-5234
Date: Monday, September 26, 2011 1:34:43 PM
Attachments: disclosure_e_form_jama11-5234_walsh_dyomrl.pdf

fyi

Michele Walsh, MD
Chief, Division of Neonatology
216.844.3759

It's not what you look at that matters, it's what you see. Thoreau

---

From: Gwenn.Gregg@jama-archives.org [mailto:Gwenn.Gregg@jama-archives.org]
Sent: Monday, September 26, 2011 8:08 AM
To: michele.walsh@cwru.edu
Cc: Gwenn.Gregg@jama-archives.org
Subject: ICMJE Disclosure Form Received for JAMA11-5234

Dear Dr. Walsh,

Thank you for submitting your ICMJE Form for Disclosure of Potential Conflicts of Interest for JAMA. A PDF copy of the form is attached for your reference.

Sincerely yours,

Gwenn Gregg
Editorial Assistant, JAMA
E-mail: Gwenn.Gregg@jama-archives.org
Phone: 312.464.5204
Fax: 866.422.4442

From: Finer, Neil
To: Gantz, Marie
Cc: Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]
Date: Sunday, September 25, 2011 12:54:10 PM

Hi Marie
I have carefully looked at the analyses you have done and shared this with Wally
We would like to ask that you look at the gestational age strata in the SpO2 study and see if CPAP vs SURF altered or effected the outcomes for death/ROP, death/NDI and death ROP and NDI alone.
It may be that what we are seeing is an effect of CPAP
Please let me know if you can run these.

Thanks
Neil

Neil N. Finer, M.D.
Professor of Pediatrics
Director, Division of Neonatology
Department of Pediatrics
UC San Diego School of Medicine
UC San Diego Medical Center
402 Dickinson Street, MPF 1-140
San Diego, CA 92103

From: Vaucher, Yvonne
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Hot Topics.
Date: Friday, September 23, 2011 4:07:05 PM

Rose,
Myriam And I have gotten the methods section congruent and have been working on doing so as much as possible with the Tables which I have updated the Tables with the latest cleaned data. I need to update the text this weekend so I will send you the latest draft on Monday to distribute to the subcommittee.

Yvonne

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, September 23, 2011 12:59 PM
To: Vaucher, Yvonne
Cc: Myriam Peralta, M.D.; Finer, Neil; 'Wally Carlo, M.D.'; Gantz, Marie; Das, Abhik
Subject: RE: Hot Topics.

Yes, please send so I can get input.

Also, how are we doing on the papers? I believe we had discussed having them this week to send out for comments.

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]
Sent: Friday, September 23, 2011 3:57 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Myriam Peralta, M.D.; Vaucher, Yvonne
Subject: Hot Topics.

Rose,

The Hot Topics syllabus handouts and bibliographies are due October 1. I assume this refers to our

background and methods slides. If so, should we send them to you earlier next week for approval? Thanks.

Yvonne

Yvonne E. Vaucher, M.D., M.P.H.
Division of Neonatal/Perinatal Medicine
Clinical Professor of Pediatrics
UCSD School of Medicine

tele: 619-543-3759
FAX: 619-543-3812

From: Walsh, Michele
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Latest Plan for Growth Sec Analysis--Availability Request
Date: Friday, September 23, 2011 11:42:36 AM

Not yet: (b)(6) all is well.
Will tell her you asked!

Michele Walsh, MD
Chief, Division of Neonatology
216.844.3759

It's not what you look at that matters, it's what you see. Thoreau

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, September 23, 2011 10:19 AM
To: Walsh, Michele
Subject: RE: Latest Plan for Growth Sec Analysis--Availability Request

Neil and Wally will be on - given the data collected, each site will get an author. Will send the manuscript

Thanks
Did (b)(6) IS all well??
Rose

Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
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Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

-----Original Message-----
From: Walsh, Michele [mailto:Michele.Walsh@UHhospitals.org]
Sent: Friday, September 23, 2011 10:17 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Latest Plan for Growth Sec Analysis--Availability Request

If I don't participate in the calls
(which I really cant do now)- I would not feel that
I meet criteria for authorship. Happy to review manuscript
Etc. If you feel I need to do this (bc you need more senior input?)
, will need to drop Something else. (b)(6) So can not ask her to sub.

Michele Walsh, MD

Chief, Division of Neonatology
216.844.3759

It's not what you look at that matters, it's what you see. Thoreau

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Friday, September 23, 2011 10:15 AM
To: Walsh, Michele; Gabrio, Jenna
Subject: RE: Latest Plan for Growth Sec Analysis--Availability Request

Michele
This was a predefined secondary study for SUPPORT, so I had envisioned the entire subcommittee as authors. Even if you are not on the calls, given your involvement in SUPPORT, I would still recommend that you are an author.

Is that ok once we get a manuscript draft??
thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
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MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

-----Original Message-----
From: Walsh, Michele [mailto:Michele.Walsh@UHhospitals.org]
Sent: Friday, September 23, 2011 10:12 AM
To: Gabrio, Jenna; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Latest Plan for Growth Sec Analysis--Availability Request

I do not need to be on this project or the calls.

Michele Walsh, MD
Chief, Division of Neonatology
216.844.3759

It's not what you look at that matters, it's what you see. Thoreau

-----Original Message-----
From: Gabrio, Jenna [mailto:jgabrio@rti.org]
Sent: Thursday, September 22, 2011 5:30 PM
To: Navarrete, Cristina; Duara, Shahnaz; Bauer, Charles R; Yvonne Vaucher; richard.ehrenkranz@yale.edu; Poindexter, Brenda B; alaptook@WIHRI.org; Bradley Yoder; adas@rti.org; mgantz@rti.org; Higgins, Rosemary (NIH/NICHD) [E]; kurt.schibler@cchmc.org; mcw3@cwru.edu; MPeralta@PEDS.UAB.EDU; nancy newman;

nfiner@ucsd.edu; Roger.Faix@hsc.utah.edu; Wallace, Dennis; Wally Carlo, M.D.; wrich@ucsd.edu
Cc: Cunningham, Meg; Zaterka-Baxter, Kristin; Higgins, Rosemary (NIH/NICHD) [E]; Archer, Stephanie (NIH/NICHD) [E]; Brenda Vecchio; fmartinez@ucsd.edu; Starlett Williams
Subject: RE: Latest Plan for Growth Sec Analysis--Availability Request

Dear all,

We would like to setup a SUPPORT Growth Call. Please provide your updated availability on this Doodle poll (http://www.doodle.com/9wee6cs3dyz57vik) for the following dates:

9/28, W
9/29, Th
9/30, F

10/3, M
10/4, Tu

Thanks,
Jenna

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, September 21, 2011 10:24 AM
To: 'Navarrete, Cristina'; Duara, Shahnaz
Cc: Das, Abhik; Cunningham, Meg; Gabrio, Jenna
Subject: FW: Latest Plan for Growth Sec Analysis

Hi,
I think it would be good to have a call once we have some of the analysis.

Can we set this up?
thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network Pregnancy and Perinatology Branch CDBPM, NIH 6100 Executive Blvd., Room 4B03 MSC 7510 Bethesda, MD 20892 For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

-----Original Message-----
From: Navarrete, Cristina [mailto:CNavarrete@med.miami.edu]
Sent: Friday, September 16, 2011 3:07 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Duara, Shahnaz
Subject: Latest Plan for Growth Sec Analysis

Hi Dr. Higgins,
Here's a copy of the latest plan with all the suggestions taken into account, for final review and forwarding to RTI.
Thanks, Cristina

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Federal and Ohio law protect patient medical information, including psychiatric_disorders, (H.I.V) test results, A.I.Ds-related conditions, alcohol, and/or drug_dependence or abuse disclosed in this email. Federal regulation (42 CFR Part 2) and Ohio Revised Code section 5122.31 and 3701.243 prohibit disclosure of this information without the specific written consent of the person to whom it pertains, or as otherwise permitted by law.

From: Karen Osborne RN
To: Higgins, Rosemary (NIH/NICHD) [E]; Roger Faix; Bradley Yoder; abodnar@utah.gov; Shawna Baker
Cc: "Auman, Jeanette O."
Subject: RE: SUPPORT TRACKING
Date: Thursday, September 22, 2011 7:53:52 PM

Hi Rose,

Here is our update:

Patient #	Folnum:	Comments
(b)(6)		

Please let me know if you have further questions.

Thanks!
Karen

Karen Osborne RN, CCRC
Clinical Research Manager
Division of Neonatology
University of Utah
295 Chipeta Way,
SLC, UT 84108
Ph: 801-213-3298
Fax: 801-587-3618
Pager: 801 (b)(6)

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, September 14, 2011 1:45 PM
To: Roger Faix; Bradley Yoder; abodnar@utah.gov; Karen Osborne RN; Shawna Baker
Cc: 'Auman, Jeanette O.'
Subject: SUPPORT TRACKING

Hi,
We are missing tracking outcome form(s) for SUPPORT NEUROIMAGING tracking. Please let us know how you are doing.

Thanks for all the effort!!
Rose

CENTER	NETWORK	FOLNUM	_3YRDT	_4YRDT	Follow-up CENTER		NICU CENTER
25	66371	1101	10/28/2009	10/28/2010	.		.
25	66611	1127	11/16/2009	11/16/2010		18	25
25	68221	1003	8/5/2010	8/5/2011	.		.
25	68311	1055	8/10/2010	8/10/2011	.		.
25	68361	1007	8/15/2010	8/15/2011	.		.
25	68381	1004	8/15/2010	8/15/2011	.		.
18	66611	2075	11/16/2009	11/16/2010		18	25

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Finer, Neil
To: Rich, Wade; Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.
Subject: Re: (No subject)
Date: Thursday, September 22, 2011 3:10:14 PM

Great
Which form is that and how is the location noted ie a check box or an actual description?
Thanks
Neil

On Sep 22, 2011, ation
Thanks
Neil

9:07 PM, "Rich, Wade" <wrich@ucsd.edu<mailto:wrich@ucsd.edu>> wrote:

Usually, but we could review actual placement, as it is recorded.

----- Reply message -----
From: "Finer, Neil" <nfiner@ucsd.edu<mailto:nfiner@ucsd.edu>>
Date: Thu, Sep 22, 2011 11:24 am
Subject: (No subject)
To: "Rich, Wade" <wrich@ucsd.edu<mailto:wrich@ucsd.edu>>

OK
What did we and others do?
Mostly r arm preductal?
Neil

On Sep 22, 2011, at 6:45 PM, "Rich, Wade"
<<mailto:wrich@ucsd.edu>wrich@ucsd.edu<mailto:wrich@ucsd.edu>> wrote:

I don't think we specified.

----- Reply message -----
From: "Finer, Neil" <<mailto:nfiner@ucsd.edu>nfiner@ucsd.edu<mailto:nfiner@ucsd.edu>>
Date: Thu, Sep 22, 2011 7:38 am
Subject:
To: "Rich, Wade" <<mailto:wrich@ucsd.edu>wrich@ucsd.edu<mailto:wrich@ucsd.edu>>

Wade
Where the oximeters in SUPPORT always pre ductal or did we specify?
Did we record the site??
I could not find anything in the manual - probably missed it
Thanks
Neil

From: Finer, Neil
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Rich, Wade; wcarlo@peds.uab.edu
Subject: Re: Re: RE: RE:
Date: Thursday, September 22, 2011 2:26:14 PM

I agree
I am dismayed that we didn't address this sooner
I suspect that most were Right arm preductal
Neil

On Sep 22, 2011, at 5:04 PM, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> wrote:

> It can be acknowledged as a potential limitation, I am not sure we can say much more.
>
> Thanks
> Rose
>
> ----- Original Message -----
> From: Finer, Neil <nfiner@ucsd.edu>
> To: Higgins, Rosemary (NIH/NICHD) [E]
> Cc: Rich, Wade <wrich@ucsd.edu>; Wally Carlo, M.D. <WCarlo@peds.uab.edu>
> Sent: Thu Sep 22 10:59:15 2011
> Subject: Re: RE: RE:
>
> Thanks for looking
> I could not find it either
> I think we need to discuss as to our findings
> If they are not all pre ductal then we have the potential that we are reporting mixed data especially early when the duct is open etc
> What do you think?.
> Thanks again Rose
> Neil
>
> On Sep 22, 2011, at 4:57 PM, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> wrote:
>
>> Not on the forms
>>
>> Rose
>>
>> Rosemary D. Higgins, MD
>> Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network
>> Pregnancy and Perinatology Branch
>> CDBPM, NIH
>> 6100 Executive Blvd., Room 4B03
>> MSC 7510
>> Bethesda, MD 20892
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>> 301-496-5575
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>> higginsr@mail.nih.gov
>>
>>
>> -----Original Message-----

>> From: Finer, Neil [mailto:nfiner@ucsd.edu]
>> Sent: Thursday, September 22, 2011 10:53 AM
>> To: Higgins, Rosemary (NIH/NICHD) [E]
>> Cc: Wally Carlo, M.D.; Rich, Wade
>> Subject: Re: RE:
>>
>> That's what I thought
>> I think we need to be able to state the site. Ie pre vs post ductal
>> Was it on any of the forms?..
>> Thanks Rose
>>
>> On Sep 22, 2011, at 4:44 PM, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> wrote:
>>
>>> I went through the MOP and protocol and we do not state preductal anywhere that I can find. I think it was discussed but not specifically stated in the MOP or protocol.
>>>
>>> Rose
>>>
>>> Rosemary D. Higgins, MD
>>> Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network
>>> Pregnancy and Perinatology Branch
>>> CDBPM, NIH
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>>> higginsr@mail.nih.gov
>>>
>>>
>>> -----Original Message-----
>>> From: Finer, Neil [mailto:nfiner@ucsd.edu]
>>> Sent: Thursday, September 22, 2011 10:32 AM
>>> To: Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.
>>> Subject:
>>>
>>> Hi Rose and Wally
>>> In the protocol for SUPPORT did we specify pre ductal sat probe placement?
>>> I can't find that stated but I may be missing it
>>> If not did we record the site?
>>> thanks
>>> Neil

From: Juliann Di Fiore
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: "Wally Carlo, M.D."; Michele Walsh; Richard Martin; Neil Finer; Wade Rich; Wrage, Lisa Ann
Subject: Re: Draft effect of low target range on the incidence of IH_9_14
Date: Thursday, September 22, 2011 9:35:01 AM

Thanks for catching that, I had meant to include that in the discussion.

Take care,

Julie

On 9/22/2011 9:22 AM, Higgins, Rosemary (NIH/NICHD) [E] wrote:
> Julie
> You may want to state in the abstract that the only the subcohort had high resolution oximetry.
> "A subcohort of 115 preterm infants with high resolution pulse oximetry (2 sec sample rate and 2 sec averaging) enrolled in the SUPPORT trial, were randomized to low (85-89%) or high (90-95%) oxygen saturation target ranges. Oxygen saturation was monitored until 36wks postmenstrual age or until the infant was breathing without respiratory support for =72hrs."
>
> I think there needs to be some mention that the majority of SUPPORT Trial enrollees had a 10 second averaging, so not able to be evaluated with the detail of the subcohort. You can mention this in the discussion as a limitation.
>
> Thanks
> Rose
>
> Rosemary D. Higgins, MD
> Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network
> Pregnancy and Perinatology Branch
> CDBPM, NIH
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> higginsr@mail.nih.gov
>
>
> -----Original Message-----
> From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
> Sent: Friday, September 16, 2011 7:04 PM
> To: jmd3@case.edu; Michele Walsh; Richard Martin; Neil Finer; Wade Rich; Wrage, Lisa Ann; Higgins, Rosemary (NIH/NICHD) [E]
> Subject: RE: Draft effect of low target range on the incidence of IH_9_14
>
> Hi Julie:
>
> I have included minor comments.
>
> One issue you may want to address in the Discussion is that one may expect more IH episodes if a lower target is the aim. I guess the counter argument is that in the trial we set alarms at the same oxygen saturation level in both target groups, which were well above the IH level. Nonetheless, it may be hard for clinicians to maintain low saturations while also preventing the most severe ones.

>
> Hope this helps.
>
> GREAT job putting this together.
>
> Wally
> Wally Carlo, M.D.
> Edwin M. Dixon Professor of Pediatrics
> University of Alabama at Birmingham
> Director, Division of Neonatology
> Director, Newborn Nurseries
> 1700 6th Avenue South
> 176F Suite 9380R
> Birmingham, AL 35233-7335
> Phone: 205 934 4680
> FAX: 205 934 3100
> Cell: 205 (b)(6)
>
>
> -----Original Message-----
> From: Juliann Di Fiore [mailto:jmd3@case.edu]
> Sent: Friday, September 16, 2011 11:30 AM
> To: Michele Walsh; Richard Martin; Neil Finer; Wally Carlo, M.D.; Wade
> Rich; Wrage, Lisa Ann; Higgins, Rosemary (NIH/NICHD) [E]
> Subject: Draft effect of low target range on the incidence of IH_9_14
>
> Hi Everyone,
>
> Here is the next draft of the IH paper for your comments. It has been
> decided to send it Journal of Pediatrics.
>
> Thanks,
>
> Julie
>
> PS- Could you please send me any financial support and conflict of
> interest information that is relevant for submitting to the journal?
> Thanks!
>
>

--
Juliann Di Fiore
Research Engineer
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alcohol, and/or drug_dependence or abuse disclosed in this email. Federal regulation (42 CFR Part 2) and Ohio Revised Code section 5122.31 and 3701.243 prohibit disclosure of this information without the specific written consent of the person to whom it pertains, or as otherwise permitted
by law.

From: Juliann Di Fiore
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Richard Martin; Michele Walsh
Subject: Re: saturation data in SUPPORT cohort
Date: Wednesday, September 21, 2011 2:36:31 PM

Sure.

Thanks,

Julie

On 9/21/2011 2:04 PM, Higgins, Rosemary (NIH/NICHD) [E] wrote:
> Data release is approved by the steering committee. We need a protocol for the subcommittee to review/approve and send on to the steering committee.
> Can you send me something for the pilot look at 40 patients
> Rose
>
> Rosemary D. Higgins, MD
> Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network
> Pregnancy and Perinatology Branch
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> higginsr@mail.nih.gov
>
>
> -----Original Message-----
> From: Juliann Di Fiore [mailto:jmd3@case.edu]
> Sent: Wednesday, September 21, 2011 10:54 AM
> To: Higgins, Rosemary (NIH/NICHD) [E]
> Cc: Richard Martin; Michele Walsh
> Subject: saturation data in SUPPORT cohort
>
> Hi Rose,
>
> Richard and I were discussing the saturation data in the rest of the
> SUPPORT cohort. Although the saturation data at the other sites are over
> filtered and under sampled for our purposes we'd like to run a small
> sample of the infants just to see if there might be something
> salvageable to pursue. If it looks promising I would submit a protocol
> to look at the entire SUPPORT cohort. Would it be possible for me to
> easily get maybe 40 infants (20 in each group) to look at or do I need
> to submit a protocol to the committee?
>
> Regards,
>
> Julie
>

--
Juliann Di Fiore
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Cleveland, OH 44106
(216) 844-1478

From: Vaucher, Yvonne
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Hot Topics
Date: Monday, September 19, 2011 2:12:12 PM

Thanks.

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, September 19, 2011 7:45 AM
To: Vaucher, Yvonne
Cc: Finer, Neil
Subject: RE: Hot Topics

Yvonne -
Growth will go into separate growth paper.
I have asked that both you and Myriam be included on the SUPPORT calls for the interaction piece.

For the hot topics submission, background and methods is fine. The SUPPORT Subcommittee and steering committee should approve these prior to submission.

PAS timelines are attached. Specifically:

September 30, 2011 - Initial abstract draft due to subcommittee. This need not contain final data analyses results.

October 17, 2011 - Final abstract due to subcommittee. Approvals for abstracts must be obtained in advance of NICHD Clearance

Thanks for all your help

Rose

Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network Pregnancy and Perinatology Branch CDBPM, NIH 6100 Executive Blvd., Room 4B03 MSC 7510 Bethesda, MD 20892 For overnight delivery use Rockville, MD 20852
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-----Original Message-----
From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]
Sent: Friday, September 16, 2011 3:26 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Vaucher, Yvonne; Finer, Neil
Subject: Hot Topics

Rose,

Sorry you couldn't hear me. I am in the Nevada foothills of the Sierra Nevada and apparently AT&T does much better here than my my carrier (Verizon). I managed to hear most of the conversation despite 3 disconnects, however.

Re growth: all growth data will go in the growth paper

Re interaction/stratification CPAP/O2 saturation: separate abstract/paper. We will need to avoid any conflicting statements in our FUP papers. It will be helpful to sit in on the conference calls so we know how what transpires. Thanks for you suggestion.

Myriam and I will get together on the methods/tables. The methods will be the same; most tables will be identical; some may vary a little. Is it possible that the NEJM may want us to make one paper out of this? We should include some stratification for the ND outcome results as they are very different between strata and frankly the ND folks would like useful outcome information for these extremely high risk infants (such as number entirely "normal" in each stratum (50% for 24-25 and 66% for 26-27 weeks gestation). We will get our next iteration to you this coming week.

Re Hot Topics...we are such a "hot" topic that we shouldn't be in the "book" at all! However as they will want something, my understanding from the call was that we won't include any results. This would leave only the background and a description of the methods. Is this correct? Also my understanding is that the SUPPORT subcommittee needs to approve all the slides-those in the book and those we present.

Re PAS....When is the deadline for subcommittee review of a PAS abstract?

Yvonne

From: Kennedy, Kathleen A
To: Wrage, Lisa Ann
Cc: dale_phelps@urmc.rochester.edu; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik (adas@rti.org); Gantz, Marie (mgantz@rti.org)
Subject: RE: ROP Natural History analysis update
Date: Monday, September 19, 2011 11:47:13 AM

I still don't understand what you're saying in footnote 2. It seems like we continued to collect information after the babies were withdrawn (ok with me) because we know that one died. I don't understand why the other one was adjudicated if we had information about the ROP exams. Is it because we didn't have exams after discharge?

For footnote 4, we'll need to specify here or in the Methods section of the paper what criteria were used to determine that adjudication was needed and how adjudication was done.

I think I asked before if we could have a column for 100% in Table 3. Is there a reason we can't do that?

About the new figures that you've generated, it seems to me that there are no obvious differences between the High sat and Low sat groups. It would probably be easier to say this with confidence if we looked at all GAs combined so that there are more babies in each plot.

Kathleen A. Kennedy, MD, MPH
Richard W. Mithoff Professor of Pediatrics
Director, MS in Clinical Research Degree Program
UT-Houston Medical School
6431 Fannin, Suite 2.106
Houston, TX 77030
713 500-6708

From: Wrage, Lisa Ann [mailto:wrage@rti.org]
Sent: Friday, September 02, 2011 11:55 AM
To: Kennedy, Kathleen A; Phelps, Dale; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik; Gantz, Marie
Subject: RE: ROP Natural History analysis update

Hi,
I have attached an update (changes noted at the top of the document). Please take a look at the DRAFT graphs on the last page and let me know if this is the sort of thing you were looking for. These graphs are the first set of graphs described in your document as:

Graphs - Cumulative Incidence (among consented inborn infants with ROP outcome and timing determined) of Type 1/Treated ROP:

Although I don't anticipate a difference, I think we ought to first generate these graphs separately for infants in the low and high O_2 sat groups. If there isn't a difference (either by inspection or by formal comparison of time-to-event), we can just present combined data for both study groups and make a statement that there was no difference.

For infants who achieved "final outcome" and had Type 1/Treated ROP, generate a separate plot for each week of gestation on each of 2 graphs with cumulative incidence of Type 1/Treated ROP on the y-axis

and postmenstrual age (first graph) or postnatal age (second graph) on the x-axis.

I think these are the most critical graphs. If these do not show any suggestion that there is a difference between the O_2 sat groups, we probably don't need to separate the remaining graphs by treatment group.

A couple of comments:
Because we are looking at single week of GA the graphs by chronologic age and postmenstrual age obviously look pretty similar.
The last pair of graphs looks weird because there is only one infant in one of the groups. For all of the graphs the x scale is kind of long because there is one infant in GA=24 with age of onset quite a bit farther out than the others (this infant was born in 6/2006 and had laser surgery 1/2007). Also, I have not yet tested between groups.

Thanks.
Lisa

From: Kennedy, Kathleen A [mailto:Kathleen.A.Kennedy@uth.tmc.edu]
Sent: Tuesday, August 23, 2011 8:00 AM
To: Wrage, Lisa Ann; Phelps, Dale; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik; Gantz, Marie
Subject: RE: ROP Natural History analysis update

The table above the highlighted section asks for information (%iles) about any ROP and a separate row for Type 1 or treated ROP. The highlighted request for a graph is for cumulative incidence of Type 1 or treated ROP. (That's what determines when the clinician can stop looking for treatable ROP.) If you want to put both sets of data in a single graph, as they did in the paper you attached, that would be great. The cohort for these analyses is supposed to be those with ROP outcome and timing of ROP determined, so deaths would not be included in these analyses.

I think we need to see the previously requested analyses before we can proceed. I'm hoping we won't need anything more.

I'm not sure what to say about the PAS plan. This analysis request just barely missed the deadline for the 2011 PAS meeting. I was thinking we'd have it submitted as a manuscript long before the 2012 PAS meeting so I didn't submit it for that deadline. If putting this in the 2012 PAS queue will get this done more quickly, that would be fine with me. I'd be happy to put an abstract together if we have the analyses finished.

Kathleen A. Kennedy, MD, MPH
Richard W. Mithoff Professor of Pediatrics
Director, MS in Clinical Research Degree Program
UT-Houston Medical School
6431 Fannin, Suite 2.106
Houston, TX 77030
713 500-6708

From: Wrage, Lisa Ann [mailto:wrage@rti.org]
Sent: Friday, August 12, 2011 3:38 PM
To: Kennedy, Kathleen A; Phelps, Dale; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik; Gantz, Marie
Subject: FW: ROP Natural History analysis update

Hello,

The next update for the ROP Natural History analysis will address the comments on previous analysis and (going in order of your outline) some graphs that you describe as 'cumulative incidence' graphs. For this section I need some clarification as to what analysis question (or questions) you are trying to address, I have highlighted this section in yellow in your outline (attached.)

For example, what I need to know is: are you essentially trying to expand upon the age of onset information in the preceding table (Table 3 in previously sent analysis report) by comparing age of onset of ROP by subgroups (e.g. age of onset of severe ROP by GA week, etc.). ***Or*** are you interested in comparing actual cumulative incidence of severe ROP by these subgroups.

I ask because the different questions require different types of analyses, for the first we could use the specific subset of infants in the ROP group of interest and look at cumulative frequency distributions (see the figures in one of your reference papers (attached)) and also compare median age of onset between groups; for actual cumulative incidence we would use all the data including deaths and use some type of time-to-event model to estimate cumulative incidence and compare between groups

If you have any questions let me know.

Also, it would also be helpful for you to let me know if there is anything that I have not yet addressed that you know that you will need for your PAS abstract so that I can prioritize.

Thank-you,
Lisa

From: Wrage, Lisa Ann
Sent: Wednesday, August 10, 2011 9:45 AM
To: 'Phelps, Dale'; Kennedy, Kathleen A; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik; Gantz, Marie
Subject: RE: ROP Natural History analysis update

Hi All,

Just fyi, I am working on the next update to this analysis and will have questions for you sometime this week.

Lisa

Lisa Wrage, MPH

Research Statistician
Statistics & Epidemiology
RTI International
wrage@rti.org
919-220-2653

From: Phelps, Dale [mailto:Dale_Phelps@URMC.Rochester.edu]
Sent: Wednesday, August 10, 2011 2:41 AM
To: Gantz, Marie; Wrage, Lisa Ann; Kennedy, Kathleen A; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik
Subject: RE: ROP Natural History analysis update

Hi Marie,
You are correct that it is better to reference time of diagnosis. Unfortunately, we would all love to know when the onset was, but we usually can not know this.
Dale Phelps

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Friday, June 03, 2011 1:26 PM
To: Wrage, Lisa Ann; Kennedy, Kathleen A; Higgins, Rosemary (NIH/NICHD) [E]; Phelps, Dale
Cc: Das, Abhik
Subject: RE: ROP Natural History analysis update

I just had a chance to look at this. Would it be more accurate to reference time of "diagnosis" rather than "onset" of ROP, since we know the date of the exam during which ROP was diagnosed, but onset probably occurred some amount of time earlier?

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Wrage, Lisa Ann
Sent: Thursday, May 26, 2011 10:41 AM
To: 'Kennedy, Kathleen A'; Higgins, Rosemary (NIH/NICHD) [E]; Phelps, Dale
Cc: Das, Abhik; Gantz, Marie
Subject: ROP Natural History analysis update

Hello,
I attach an update to the ROP Natural History analysis (I have updated the flowchart and added the first few tables & a draft of the first figure). I look forward to any comments you have.
I will continue on to the next items in June.
Thanks.
Lisa

Lisa Wrage, MPH
Research Statistician
Statistics & Epidemiology
RTI International
wrage@rti.org
919-220-2653

From: Vaucher, Yvonne
To: Gantz, Marie
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Vaucher, Yvonne
Subject: RE: Hearing impairment
Date: Friday, September 16, 2011 4:34:45 PM

Thanks Marie for resending the list.
I don't want to belabor this but the numbers are so few and one child either way can make a difference. It looks like 5/11 with impairment and no amplification had not had any or appropriate diagnostic tests (# 16,20,3031,32) so we don't know their "permanent" status. As you suggest, I would be happy to say that "24 children been assessed as hearing impaired at the time of the 18-22 month visit" but that is quite not the current NRN definition of NDI.

Yvonne

From: Gantz, Marie [mgantz@rti.org]
Sent: Friday, September 16, 2011 12:53 PM
To: Vaucher, Yvonne; Higgins, Rosemary (NIH/NICHD)
Subject: RE: Hearing impairment

Yvonne,

To clarify, there were actually 11 cases of hearing impairment without amplification and 13 cases with amplification.

With respect to re-querying the centers, if our goal is simply to clarify whether hearing impairment can be described as "permanent" in the paper, then I think we already have our answer. After looking back at the query responses I sent you earlier (attached to this email again), there was at least (b)(6) (b)(6) (b)(6) This was the comment from the center: "patient was in process of audiology assessment when seen (abnormal initial screen) At next visit age 30 mo, language skills improved, no hearing deficit (but NOT at the study visit when language skills delayed)." Perhaps it would be most accurate to describe the 24 children coded as impaired as having been assessed as hearing impaired at the time of the 18-22 month visit.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

-----Original Message-----
From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]
Sent: Friday, September 16, 2011 2:49 PM
To: Higgins, Rosemary (NIH/NICHD)
Cc: Gantz, Marie; Vaucher, Yvonne
Subject: Hearing impairment

P Per Marie's new tables and what Marie said today (11 with amplification/all permanently impaired); there are 24 "hearing impaired" of whom 11 have amplification so 13 would be in the category of hearing impaired but no amplification. From reviewing the records of each of these children most had not had diagnostic studies and as I recall 3-4 had consults "pending". there is no way to know that it is permanent without the appropriate diagnostic studies. So the problem is calling all these 13 children's hearing loss as "permanent" per the NDI algorithm.

S So I think we should re-ask the centers reporting the "hearing impaired" without amplification if they would label the hearing loss as "permanent" or not. Then we can be consistent with the NDI analog definition. Otherwise we would have to say "hearing impairment "instead. Certainly hearing impairment of this degree is a disability and I don't have any problem using it as part of the NDI but it is not consistent with the "official" definition.

Y Yvonne

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "adas@rti.org"
Subject: Fw: Latest Plan for Growth Sec Analysis
Date: Friday, September 16, 2011 3:14:05 PM
Attachments: Suggestions Incorporated SUPPORT Growth Sec.docx

Here is the growth secondary revisions.

----- Original Message -----
From: Navarrete, Cristina <CNavarrete@med.miami.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Duara, Shahnaz <SDuara@med.miami.edu>
Sent: Fri Sep 16 15:07:11 2011
Subject: Latest Plan for Growth Sec Analysis

Hi Dr. Higgins,
Here's a copy of the latest plan with all the suggestions taken into account, for final review and forwarding to RTI.
Thanks, Cristina

SUPPORT: GROWTH SECONDARY STUDY

Final plans based on sub-committee recommendations:

1. Focus on first 2 hypothesis- done
2. Primary outcome
    a. Dichotomize to include deaths- done
    b. Analysis by GA strata (main analysis)
    c. Analysis by AGA and SGA (secondary analysis)
3. For RTI: Trajectory analysis, needs censoring method to analyze missing data from death cases, especially that there are more number of deaths in the low saturation group in the main trial
    a. Pattern after Patel's growth trajectory methods (Pediatrics 2005)
        i. exponential method
4. Reference growth curves
    a. In-hospital growth:
        i. Olsen 2010
    b. 18-22m growth:
        i. WHO 2006
5. Calorie calculations:
    a. all calories
6. Correction factor for multiple analyses- (not to be done, as with main SUPPRORT analyses)

SUPPORT Oxygen Saturation Arm (randomized from birth, stratified into 24-25 and 26-27w):

- LOW Saturation = 85-89%
- HIGH Saturation= 91-95%

Hypotheses:

1. Low O_2saturation infant group less death or <10%ile for weight (=poor growth) at 36wk or discharge and at 18-22m follow-up
2. Low O_2saturation infant group better in-hospital growth trajectory

Specific Aims:

1. To determine anthropometric measurements (wt, HC, length) in infants randomized to low and high oxygen saturation arms, from birth to hospital discharge and again at 18-22 months corrected age (Data: wt, length, HC at birth, days 7, 14, 21, 28, 32wk PMA, 36wk PMA OR discharge, and 18-22month follow-up)

2. To determine nutritional intake (parenteral and enteral) during hospital stay (Data: 24h intake (enteral/parenteral): volume and composition (mL/kg/g & kcal/kg/d) on days 7, 14, 21, 28, 32wk PMA, 36wk PMA OR discharge

3. To determine the percentage of infants with growth <10 percentile at 36 weeks PMA or discharge, whichever comes first (Data: <10th% for wt, length, HC at 36wks PMA or discharge)

4. To determine the percentage of infants with growth <10 percentile at 18-22 months corrected age (Data: <10th% for wt, length, HC at follow-up)

5. To determine in-hospital growth velocity/trajectory in low and high saturation arms (Data: Anthropometrics from birth to PMA 36 OR discharge (6 time points)OR between EACH measurement period WT: gain of gm/kg/day, HC: gain of cm/week, Length: gain of cm/week) (

6. To determine long-term growth velocity/trajectory, from hospital discharge to follow up at 18-22 months corrected age in low and high saturation arms (Data: Anthropometrics at discharge and 18-22m FU (2 time points)

POPULATION: SUPPORT Cohort minus ~300 (enrolled prior to initiation of secondary)

TABLE: POPULATION CHARACTERISTICS (GDB data)

Population Characteristics	LOW Saturation	HIGH Saturation	Statistic Comparison
N	n/N (%)	n/N (%)	
Gestational Age, wk (mean ± SD)			t test
Birth weight, g (mean ± SD)			t test
Weight at birth <10%, n/N (%)			Chi-square
Head Circumference at birth, cm (mean ± SD)			t test
Head Circumference at birth <10%, n/N (%)			Chi-square
Length at birth, cm(mean ± SD)			t test
Length at birth <10%, n/N (%)			Chi-square
Race (black, not black), n/N (%)			Chi-square
Multiple birth (yes, no), n/N (%)			Chi-square
Antenatal steroids (yes, no), n/N (%)			Chi-square
Method of delivery (SVD), n/N (%)			Chi-square
Mother education: HS grad (yes, no), n/N (%)			Chi-square

TABLE: CLINICAL CHARACTERISTICS (GDB and SUPPORT data)

Clinical Characteristics	LOW Saturation	HIGH Saturation	Statistic Comparison
N	n/N (%)	n/N (%)	
% Mortality at 36wk PMA			Chi-square
BPD, physiologic (yes, no)			Chi-square
BPD, oxygen at 36wk PMA (yes, no)			Chi-square
BPD, moderate: <30% O2 at 36wk (yes, no)			Chi-square
BPD, severe: >30% O2 at 36wk (yes, no)			Chi-square
Postnatal Steroids for BPD (yes, no)			Chi-square
Duration of Mech Vent (d) (mean ± SD)			t-test
Duration of suppl O2 (d) (mean ± SD)			t-test
Severe IVH (yes, no)			Chi-square
PVL (yes, no)			Chi-square
NEC (yes, no)			Chi-square
Sepsis, late onset (yes, no)			Chi-square
PDA (yes, no)			Chi-square

TABLE: NUTRITIONAL INTAKE (GRO and GDB data) *(mean ± SD) (IF NO DIFFERENCE, will just describe in manuscript)

Total energy intake (kcal/kg/d) (parenteral and enteral)	LOW Saturation	HIGH Saturation	Statistic Comparison
Day 7 total			2 way, Repeated measures ANOVA
Day 14 total			
Day 21 total			
Day 28 total			
32 wk PMA			
36wk PMA			
Age at first enteral feed (median, 25%, 75%)			Log-rank test (Kaplan-meier)
Age at full enteral feed (median, 25%, 75%)			
Duration of PN≥75%			t-test

TABLE: Nutritional Intake by component *(mean ± SD) (IF NO DIFFERENCE, will just describe in manuscript)

	Nutritional Intake by Component (g/kg)(parenteral and enteral combined)					
	Carbohydrate		Protein		Fat	
Saturation Target	Low	High	Low	High	Low	High
Day 7						
Day 14						
Day 21						
Day 28						
32 wk PMA						
36wk PMA						

TABLE AND/OR FIGURE: GROWTH IN-HOSPITAL AND AT 18-22m FOLLOW-UP

WEIGHT		Absolute numbers (g) mean ± SD			<10th%ile, n/N (%)		
	N=	LOW Sat	HIGH Sat	p	LOW Sat	HIGH Sat	p
Birth							
Day 7							
Day 14							
Day 21							
Day 28							
32wk PMA							
36wk PMA							
18-22m FU							
LENGTH		LOW Sat	HIGH Sat	p	LOW Sat	HIGH Sat	p
Birth							
Day 7							
Day 14							
Day 21							
Day 28							
32wk PMA							
36wk PMA							
18-22m FU							
HEAD CIRC		LOW Sat	HIGH Sat	p	LOW Sat	HIGH Sat	p
Birth							
Day 7							
Day 14							
Day 21							
Day 28							
32wk PMA							
36wk PMA							
18-22m FU							

TABLE AND/OR FIGURE: GROWTH IN-HOSPITAL AND AT 18-22m FOLLOW-UP (Stratified by GA) (analyze but may just be described in manuscript discussion)

WEIGHT	Absolute numbers (g) mean ± SD					<10th %ile n/N (%)				
	LOW Sat		HIGH Sat		p	LOW Sat		HIGH Sat		p
GA (w)	24-25	26-27	24-25	26-27		24-25	26-27	24-25	26-27	
Birth										
Day 7										
Day 14										
Day 21										
Day 28										
32wk PMA										
36wk PMA										
18-22m FU										
LENGTH	LOW Sat		HIGH Sat		p	LOW Sat		HIGH Sat		p
GA (w)	24-25	26-27	24-25	26-27		24-25	26-27	24-25	26-27	
Birth										
Day 7										
Day 14										
Day 21										
Day 28										
32wk PMA										
36wk PMA										
18-22m FU										
HEAD CIRC	LOW Sat		HIGH Sat		p	LOW Sat		HIGH Sat		p
GA (w)	24-25	26-27	24-25	26-27		24-25	26-27	24-25	26-27	
Birth										
Day 7										
Day 14										
Day 21										
Day 28										
32wk PMA										
36wk PMA										
18-22m FU										

PRIMARY OUTCOME:

GROWTH OUTCOMES at 36wk PMA and at 18-22m ASSESSED BY Relative Risk for growth failure (weight <10%ile) in LOW vs. HIGH SATURATION Target while on supplemental oxygen

Adjust for the ff. confounders AND include any that may be unbalanced with p<0.1 in analysis above:

1. Gestational age (adjusted in main trial)
2. Study center (adjusted in main trial)
3. Familial clustering (adjusted in main trial)

WHOLE COHORT	LOW Saturation	HIGH Saturation	RR (95% CI)
36wk PMA			
Death or wt<10th%ile			
Wt <10th%ile			
18-22m F/U			
Death or wt<10th%ile			
Wt <10th%ile			

According to Stratification by Gestational Age

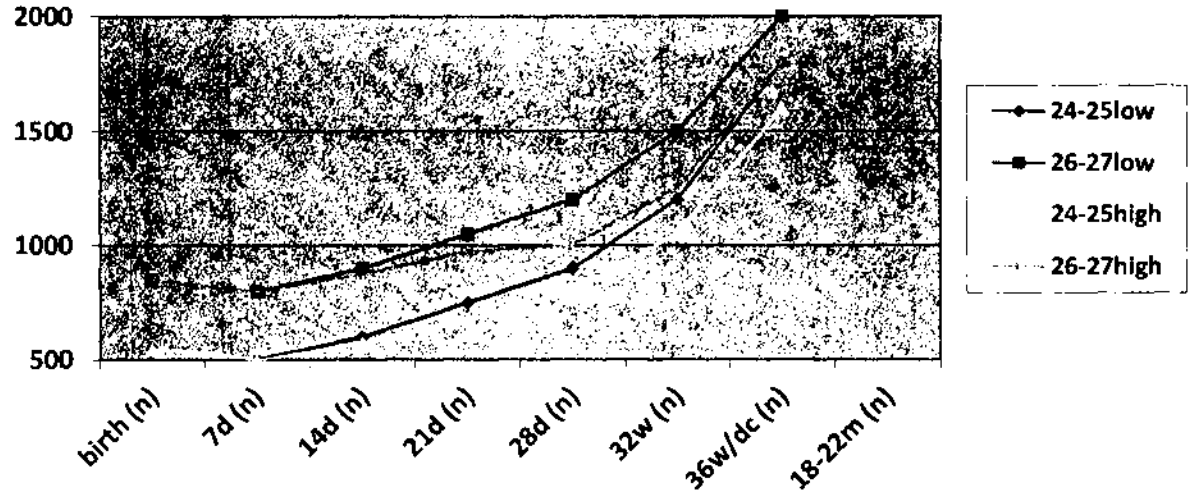
24-25wk (n)	LOW Saturation	HIGH Saturation	RR (95% CI)
36wk PMA			
Death or wt<10th%ile			
Wt <10th%ile			
18-22m F/U			
Death or wt<10th%ile			
Wt <10th%ile			
26-27wk (n)	**LOW Saturation**	**HIGH Saturation**	**RR (95% CI)**
36wk PMA			
Death or wt<10th%ile			
Wt <10th%ile			
18-22m F/U			
Death or wt<10th%ile			
Wt <10th%ile			

According to AGA and SGA status at birth

AGA	LOW Saturation	HIGH Saturation	RR (95% CI)
36wk PMA			
Death or wt<10th%ile			
Wt <10th%ile			
18-22m F/U			
Death or wt<10th%ile			
Wt <10th%ile			

SGA	LOW Saturation	HIGH Saturation	RR (95% CI)
36wk PMA			
Death or wt<10th%ile			
Wt <10th%ile			
18-22m F/U			
Death or wt<10th%ile			
Wt <10th%ile			

LONGITUDINAL GROWTH ANALYSIS <u>of survivors</u> (by hierarchical modeling) (Multilevel-regression analysis) similar to NICHD Ehrenkranz 1999 where weight is first analyzed over time and then by exposure. (FIGURE with plots of change in wt/time for each time period)



GROWTH TRAJECTORY ANALYSIS (Patel's exponential method): wt gain/kg/d

CALORIE CALCULATIONS:

Total calorie intake (kcal/kg/d):

Parenteral [tpn dextrose (%) x mL/kg x 0.034] + [intralipid (grams/kg) x 9] + [AA (gm/kg) x4] +
Enteral [(type of milk (kcal/oz) x mL/kg] + supplements [type of suppl. (kcal/vol) x amt/kg)]

Assume breastmilk to be 20kcal/oz

From: Vaucher, Yvonne
To: Gantz, Marie
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Vaucher, Yvonne
Subject: RE: Updated SUPPORT results
Date: Friday, September 16, 2011 2:51:46 PM

Marie,

My questions:

relate to comment #2) "Hearing impairment for one infant in the surfactant (YEV ?CPAP?) group was edited by the center since the last tables were run; there is now one less case of hearing impairment and NDI in the group due to that edit. "

YEV Re new Table 2 -Comparing to my tables (old Table 2 and tables sent with paper) there is one less hearing impaired child in the CPAP group (old 18/511 to new 17/511) and one more hearing impaired child and one more total followed (old 6/478 to new 7/479) resulting in a change in p from 0.03 to 0.06. Is this correct?

If we run the CPAP vs Surf comparison just for hearing impaired with amplification what is the p value?

Yvonne

From: Gantz, Marie [mgantz@rti.org]
Sent: Tuesday, September 13, 2011 11:15 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Myriam Peralta, M.D.; Vaucher, Yvonne; Wally Carlo, M.D.; Finer, Neil; Das, Abhik
Cc: Zaterka-Baxter, Kristin
Subject: RE: Updated SUPPORT results

Medians and IQR for the Bayley scores are attached.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255
From: Gantz, Marie
Sent: Monday, September 12, 2011 7:09 PM
To: 'Higgins, Rosemary (NIH/NICHD) [E]'; 'Myriam Peralta, M.D.'; 'yvaucher@ucsd.edu'; 'Wally Carlo, M.D.'; 'Finer, Neil'; Das, Abhik
Cc: Zaterka-Baxter, Kristin
Subject: RE: Updated SUPPORT results

Hi all,

Attached are updated tables of SUPPORT results. They include the following changes from the July 29 versions, and I believe they can be considered final data.

1) One additional infant in the CPAP group was followed up; that infant had NDI.

2) Hearing impairment for one infant in the surfactant group was edited by the center since the last tables were run; there is now one less case of hearing impairment and NDI in the group due to that edit.

3) Survival status has been added for several children who were lost to FU based on centers' verification that the children were alive at the time of last contact (at 18+ months adjusted age).

4) CPAP/surfactant and High/Low SpO2 were added to Table 1 since those are other variables that could have become unbalanced in the FU cohort (the differences are not significant).

5) A few variables were added to Table 3 at Yvonne's request.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255
From: Gantz, Marie
Sent: Friday, July 29, 2011 4:54 PM
To: 'Higgins, Rosemary (NIH/NICHD) [E]'; 'Myriam Peralta, M.D.'; 'yvaucher@ucsd.edu'; Wally Carlo, M.D.; 'Finer, Neil'; Das, Abhik
Cc: Zaterka-Baxter, Kristin; Auman, Jeanette O.
Subject: Updated SUPPORT results

Hi all,

Attached are updated FU results from SUPPORT. Please note the following.

1) Centers responded to the hearing queries, but in three cases the edit that the center said they made did not appear in the data. Jenny manually edited the data to match the email response from the center and prompted them to change the data on their end.

2) There were two cases where an SF09a was deleted (correctly) by a center at Jenny's request (because both SF and NF forms had been entered) but there was no NF09a entered, which resulted in a missing NDI outcome. Jenny requested that the center enter the NF09a (which they did) but for purposes of this report I used archived SF09a data for those two children.

3) I have added z scores to Table 3. They are based on the WHO growth curves. A few values (fewer than 10) were flagged as being extreme (unlikely), and I have run the numbers with and without those flagged values. It makes no difference in the results.

4) I have included comparisons of infants lost to FU vs. those with a FU visits (excludes deaths prior to FU) in Table 6.

5) With regard to survival to 18-22 months, there are 17 children who are lost to FU, and do not have the question about when the child was last known to be alive answered on the NF12, but the date of last contact was when the child was 17+ months adjusted age. If we could confirm that the child was alive at that point in time, we could fill in some of the missing survival data. A list of those IDs are attached.

Despite the issues noted above, I think we can consider these data to be final if the group agrees (and unless we want to pursue the survival to 18-22 months issue). I will be out of the office on vacation next week (and Abhik will also be out) but I will be back on August 15. Please circulate these results to the subcommittee as appropriate – I am only sending them directly to this small group.

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Gabrio, Jenna"
Subject: SUPPORT SUBCOMMITTEE
Date: Friday, September 16, 2011 1:59:00 PM

We will need a SUPPORT subcommittee call (preferably in the next 3 weeks) for the entire SUPPORT subcommittee + Myriam Peralta and Yvonne Vaucher

Thanks
Rose

Rosemary D. Higgins, MD
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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Wally Carlo, M.D."
Subject: RE: Publication | Peralta, SUPPORT FU Oximetry
Date: Friday, September 16, 2011 1:54:00 PM

Yes,
I have seen this one

Thanks
Rose

Rosemary D. Higgins, MD
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From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Friday, September 16, 2011 1:54 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: Publication | Peralta, SUPPORT FU Oximetry

This is the last paper I sent her. I am not sure if she sent it to you

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
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Director, Division of Neonatology
Director, Newborn Nurseries
1700 6th Avenue South
176F Suite 9380R
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Phone: 205 934 4680
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Cell: 205 (b)(6)

From: Becky Brazeel
Sent: Tuesday, September 06, 2011 3:13 PM
To: Myriam Peralta, M.D.; Wally Carlo, M.D.
Subject: Publication | Peralta, SUPPORT FU Oximetry

Dear Drs. Peralta and Carlo:

Attached please find version 2.1 of paper with the boilerplate and author list in APA/NEJM style.

Best regards,
Becky

From: Wally Carlo, M.D.
Sent: Tuesday, September 06, 2011 12:42 PM
To: Becky Brazeel
Subject: FW: Publication | Peralta, SUPPORT FU Oximetry

Please add this to the paper.
wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
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From: Archer, Stephanie (NIH/NICHD) [E] [mailto:archerst@mail.nih.gov]
Sent: Tuesday, September 06, 2011 10:50 AM
To: Wally Carlo (wacarlo@uab.edu)
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Publication | Peralta, SUPPORT FU Oximetry

Hi Wally,

Attached is a version of the paper with the boilerplate and author list included.

Stephanie

Stephanie Wilson Archer
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From: Becky Brazeel [mailto:bbrazeel@peds.uab.edu] **On Behalf Of** Wally Carlo, M.D.
Sent: Friday, September 02, 2011 1:36 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Yvonne Vaucher; Myriam Peralta, M.D.
Cc: nfiner@ucsd.edu; Wally Carlo, M.D.; Gantz, Marie; Wallace, Dennis; Das, Abhik; brazeel@uab.edu
Subject: SUPPORT FU PAPERS??

Hi,

Myriam and I have worked on this oxygen saturation follow-up paper. It is still a work in progress, but we wanted to share this so we can start getting some feed back. (b)(6)

(b)(6)

We look forward to hearing your comments,

Thanks,

Wally

From: Juliann Di Fiore
To: Michele Walsh; Richard Martin; Neil Finer; Wally Carlo; Wade Rich; Wrage, Lisa Ann; Higgins, Rosemary (NIH/NICHD) [E]
Subject: Draft effect of low target range on the incidence of IH_9_14
Date: Friday, September 16, 2011 12:33:01 PM
Attachments: Draft effect of low target range on the incidence of IH_9_14.docx

Hi Everyone,

Here is the next draft of the IH paper for your comments. It has been decided to send it Journal of Pediatrics.

Thanks,

Julie

PS- Could you please send me any financial support and conflict of interest information that is relevant for submitting to the journal? Thanks!

--
Juliann Di Fiore
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(216) 844-1478

Low oxygen saturation target range is associated with increased incidence of intermittent hypoxemia

Juliann M. Di Fiore, BSEE[1], Michele Walsh, MD[1], Lisa Wrage[2], Wade Rich, RRT[3], Neil Finer,MD[3], Waldemar A. Carlo, MD[4], Richard J. Martin, MD[1], and the SUPPORT Study Group of the NICHD Neonatal Network

[1] Division of Neonatology, Department of Pediatrics, Rainbow Babies & Children's Hospital, Case Western Reserve University, Cleveland, Ohio

[2] RTI International Research Triangle Park, North Carolina

[3] Division of Neonatology, Department of Pediatrics, University of California, San Diego, California

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Financial Assistance:

Supported by the National Institute of Child Health and Human Development Cooperative Multicenter Neonatal Research Network (Grant HD021364-23)

The authors state no conflicts of interest

Abstract:

Objective:

To test the hypothesis that preterm infants randomized to a low versus high O_2 saturation target range would have a higher incidence of intermittent hypoxemia (IH).

Study Design:

A subcohort of 115 preterm infants enrolled in the SUPPORT trial, were randomized to low (85-89%) or high (90-95%) oxygen saturation target ranges. High resolution pulse oximetry (2 sec sample rate and 2 sec averaging) was used to continuously monitor oxygen saturation until 36wks postmenstrual age or until the infant was breathing without respiratory support for ≥72hrs.

Results:

The low target oxygen saturation group had a higher rate of IH events prior to 12 days and beyond 57 days of life ($p<0.05$). The mean duration shortened ($p<0.01$) and the severity increased ($p<0.05$) with increasing postnatal age with no differences between groups. The higher rate of IH events in the low target group was associated with a time interval between events of <1min.

Conclusion:

A low oxygen saturation target range was associated with an increased rate of IH events that was dependent on postnatal age. The duration and severity of events was comparable between the target groups. Further investigation is needed to assess the role of timing of IH events and morbidity.

Background:

There is increasing evidence that intermittent hypoxemia (IH) may be associated with perinatal morbidity. In newborn animal models, administered IH paradigms have been shown to impair dopamine signaling[1], contribute to neurological handicap[1-3], and exacerbate retinal neovascularization[4]. Although it is known that IH events are common in preterm infants, data relating to the prevalence of these events has been limited. Pulse oximetry technology has enabled non-invasive recording of spontaneous intermittent hypoxemic events in preterm infants over prolonged periods of time. This has allowed for accurate documentation of the temporal changes in the incidence of IH events over the first few months of life. Recent data in preterm infants of 24-28 weeks gestation have shown relatively few IH events over the first week of life, a progressive increase in events until approximately 5 weeks post natal age followed by a decline thereafter[5]. In contrast, a sustained increase in the incidence of IH events was shown to be associated with severe retinopathy of prematurity (ROP)[5].

The multi-center SUPPORT trial examined the role of high versus low O_2 saturation target ranges on retinopathy of prematurity. Following randomization to lower (85-89%) or higher (91-95%) oxygen saturation target ranges, infants in the lower target group were found to have a lower incidence of severe ROP. This was associated with an unexpected higher mortality in infants targeted to low baseline oxygen saturation[6,7]. However, the effect of these oxygenation target ranges on the occurrence of intermittent hypoxemia (IH) is unknown. Therefore, the purpose of this study was to test the hypothesis that infants randomized to a low compared to

high O_2 saturation target range would have an increase in the incidence of intermittent hypoxemia.

Methods:

The study population included a subcohort of 115 preterm infants enrolled in the multi-center SUPPORT study from two sites: Rainbow Babies & Children's Hospital, Cleveland, and University of California San Diego. The study was approved by the Institutional Review Board at each site and by RTI Internatinal, which is the independent data coordinating center for the Neonatal Research Network. Written informed consent was obtained from the parent or guardian of each child before delivery.

Enrollment criteria included infants who were born between 24 weeks 0 days and 27 weeks 6 days of gestation for whom a decision had been made to provide full resuscitation. Infants born in other hospitals and those known to have major anomalies were excluded. Using a permuted-block randomization design, with stratification according to study center and gestational age (24 weeks 0 days to 25 weeks 6 days or 26 weeks 0 days to 27 weeks 6 days), infants were randomized to a low (85-89%) or high (91-95%) oxygen saturation target group within two hours of birth. Infants who were part of multiple births were randomly assigned to the same group.

Electronically altered pulse oximeters (Radical SET, Masimo, Irvine, CA) were used to blind the staff to the randomization group. The clinical staff was instructed to maintain infants in an oxygen saturation range of 88-92%, with altered monitors showing target levels of 88-92% with a maximum offset of 3%. For example a displayed value of 90% corresponded to an actual

oxygen saturation value of 87% in the low target group and 93% in the high target group[6]. Actual values were displayed when the oxygen saturation values were <85% or ≥95% in both treatment groups.

Targeting of oxygen saturation and high resolution (2 sec sample rate and 2 sec time averaging) data collection began within 2 hours after birth and continued until 36 wks PMA or until the infant was breathing air without respiratory support, defined as high frequency ventilation, conventional mechanical ventilation, Nasal SIMV, CPAP, nasal cannula, or hood, for ≥ 72 hours, whichever came first. Infants weaned to room air but re-administered supplemental oxygen were returned to the original randomization group. As previous studies have suggested that the timing and pattern of IH events may play a role in morbidity[4], the number of IH (≤80% for ≥10sec and ≤3min), the duration of IH events and the time interval between events (Figure 1) were calculated for each day.

Demographic and clinical variables were compared between high and low SaO_2 target groups using GEE regression models, adjusting for SUPPORT study stratification variables site and gestational age group, where appropriate. Due to sparse data a Fisher's exact test was used to evaluate death prior to 36 weeks. To model counts of intermittent hypoxemia events a GEE regression model assuming a negative binomial distribution was used. The GEE model provided robust standard error estimates which take into account the correlations within multiple-birth clusters, including correlations between repeated measurements. Variables included in the final model for intermittent hypoxemia events were treatment group, linear and quadratic terms for postnatal age, interactions between treatment group and postnatal age variables,

gestational age group, and respiratory support (yes or no, per day). Gestational age (GA) group was included to adjust for the fact that randomization was stratified by GA (24-25 weeks and 26-27 weeks). An additional quadratic term which allowed the quadratic relationship of postnatal age and IH events to vary before and after 28 days was also included; this spline regression approach provided a better fit than simpler models[8]. Also considered were interactions between GA group and postnatal age, between GA group and treatment group, and between the additional quadratic term and treatment group, as well as variables for gender, race, center, CPAP versus surfactant treatment group (an additional randomization of the main SUPPORT trial protocol), and caffeine use. Each of these additional terms considered were not significant and thus were not included in the final model. Similar models for the <1 minute and 1 to 20 minute time interval between event subsets of intermittent hypoxemia events were run with the same final set of variables as the overall model. Additional models were run to model duration and severity of intermittent hypoxemia events. These models included variables for treatment group, linear and quadratic terms for age, gestational age group, and center.

Results:

The population of 115 infants had a mean birth weight of 830±181gm and gestational age of 25.8 ±1.0wks. There were 50 infants in the gestational age range of 24 to 25 weeks 6 days and 65 infants in the gestational age range of 26 to 27 weeks 6 days range. Fifty one percent of the infants were male and 35% were non-Hispanic white. Characteristics of infants randomized to the high (n=62) and low (n=53) target group are presented in Table 1. There were no

differences between groups in birth weight, gestational age, incidence of bronchopulmonary dysplasia or severe retinopathy of prematurity (ROP). In this small cohort, there was a trend towards a higher mortality in the low target group (p=.09), mirroring the finding in the main trial, but this did not reach statistical significance. Caffeine use occurred on approximately 80% of days during the monitoring period in both infant groups.

The model based estimates showed an increase in IH events over the first 3 weeks of life in both infant groups followed by a decrease in IH events in the high target group compared to a plateau in the low target group (Figure 2a). The adjusted relative rate of IH events (RR), (the ratio of the adjusted mean number of IH events in the low target group/ the adjusted mean number of IH events in the high target group, per day), revealed a significantly higher rate of IH events prior to 12 days, and beyond 57 days of age in the low target group ($p<0.05$, Figure 2b). Higher rates of IH events were associated with lower gestational age, adjusted RR 1.24 (95% CI 1.01-1.5, p=.032), and respiratory support, adjusted RR 1.85 (95% CI 1.52-2.49, p<.0001). Infants in the low target group received respiratory support for 86% of the monitoring period infants compared with 92% in the high target group (adjusted RR low versus high target, .93 (95% CI 0.86-0.99, p=.029).

The mean duration of IH events shortened (p<.01) and the severity worsened (p<.01) with increasing day of life (Figure 3). However, there were no differences in duration or severity between infant groups.

There was a wide range in the time interval between sequential IH events both within and between infants. To address the association between the timing of IH events and the oxygen

saturation target group, the number of IH events was documented for three time interval ranges 1) <1 minute, 2) 1-20 minutes and, 3) >20 minutes between IH events. The highest incidence of events occurred with a time interval between events of <1 min, followed by a time interval of 1-20 minutes between events. There were relatively few IH events that occurred with a time interval of >20 minutes between events (Figure 4). IH events occurring with a time interval between events of <1 minute were associated with a significantly higher relative rate of IH events in the low target group at <15 and >54 days of life ($p<0.05$). After 65 days of life, there were a significantly higher number of IH with a time interval of 1-20 minutes between events in the low target group ($p<.05$) with no differences between groups with a time interval of >20 minutes between events.

The above analysis examined the characteristics of IH events with increasing postnatal age. In addition, the effect of post menstrual age on the occurrence of IH events was also assessed. While the number of IH events decreased with postmenstrual age, the number of IH events was not significantly different by treatment group, at any post menstrual age.

Discussion:

This study showed an association between a low oxygen saturation target range and an escalation in the incidence of IH events that changed with increasing day of life. Infants in the low target range had a higher number of IH events during the first two weeks and after 57 days of life but followed a similar trajectory as the high saturation target group between these time periods. IH events became shorter and more severe with increasing post natal age, however, there were no differences in duration or severity between infant groups. Lastly, the higher

incidence of IH events in the low target group was predominantly associated with a time interval between IH events of <1minute in duration.

Intermittent hypoxemic events are ubiquitous in preterm infants, both ventilated[9,10] and spontaneously breathing[11]. Nonetheless, the precise incidence of these events has not been well documented. This is important in order to address their potential pathophysiological consequences. This study showed a higher incidence of IH in the low target group which is consistent with McEvoy et al[12] showing a relationship between oxygen levels and IH in former preterm infants with chronic lung disease. Although these events are thought to be a consequence of immature respiratory control, this study and previous data in a similar infant cohort[5] suggest that other developmental phases may be contributing. There were relatively few IH events during the 1st week of life regardless of the level of oxygen exposure. This early phase was followed by a linear increase in IH events through weeks two to three of life that was not affected by the oxygen saturation target range. The third phase of IH events began after four weeks of age with a plateau in IH events. After this time group differences emerge with a decline in events in the high target group while remaining relatively constant in the low target group. This may be due to a low baseline alveolar PO2 in the low target group which, in a model based analysis, has been shown to cause early onset of desaturation[13]. It remains unclear why this low reserve did not consistently result in a higher number of IH events at earlier post natal ages.

Caffeine use and respiratory support are the main clinical therapies for apnea and accompanying desaturation. Although caffeine has been shown to decrease apnea[14],

interestingly, it has been shown to have little if any effect on desaturation episodes[15] although this is based on a single small series. Both infant groups spent a high percentage of the monitoring period on caffeine therapy with no significant difference in caffeine usage between infant groups, therefore, it is unlikely that caffeine use affected the results of this study. Respiratory support was associated with a higher incidence of IH events within each treatment group. However, with the high target group having a higher percentage of time receiving respiratory support, this cannot explain the increased incidence of IH in the low target infants.

Both groups showed a comparable decrease in duration and increase in severity of IH events during the first four weeks of life with no further changes throughout the study monitoring period. Previous data have suggested that infants with increased spontaneous apnea have an augmented ventilatory response to acute hypoxia[16]. Thus, although infants in the low target group may have been more susceptible to initiation of a hypoxic event, they may have been able to rally a compensatory ventilatory response and recover as well as infants in the high target group.

The lower incidence of severe ROP in the main trial is in contrast to our previous findings of an association between IH and severe ROP[5]. This discrepancy may relate to the fact that the initial hyperoxia induced inhibition of angiogenesis is enhanced in the high oxygen target group at a time when IH episodes are not prominent. Time interval between IH events may also play a role. Previous data in animal models have suggested that the timing of patterns of IH events are important and may affect morbidity. Clustered patterns of IH events have been shown to be associated with enhanced retinal neovascularization when compared to equally dispersed

patterns[4]. This may be a result mediated by a hypoxia induced factor (HIF)[17] or reactive oxygen species (ROS) cascade known to occur in response to IH[18]. In response to hypoxic exposure, measurements of reactive oxygen species have shown an increase in superoxide anion concentration during the recovery phase, with a delayed response of several minutes[19]. Current preterm infant data from our group suggest that ROP is associated with a time interval between events of 1-20 min potentially consistent with the ability to initiate an increase in reactive oxygen species (ROS) (submitted, in press). In contrast, the higher number of IH events in the low target group predominantly occurred with a time interval between events of less than 1 minute which may have limited the ROS response. However, the effect of the duration of recovery time on the resultant oxidative stress response has yet to be determined and merits further investigation.

There are limited data on the long term consequences of IH events in preterm infants[20]. A history of apnea of prematurity during hospitalization[21] and cardiorespiratory events in the home[22] have been associated with neurodevelopmental impairment. These studies have focused on apnea rather than the accompanying hypoxemic events. The only study to address the latter issue is the observation that mean oxygen saturation during apnea has been shown to predict motor scores[23]. Further analysis is ongoing to assess the relationship between IH events and neurodevelopmental outcome in this infant cohort.

This study was limited by the known challenge of keeping infants in a designated oxygen saturation target range[24,25]. The main SUPPORT trial revealed overlap in the median level of oxygen saturation between target groups with actual median oxygen saturation levels slightly

higher than targeted levels in both treatment groups[6]. This may have affected the number of IH events as lowering the median baseline saturation and increasing the time in the actual low target level may have resulted in an even higher incidence of IH events. In addition, the data used in this analysis were collected via pulse oximeters which remained in use from birth up to 36 weeks postmenstrual age (PMA), but only during times when the infants were receiving respiratory support and during the three days after respiratory support was discontinued. Thus, data do not exist for time points four or more days after discontinuation of respiratory support, transfer to a non-study hospital, discharge, or 36 weeks PMA (whichever came first). The GEE models used in this analysis assume that any missing data are missing completely at random. This assumption may be violated by these data, because infants who dropped out of the data due to a poor outcome such as death, or a favorable outcome such as discharge or being able to breathe room air without support, are likely to differ from those who remained on respiratory support through 36 weeks PMA. Thus, this should be considered a conditional analysis; that is, it is conditioned upon being alive and on respiratory support, and the results provided by the GEE model for any given point in time should be interpreted as applying only to the subset of infants who were alive and on respiratory support at that time.

In conclusion, a low oxygen saturation target range is associated with an increased incidence of intermittent hypoxemic events that is dependent on postnatal age. These events tend to occur less than one minute apart but are of comparable duration and severity regardless of level of oxygen exposure. Two clinical trials have now demonstrated an association between low oxygen targets and increased mortality. While the etiology of such a mortality increase is unknown at this time, we speculate that the association between a low oxygen saturation

target and increasing incidence of IH might provide insight to unraveling underlying pathophysiology. Further studies are needed to assess the contribution of timing of IH events and morbidity. We speculate that, to minimize episodes of IH, the optimal O_2 saturation target may need to be adjusted by postnatal age.

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Figure Legends:

Figure 1

A raw SaO2 waveform with the duration of the event and the time interval between events denoted by the arrows.

Figure 2

A) The model based estimates showed an increase in IH events over the first 3 weeks of life in both infant groups followed by a decrease in IH events in the high target group ( )compared to a plateau in the low target group ( ) . B) The relative rate of IH events (RR), (the ratio of the adjusted mean number of IH events in the low target group/ the adjusted mean number of IH events in the high target group, per day), revealed a higher rate of IH events from <12 days, and >57 days of age in the low target group (* $p<0.05$).

Figure 3

IH event duration decreased and severity worsened with increasing postnatal age in both the low and high target groups with no differences between groups.

Figure 4

A) The number of IH events was documented for three time interval ranges; <1 minute, 1-20 minutes and, >20 minutes between IH events. The highest incidence of events occurred with a time interval between events of <1 min, followed by a time interval of 1-20 minutes. There were relatively few IH events that occurred with a time interval of >20 minutes between

events. B) IH events occurring with a time interval between events of <1 minute were associated with a significantly higher relative rate of IH events in the low target group at <15 and >54 days of life ($p<0.05$). IH events occurring with a time interval of 1-20 minutes between event had a higher relative rate of IH events >65 days of life ($p<0.05$). IH events occurring >20 min apart were comparable between target groups with a relative rate of approximately one throughout the monitoring period.

	Low Target (53)	High Target (62)	p value*
Birth Weight (gm), mean(SD)	855(191)	808(171)	0.47
Gestational Age (wk), mean(SD)	25.8(1.1)	25.8(1.0)	0.76
BPD (O_2 @ 36 wk), n/N(%)	14/15(28%)	24/62(39%)	0.45
Death before 36 wk PMA, n(%)	3 (6%)	0 (0%)	0.09
Severe ROP, n/N(%)	8/49(16%)	13/58(22%)	0.41
Caffeine, n/N(%) of monitored days	2245/2838 (79%)	2757/3417 (81%)	0.87
Respiratory Support[‡], n/N(%) of monitored days	2451/2849 (86%)	3085/3369 (92%)	0.03

*results adjust for stratification factors (study center and gestational age group) and familial clustering except for gestational age (adjusted for study center and familial clustering) and death (Fisher's exact test).

[‡]High frequency jet ventilation, CPAP, conventional ventilation, nasal cannula, Nasal SIMV, or hood

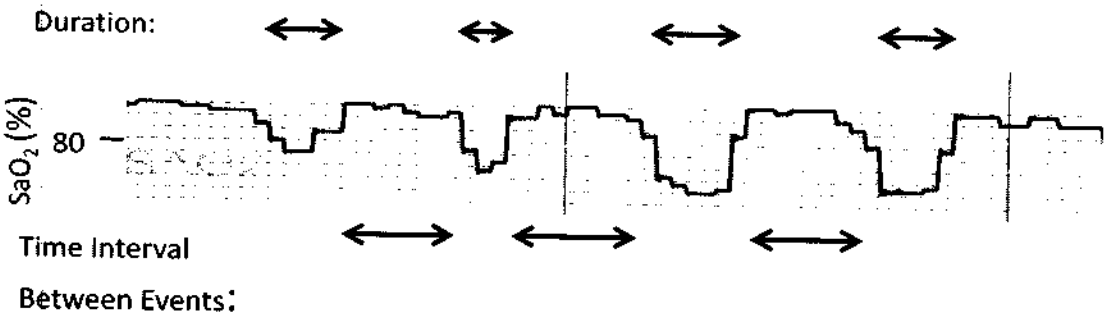
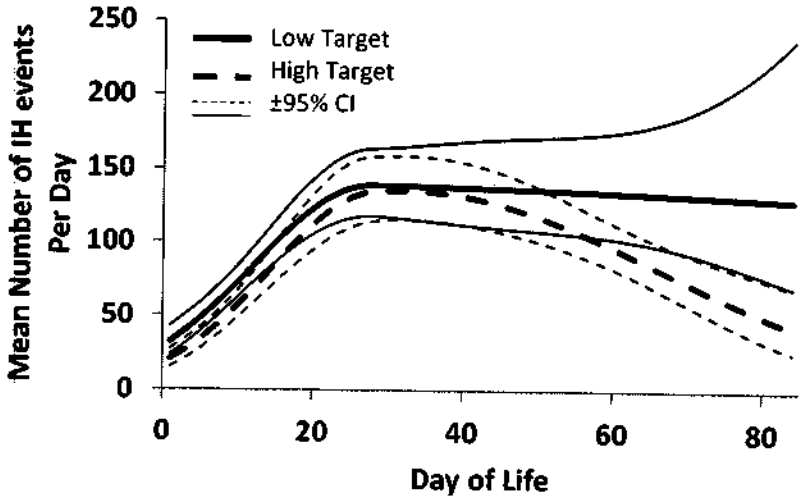


Fig 1

A



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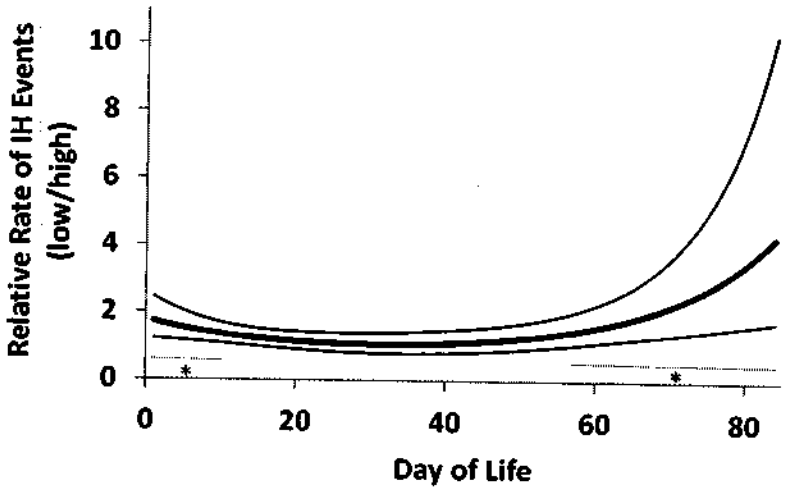
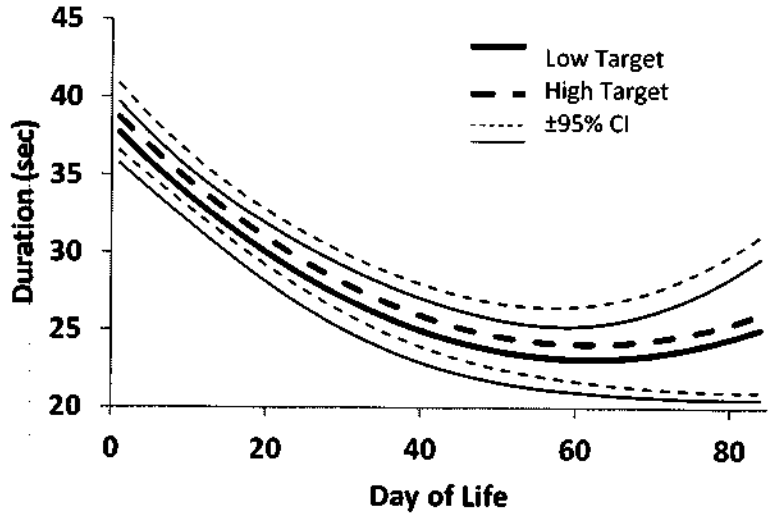


Fig 2

A



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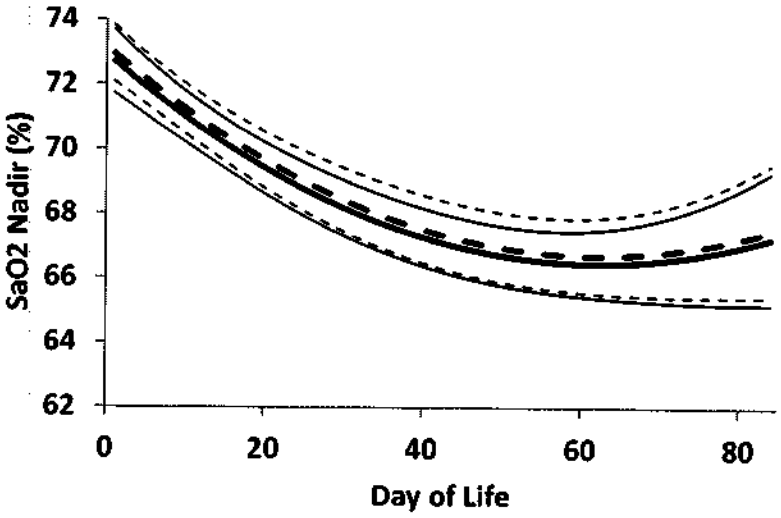

Fig 3

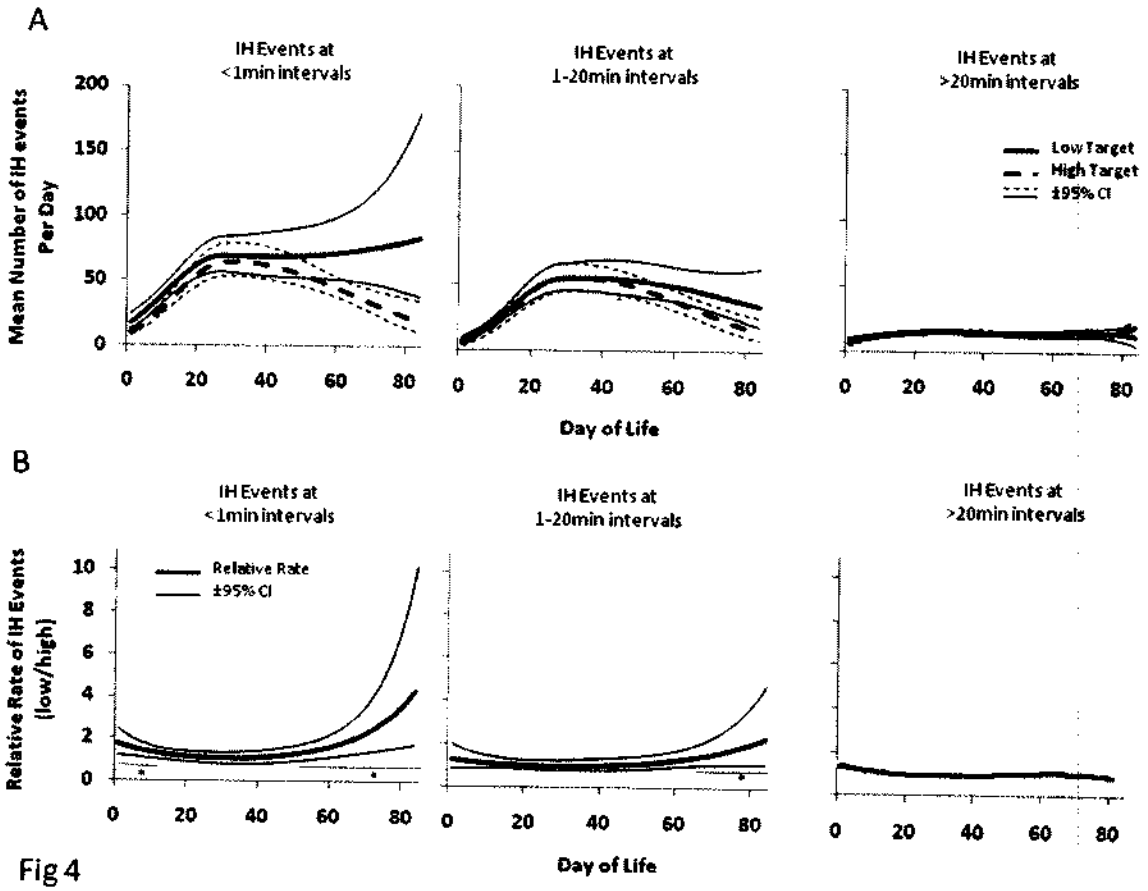

Fig 4

From: Barbara Stoll
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT TRACKING
Date: Wednesday, September 14, 2011 11:02:21 PM

THANK you Rose

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From: Poundstone, Margaret
To: Higgins, Rosemary (NIH/NICHD) [E]; Kennedy, Kathleen A; Evans, Patricia W; Mcdavid, Georgia E
Cc: "Auman, Jeanette O."
Subject: RE: SUPPORT TRACKING
Date: Wednesday, September 14, 2011 5:01:17 PM

(b)(6) is the same patient. I honestly can't remember if I told her about school age FU . I just called grandma and left a message for her to call me back. They live in (b)(6) which is about a (b)(6) (b)(6) drive.

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, September 14, 2011 3:58 PM
To: Poundstone, Margaret; Kennedy, Kathleen A; Evans, Patricia W; Mcdavid, Georgia E
Cc: 'Auman, Jeanette O.'
Subject: RE: SUPPORT TRACKING

Were the patients (b)(6) told they could have their school age FU in (b)(6) Do they live close – these patients have also gone in a query to (b)(6) but I haven't heard back from them.

Jenny – can you check to see why the other child isn't showing up I the DMS>

Thanks
Rose

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From: Poundstone, Margaret [mailto:Margaret.Poundstone@uth.tmc.edu]
Sent: Wednesday, September 14, 2011 4:56 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Kennedy, Kathleen A; Evans, Patricia W; Mcdavid, Georgia E
Cc: 'Auman, Jeanette O.'
Subject: RE: SUPPORT TRACKING

Rose,

(b)(6) was entered at the end of (b)(6) so they will show up completed for next month's report.

As for (b)(6) am I supposed to be tracking him? He was originally (b)(6) we just saw him for his 18 month visit.

Layne

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, September 14, 2011 2:42 PM
To: Kennedy, Kathleen A; Poundstone, Margaret; Evans, Patricia W; Mcdavid, Georgia E
Cc: 'Auman, Jeanette O.'
Subject: SUPPORT TRACKING

Hi,
We are missing tracking outcome form(s) for SUPPORT NEUROIMAGING tracking. Please let us know how you are doing.

Thanks for all the effort!!
Rose

CENTER	NETWORK	FOLNUM	3YRDT	4YRDT	Follow-up CENTER	NICU CENTER
(b)(6)						

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Wally Carlo, M.D."; "Das, Abhik"; "Navarrete, Cristina"; "Duara, Shahnaz"
Cc: "Finer, Neil"; "Wrage, Lisa Ann"; "Gantz, Marie"
Subject: RE: 7.11 growth secondary discussion
Date: Wednesday, September 14, 2011 4:06:00 PM

I agree with Wally's suggestions
Rose

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From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Wednesday, September 14, 2011 2:42 PM
To: Das, Abhik; Navarrete, Cristina; Duara, Shahnaz
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; Wrage, Lisa Ann; Gantz, Marie
Subject: RE: 7.11 growth secondary discussion

Hi All:

I understand arguments by both Brenda and Richard. I suspect that about 25% are going to be SGA so we may have enough power. I suggest to do the primary analysis for all babies together and secondary analyses by SGA/AGA status.

I agree to use Olsen's charts.

We have not corrected for multiple comparisons. I would prefer not to do a correction but should be cognizant of this if multiple comparisons are done.

Wally

From: Das, Abhik [mailto:adas@rti.org]
Sent: Wed 9/14/2011 1:24 PM
To: Navarrete, Cristina; Duara, Shahnaz
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; Wrage, Lisa Ann; Wally Carlo, M.D.; Gantz, Marie
Subject: RE: 7.11 growth secondary discussion

Hello All:

Sorry for the delay in getting back to this. Based on all these comments, we need to have some decisions finalized before Lisa can get on with this analysis in time for PAS. For example Richard suggested doing the tables for subsets of SGA and AGA, and Brenda seemed to suggest NOT doing that. Also, it looks like the Olsen growth charts were the #1 choice for in-hospital growth outcomes (WHO for follow-up) – we need to verify that this is the final decision before we start analyses. Also there was a comment about correction of p-values for multiple comparisons. Note that we typically don't do that for most NRN analyses and haven't done that for any SUPPORT analyses thus far.

Please let Lisa and me know how you want to proceed.

Thanks

Abhik

From: Poindexter, Brenda B [mailto:bpoindex@iupui.edu]
Sent: Tuesday, August 02, 2011 2:17 PM
To: 'Richard Ehrenkranz'; Wally Carlo, M.D.
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; kurt.schibler@cchmc.org; alaptook@WIHRI.org; yvaucher@ucsd.edu; Myriam Peralta, M.D.; mcw3@cwru.edu; Roger Faix; Bradley Yoder; nancy newman; Rich, Wade; Das, Abhik; Wallace, Dennis; Archer, Stephanie (NIH/NICHD) [E]; sduara@miami.edu; Navarrete, Cristina
Subject: RE: 7.11 growth secondary discussion

Shahnaz and Cristina,
Thanks for including me on this. I've taken a look at this and have a few comments to add to the others.

1) A few thoughts about the inclusion of death as an outcome – since we have growth outcomes at multiple time points I think that including death or growth parameter (Wt, Length, or HC) less than 10^{th} percentile at each time point would be appropriate – so if a baby dies at 30 days of age, you still have a growth outcome at the day 7, 14, 21, and 28 d timepoints but then have death at 32 and 36 weeks PMA. In the lower saturation arm, there was a fairly wide range of when death occurred, correct? I would think you can only look at overall growth velocity in survivors – knowing that we had higher mortality in lower sat group is an issue I'd like to hear more discussion about from Abhik and Dennis.
2) I probably would not do a separate analysis of the infants SGA at birth – I don't think you will have enough of these babies/power to make meaningful conclusions of SGA vs AGA and oxygen saturation groups. Yes, most SGA babies at birth are also SGA at 36 weeks, but hopefully the % SGA at birth are equally randomized into the two saturation arms. For the primary analysis, I'm not sure why you would subdivide into the two gestational age cohorts (24-25 and 26-27); I understand that the lower GA group is at higher risk for growth failure, but again, I don't think we have adequate numbers to address these subgroups separately.
3) In-hospital growth – I agree with Richard that Irene Olsen's growth curves would be a very appropriate reference to use – Fenton would be my second choice
4) 18 month – agree with Richard that 2006 WHO curves should be used
5) Calorie calculations – remember we only have one-day "snapshots" of intake – especially in first few weeks of life this may or may not be a moving target. I would recommend John Langer to take a look at calculating the protein vs total calories of intake – the glutamine

intake forms were very similar to the growth secondary nutritional intake form – it will be labor intensive, but could be very valuable in looking at overall impact of protein intake on growth.

Let me know when the next call to discuss will be. Hope these comments are helpful.

Best,

Brenda

From: Richard Ehrenkranz [mailto:richard.ehrenkranz@yale.edu]
Sent: Tuesday, July 19, 2011 12:03 PM
To: Wally Carlo, M.D.
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; kurt.schibler@cchmc.org; alaptook@WIHRI.org; yvaucher@ucsd.edu; Myriam Peralta, M.D.; mcw3@cwru.edu; Roger Faix; Bradley Yoder; nancy newman; Rich, Wade; Das, Abhik; Wallace, Dennis; Poindexter, Brenda B; Archer, Stephanie (NIH/NICHD) [E]; sduara@miami.edu; Navarrete, Cristina
Subject: Re: 7.11 growth secondary discussion

Hi:

1. I share Wally's concern's expressed in point #1 below. However, we will probably also want to perform the analysis for survivors (whole cohort, AGA, SGA) to 36 wks PMA.

2. With respect to the choice of growth curves:

a. Consider Olsen (Pediatrics 2010; 125:e214-224) for the in-hospital growth. In contrast to Fenton's paper, Olsen's paper is based upon a Pediatrix administrative dataset and presents weight, length, and HC data (percentiles and mean ± SD) by gender on the same patients. Plus the infants were born in 33 US states from 1998-2006). I have attached a pdf of the paper.

b. The WHO 2006 curves are recommended over the CDC 2000 curves. However, it might decrease the number (%) of infants who are < 10th%tile at 18-22 mos corrected age.

3. What was meant by the statement to "include analysis by birth weight strata as in major trial"? In SUPPORT, data were reported by GA strata.

4. I agree with the need to perform analyses by AGA and SGA.

5. Page 8: How will growth velocity be calculated? I suggest the exponential method described by Patel (Pediatrics 2005; 116:1466-1473); a pdf of the paper is attached.

6. Page 8: With respect to calorie calculations: I prefer option #2-including protein calories.

Thanks for including me on this secondary study.
Richard

On 7/19/2011 3:27 AM, Wally Carlo, M.D. wrote:

I missed the call as I was on a cruise. Sorry. Here are some comments but first, congratulations to Cristina and others for putting all of this together.

1) I agree that death should be considered in the analysis. An issue is whether it should be part of the primary hypothesis which would require dichotomizing the growth outcomes (e.g. death or <10%ile weight). In view of the large difference in mortality in the saturation trial, this analytical approach may be

the best.

2) I think we need to prespecify the primary outcome better using a single measure rather than as "growth", using multiple measures (weight, length, HC).

3) Table 1 could have percent of infants with weight less than 10th percentile at birth as well as raw values for length and HC. Currently, percentile is used for HC and length versus raw data for BW. If SGA refers to 10th percentile, it may be best to be consistent with the rest of the table and use percentile.

4) Table 2 (clinical outcomes) should more closely follow the table from the original paper particularly including death as the first or second outcome measure. RDS may not be a good outcomes measure. It is difficult to rule out the diagnosis when prophylactic surfactant is given.

5) We need to be very careful with multiple comparisons. For example, just the Primary Outcomes table has 48 comparisons. In addition to specifying a single primary outcomes, we should prespecify a correction for multiple analyses.
Wally

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Mon 7/18/2011 3:56 PM
To: 'Finer, Neil'; 'kurt.schibler@cchmc.org'; 'alaptook@WIHRI.org'; Wally Carlo, M.D.; 'yvaucher@ucsd.edu'; Myriam Peralta, M.D.; 'mcw3@cwru.edu'; 'Roger Faix'; 'Bradley Yoder'; 'nancy newman'; 'Rich, Wade'; Das, Abhik; Wallace, Dennis; bpoindex@iupui.edu; Richard A. Ehrenkranz
Cc: Archer, Stephanie (NIH/NICHD) [E]; 'sduara@miami.edu'; 'Navarrete, Cristina'
Subject: FW: 7.11 growth secondary discussion

Hi
Here is the information for the growth secondary study to SUPPORT. Please send your comments by email by July 29,

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

-----Original Message-----
From: Navarrete, Cristina [mailto:CNavarrete@med.miami.edu]
Sent: Thursday, July 14, 2011 3:50 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Duara, Shahnaz
Subject: 7.11 growth secondary discussion

Hello Dr. Higgins,

Attached is the revised document that reflects the discussion on 7/11, plus the reference growth chart articles. Please forward it to the subcommittee members, including Drs. Ehrenkranz and Poindexter, for concensus. Also, please let us know if there are any objections, so that we can ammend it if needed.
Thank you,
Cristina

--
Richard A. Ehrenkranz, MD
Department of Pediatrics
Yale University School of Medicine
333 Cedar Street
PO Box 208064
New Haven, CT 06520-8064
tele: 203-688-2320
fax: 203-688-5426

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Kristi Watterberg"; "Robin Ohls (rohls@salud.unm.edu)"; "Andrea Duncan"; "Conra Lacy"
Cc: "Auman, Jeanette O."
Subject: SUPPORT TRACKING
Date: Wednesday, September 14, 2011 3:59:00 PM

Congratulations – you have no missing SUPPORT 3-4 year tracking forms currently. Thanks for all the hard work and effort!! It is much appreciated!!!
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
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Bethesda, MD 20892
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301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Vaucher, Yvonne"; "Das, Abhik"; "Wally Carlo, M.D."; "Myriam Peralta, M.D."; "Finer, Neil"; "Gantz, Marie"
Subject: RE: SUPPORT paper draft: CPAP vs Surf
Date: Wednesday, September 14, 2011 10:44:00 AM

Yvonne
I looked this over. I think we should delete the Bayley III motor information – this was not part of the originally planned study. NEJM will ask for the protocol and this will likely raise questions. Also, The methods should be nearly identical for the two papers with respect to the description of the study as well as the outcome measures of death/NDI components. I think this is well on its way and look forward to talking on Friday

Thanks for all the effort

Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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For overnight delivery use Rockville, MD 20852
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301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]
Sent: Sunday, September 11, 2011 1:22 PM
To: Das, Abhik; Wally Carlo, M.D.; Myriam Peralta, M.D.; Finer, Neil; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Vaucher, Yvonne
Subject: RE: SUPPORT paper draft: CPAP vs Surf

All,

Thanks for all your excellent suggestions, revisions, editing! Here is next draft. I incorporated most of the comments from Wally and Abhik and left the comments that are still in discussion/have questions.

Yvonne

From: Das, Abhik [mailto:adas@rti.org]
Sent: Saturday, September 10, 2011 12:31 PM
To: Wally Carlo, M.D.; Vaucher, Yvonne; Myriam Peralta, M.D.; Finer, Neil; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT paper draft: CPAP vs Surf

My comments are attached. I think we need as much consistency as possible between the two follow up papers.

Thanks

Abhik

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Tuesday, September 06, 2011 7:14 PM
To: Vaucher, Yvonne; Myriam Peralta, M.D.; Finer, Neil; Gantz, Marie; Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT paper draft: CPAP vs Surf

Forgot to copy Rose.

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
1700 6th Avenue South
176F Suite 9380R
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 (b)(6)

From: Wally Carlo, M.D.
Sent: Tuesday, September 06, 2011 6:13 PM
To: 'Vaucher, Yvonne'; Myriam Peralta, M.D.; Finer, Neil; Gantz, Marie; Das, Abhik
Subject: RE: SUPPORT paper draft: CPAP vs Surf

Hi Yvonne, Neil, Myriam, Marie, Abhik and Rose:

Yvonne: Great job on the draft. I really liked the format of Table 1 as suggested by Abhik.

All: I am enclosing comments and tracked suggestions. I think we need to be careful with exploratory analyses and other subgroup analyses. We may want to keep separate the prespecified analyses as the original tables were drafted and add to that selected exploratory analyses.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries

1700 6th Avenue South
176F Suite 9380R
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 (b)(6)

From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]
Sent: Tuesday, September 06, 2011 3:40 PM
To: Wally Carlo, M.D.; Myriam Peralta, M.D.; Finer, Neil; Gantz, Marie; Das, Abhik
Subject: FW: SUPPORT paper draft: CPAP vs Surf

All,

Here is the most recent draft of Early CPAP vs. Surfactant. There are significant differences between the GA strata which I included since the results for the entire cohort were sometimes misleading, particularly when the results were in opposite directions for the GA strata. The 24 0/7-25 6/7 wk gestation are quite different from the 26 0/7 to 27 6/7 wk gestation group. I still need some data. I would appreciate your comments, ideas, etc. Thanks.

Yvonne

Yvonne E. Vaucher, M.D., M.P.H.
Division of Neonatal/Perinatal Medicine
Clinical Professor of Pediatrics
UCSD School of Medicine

tele: 619-543-3759
FAX: 619-543-3812

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Gabrio, Jenna"
Subject: RE: SUPPORT paper draft: CPAP vs Surf -- Availability
Date: Wednesday, September 14, 2011 10:00:00 AM

Fabulous and THANK YOU for your patience.
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
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Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Gabrio, Jenna [mailto:jgabrio@rti.org]
Sent: Wednesday, September 14, 2011 10:00 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT paper draft: CPAP vs Surf -- Availability

OK, that should still work for everyone---we can go 1:00 – 2:00 PM ET. I'll send the message out now.

Thanks,
Jenna

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, September 14, 2011 9:53 AM
To: Gabrio, Jenna
Subject: RE: SUPPORT paper draft: CPAP vs Surf -- Availability

Jenna
Can we change this to 1 PM (even for 30 minutes), I just had a meeting scheduled from 12-1 at NICHD that I must attend.

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
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Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Gabrio, Jenna [mailto:jgabrio@rti.org]
Sent: Wednesday, September 14, 2011 9:34 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Wally Carlo, M.D.; Vaucher, Yvonne; Myriam Peralta, M.D.; Finer, Neil; Gantz, Marie
Cc: Starlett Williams; fmartinez@ucsd.edu; Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: SUPPORT paper draft: CPAP vs Surf -- Availability

Dear all,

The call to discuss the SUPPORT paper draft – CPAP vs. Surf has been scheduled for:

Friday, 9/16
12:30pm ET

Dial:
Within the USA
(b)(6)

or

Outside the USA
(b)(6)

Then, enter Participant Passcode:
(b)(6)

Thanks,
Jenna

From: Gabrio, Jenna
Sent: Tuesday, September 13, 2011 11:05 AM
To: 'Higgins, Rosemary (NIH/NICHD) [E]'; Das, Abhik; Wally Carlo, M.D.; Vaucher, Yvonne; Myriam Peralta, M.D.; Finer, Neil; Gantz, Marie
Cc: 'Starlett Williams'; 'fmartinez@ucsd.edu'; 'Archer, Stephanie (NIH/NICHD) [E]'
Subject: RE: SUPPORT paper draft: CPAP vs Surf -- Availability

Dear all,

Please let me know if there is any way you would be able to join the call if it were held at any of the following times:

9/14, W, 10:30 AM – 11:30 AM ET

9/15, Th, 12:30 PM – 2:00 PM ET
9/16, F, 10:30 AM – 11:30 AM ET
9/16, F, 12:30 PM – 2:00 PM ET

Thanks,
Jenna

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, September 12, 2011 9:57 AM
To: Das, Abhik; Wally Carlo, M.D.; Vaucher, Yvonne; Myriam Peralta, M.D.; Finer, Neil; Gantz, Marie
Cc: Gabrio, Jenna
Subject: RE: SUPPORT paper draft: CPAP vs Surf

OK – can we try to set the call up for later this week??
thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Das, Abhik [mailto:adas@rti.org]
Sent: Monday, September 12, 2011 9:39 AM
To: Wally Carlo, M.D.; Vaucher, Yvonne; Myriam Peralta, M.D.; Finer, Neil; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT paper draft: CPAP vs Surf

With all the color coding of the comments and suggested changes over time, the draft is perhaps getting a little harder to read! I suggest that after Marie has had a chance to weigh in, perhaps we can all get on the phone to hash out any remaining issues?

Thanks

Abhik

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Sunday, September 11, 2011 7:33 PM
To: Vaucher, Yvonne; Das, Abhik; Myriam Peralta, M.D.; Finer, Neil; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT paper draft: CPAP vs Surf

Great job, Yvonne.

I have added more comments.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
1700 6th Avenue South
176F Suite 9380R
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 (b)(6)

From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]
Sent: Sunday, September 11, 2011 12:22 PM
To: Das, Abhik; Wally Carlo, M.D.; Myriam Peralta, M.D.; Finer, Neil; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Vaucher, Yvonne
Subject: RE: SUPPORT paper draft: CPAP vs Surf

All,

Thanks for all your excellent suggestions, revisions, editing! Here is next draft. I incorporated most of the comments from Wally and Abhik and left the comments that are still in discussion/have questions.

Yvonne

From: Das, Abhik [mailto:adas@rti.org]
Sent: Saturday, September 10, 2011 12:31 PM
To: Wally Carlo, M.D.; Vaucher, Yvonne; Myriam Peralta, M.D.; Finer, Neil; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT paper draft: CPAP vs Surf

My comments are attached. I think we need as much consistency as possible between the two follow up papers.

Thanks

Abhik

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Tuesday, September 06, 2011 7:14 PM
To: Vaucher, Yvonne; Myriam Peralta, M.D.; Finer, Neil; Gantz, Marie; Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT paper draft: CPAP vs Surf

Forgot to copy Rose.

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
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Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 (b)(6)

From: Wally Carlo, M.D.
Sent: Tuesday, September 06, 2011 6:13 PM
To: 'Vaucher, Yvonne'; Myriam Peralta, M.D.; Finer, Neil; Gantz, Marie; Das, Abhik
Subject: RE: SUPPORT paper draft: CPAP vs Surf

Hi Yvonne, Neil, Myriam, Marie, Abhik and Rose:

Yvonne: Great job on the draft. I really liked the format of Table 1 as suggested by Abhik.

All: I am enclosing comments and tracked suggestions. I think we need to be careful with exploratory analyses and other subgroup analyses. We may want to keep separate the prespecified analyses as the original tables were drafted and add to that selected exploratory analyses.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
1700 6th Avenue South
176F Suite 9380R
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 (b)(6)

From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]
Sent: Tuesday, September 06, 2011 3:40 PM
To: Wally Carlo, M.D.; Myriam Peralta, M.D.; Finer, Neil; Gantz, Marie; Das, Abhik

Subject: FW: SUPPORT paper draft: CPAP vs Surf

All,

Here is the most recent draft of Early CPAP vs. Surfactant. There are significant differences between the GA strata which I included since the results for the entire cohort were sometimes misleading, particularly when the results were in opposite directions for the GA strata. The 24 0/7-25 6/7 wk gestation are quite different from the 26 0/7 to 27 6/7 wk gestation group. I still need some data. I would appreciate your comments, ideas, etc. Thanks.

Yvonne

Yvonne E. Vaucher, M.D., M.P.H.
Division of Neonatal/Perinatal Medicine
Clinical Professor of Pediatrics
UCSD School of Medicine

tele: 619-543-3759
FAX: 619-543-3812

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Gabrio, Jenna"
Subject: RE: SUPPORT OUTCOMES
Date: Wednesday, September 14, 2011 8:55:00 AM

Ok
Even if she can't make it, If Abhik can join, we need to have the call
Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network
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For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

-----Original Message-----
From: Gabrio, Jenna [mailto:jgabrio@rti.org]
Sent: Wednesday, September 14, 2011 8:55 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT OUTCOMES

She is available for the 10:30 AM slot on Friday, but Wally and Neil are not available at that time. I am checking with her to see if there is any way she can make the afternoon slot work and will let you know ASAP.

Thanks,
Jenna

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, September 14, 2011 8:51 AM
To: Gabrio, Jenna
Subject: RE: SUPPORT OUTCOMES

When is Marie available on Friday?

Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network
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301-435-7909
301-496-5575
301-496-3790 (FAX)

higginsr@mail.nih.gov

-----Original Message-----
From: Gabrio, Jenna [mailto:jgabrio@rti.org]
Sent: Wednesday, September 14, 2011 8:47 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT OUTCOMES

Hi Rose,

I was going to try and follow up with Yvonne since she said that she would be traveling these next few days. It looks like the majority can make Friday 9/16, 12:30 PM ET; however, Marie may be unable to join. Can we still have the call?

Thanks,
Jenna

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, September 14, 2011 8:42 AM
To: Gabrio, Jenna
Subject: FW: SUPPORT OUTCOMES

Jenna
Is this set up??
Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
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For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

-----Original Message-----
From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]
Sent: Wednesday, September 14, 2011 8:38 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: SUPPORT OUTCOMES

I will try to join if I can. Friday early would be best for me. Not available thursday. Thanks.
Y onne

Sent from my iPhone

On Sep 14, 2011, at 3:18 AM, "Higgins, Rosemary (NIH/NICHD) [E]"
<higginsr@mail.nih.gov<mailto:higginsr@mail.nih.gov>> wrote:

Ok
Jenna is setting up a call for the smaller group for this week
Rose

From: Finer, Neil <nfiner@ucsd.edu<mailto:nfiner@ucsd.edu>>
To: Gantz, Marie <mgantz@rti.org<mailto:mgantz@rti.org>>; Wally Carlo, M.D. <WCarlo@peds.uab.edu<mailto:WCarlo@peds.uab.edu>>
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Vaucher, Yvonne <yvaucher@ucsd.edu<mailto:yvaucher@ucsd.edu>>; Das, Abhik <adas@rti.org<mailto:adas@rti.org>>
Sent: Tue Sep 13 23:04:00 2011
Subject: RE: SUPPORT OUTCOMES

Thanks Marie
The effect of low SpO2 on Death/ROP is very striking. NDI and Death NDI is NS
We did not say much about this for the first paper – We will need to review carefully with the Subcommittee and decide how to proceed
These small babies are unique and this population unlikely to be replicated
We would have a hard time ignoring these results and analyses – especially in view of the results of the other trials and the increase death with Low SpO2 range
Rose - Lets discuss at the next Subcommittee
Neil

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Monday, September 12, 2011 1:48 PM
To: Finer, Neil; Wally Carlo, M.D.
Cc: higginsr@mail.nih.gov<mailto:higginsr@mail.nih.gov>; Vaucher, Yvonne; Das, Abhik
Subject: RE: SUPPORT OUTCOMES

Neil,

Attached is a Word document summarizing the results of the ROP/death and NDI/death analyses with interactions between GA, SpO2 target and CPAP/surfactant. As I have noted in the document, we need to be careful about drawing conclusions about which of the 4 treatment combinations is optimal for infants with GA 24-25 weeks. Although CPAP had a significant advantage over surfactant for ROP/death among infants randomized to the Low SpO2 target, much of that difference was due to ROP. If death is the more important outcome (because the long term consequences of ROP are not as severe) then, in the absence of a significant interaction between treatment arms for death, we cannot draw reliable conclusions about which of the 4 combinations is best. The only thing we can say with respect to mortality is that the death rate was lower for those randomized to CPAP vs. surfactant (as we said in the primary paper).

I am also attaching results of the subgroup analyses for ROP/death and NDI/death. Note that subgroup analyses are included even where the interactions were not significant enough to justify them (p values for interactions are noted in the page headers); thus, these results are for your information only, so you can be reassured that we are not missing anything important.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org<mailto:mgantz@rti.org>
828-254-6255
From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Friday, September 09, 2011 2:25 PM
To: Gantz, Marie; Wally Carlo, M.D.
Cc: higginsr@mail.nih.gov<mailto:higginsr@mail.nih.gov>; Vaucher, Yvonne; Das, Abhik

Subject: RE: SUPPORT OUTCOMES

Thanks Marie
Can we see these analyses please
The previous analyses still I assume are correct that there is an interaction between Low SpO2 group and Death/ROP in the small strata. Your current analysis would then say that there is no increase in NDI. Thus If I have understood this, there is a significant benefit to Death/ROP in the CPAP/Low SpO2 group?
I would like to see all these analyses
Thanks again
Neil

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Friday, September 09, 2011 10:06 AM
To: Wally Carlo, M.D.; Finer, Neil
Cc: higginsr@mail.nih.gov<mailto:higginsr@mail.nih.gov>; Vaucher, Yvonne; Das, Abhik
Subject: RE: SUPPORT OUTCOMES

Neil,

I have looked at the interaction between CPAP, SpO2 target and GA group for survival without NDI and the interaction is not significant (p=.29) which does not support doing subgroup analyses. However, I looked at the groups anyway because of your concern, and there are not significant differences between the CPAP and surfactant groups for the GA 24-25 group within either of the SpO2 targets (and the same is true for the GA 26-27 group).

I have not had time to do a thorough review of the draft papers that have been sent out, but I plan to work on that this afternoon.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org<mailto:mgantz@rti.org>
828-254-6255
From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Saturday, September 03, 2011 8:42 AM
To: nfiner@ucsd.edu<mailto:nfiner@ucsd.edu>; Gantz, Marie
Cc: higginsr@mail.nih.gov<mailto:higginsr@mail.nih.gov>; Vaucher, Yvonne; Das, Abhik; <mailto:wcarlo@peds.uab.edu> wcarlo@peds.uab.edu<mailto:wcarlo@peds.uab.edu>
Subject: RE: SUPPORT OUTCOMES

Marie, Neil and all.

I have not seen the raw numbers. Is death by itself decreased in the low sat CPAP group or is the effect all due to ROP? This is important as the ROP effect can be much larger yet the long term significance differs markedly for these outcomes (few ROP babies will be handicapped by it. Have you done the follow data analysis for the small babies?

Wally

-----Original message-----
From: "Finer, Neil" <nfiner@ucsd.edu<mailto:nfiner@ucsd.edu>>
To: "Gantz, Marie" <mgantz@rti.org<mailto:mgantz@rti.org>>
Cc: rose higgins <higginsr@mail.nih.gov<mailto:higginsr@mail.nih.gov>>, "Vaucher, Yvonne" <yvaucher@ucsd.edu<mailto:yvaucher@ucsd.edu>>, "Das, Abhik" <adas@rti.org<mailto:adas@rti.org>>, "wcarlo@peds.uab.edu<mailto:wcarlo@peds.uab.edu>" <wcarlo@peds.uab.edu<mailto:wcarlo@peds.uab.edu>>

Sent: Sat, Sep 3, 2011 05:04:48 GMT+00:00
Subject: RE: SUPPORT OUTCOMES
Many thanks Marie
The smaller strata infants are very different from the bigger strata. They have greater mortality and morbidity, more severe illness, and more subsequent handicap
Our concern was and is that since the CPAP infants in lower gestational age strata had less death 8% and less ROP, and the overall SpO2 trial had more deaths 4%, with less ROP. I became concerned that this CPAP group in the low strata had better outcomes in both death and ROP. and wondered if the additional benefit of a low SpO2 in these infants would further decrease ROP. In addition since this CPAP group had 8% less death it was possible that the increase in death from the low SpO2 if it did occur, might still result in an improved overall survival without ROP
This is what you have now found
Here is the concern
The world is now moving to increase the SpO2 acceptable range for all very preterm infants including the 24 -25 week infants because of our findings and that reported from UK and Australia NZ
These other studies did not have a respiratory intervention. and did not start the study oximeter till about 18 hrs.
If the use of CPAP and a permissive strategy actually results in improved survival without ROP, then it is possible that using the low SpO2 strategy with CPAP is the very best approach
Since we did not find more NDI . this would stand
We now need the analyses for survival without NDI evaluating the CPAP vs Surf in the strata comparing hi vs low SpO2 range.
This is vital information
I am doubtful that further studies which are as large as our small strata will never be done and thus our data may be as good as is
ever available
Before the others studies publish their data and recommend that we now raise the SpO2 range for all preterms we need to look at this a carefully as possible. The best conclusion at present may be that the combination of early CPAP and a limited vent strategy with a low SpO2 range is in fact the optimal approach for the most immature infants.
Thanks again and I would ask that you run the groups for survival without NDI to ensure that there is no adverse effect of this combination on later outcome
Be well
Neil
-----Original Message-----
From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Friday, September 02, 2011 3:07 PM
To: Finer, Neil
Cc: rose higgins; Vaucher, Yvonne; Das, Abhik
Subject: RE: SUPPORT OUTCOMES

Neil,

Attached are the analyses you requested.

To fill Abhik in, Neil and Yvonne were looking at the tables for the FU papers and were wondering if there was interaction between CPAP, oximeter and GA group for ROP and ROP/death. I did a quick look at ROP last week and found that there was significant interaction (p=.03) and that for infants with GA 24-25 weeks, those with CPAP had lower ROP, and the difference was very significant within the Low SpO2 group (but not significant in the High group). Neil and Yvonne were very interested in whether the combination of CPAP and Low SpO2 target was protective against ROP in the smaller GA stratum. Neil and Rose both called me this week to ask if I would also look at death/ROP to see if the results were similar. For death/ROP, the interaction between CPAP, oximeter and GA had a p value of .10, so I again ran the models separately for each GA group. Similar to the results for ROP, infants with GA 24-25 weeks had less ROP/death in the CPAP group, and that difference was very significant within the Low SpO2 group. I also looked at the interaction for the outcome of death, but it was not significant (p=.44) so I did not do sub-analyses.

I think this is very interesting, but what are the implications given that there was greater death in the Low SpO2 group in both GA strata, regardless of CPAP or surfactant use (although the difference in death was only significant

when the SUPPORT population was analyzed as a whole)?

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org<mailto:mgantz@rti.org>
828-254-6255

-----Original Message-----
From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Friday, September 02, 2011 2:08 PM
To: Gantz, Marie
Cc: rose higgins; Vaucher, Yvonne
Subject: SUPPORT OUTCOMES

Hi Marie
Will you be able to get us any data this week??
I would like to work on this over the long weekend Thanks Neil

From: Finer, Neil
To: Gabrio, Jenna; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Wally Carlo, M.D.; Vaucher, Yvonne; Myriam Peralta, M.D.; Gantz, Marie
Cc: Starlett Williams; Martinez, Fernando; Archer, Stephanie (NIH/NICHD) [E]
Subject: RE: SUPPORT paper draft: CPAP vs Surf -- Availability
Date: Tuesday, September 13, 2011 4:39:51 PM

I can be available for the Thursday time and the 2 times on Friday
Neil

From: Gabrio, Jenna [mailto:jgabrio@rti.org]
Sent: Tuesday, September 13, 2011 8:05 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Wally Carlo, M.D.; Vaucher, Yvonne; Myriam Peralta, M.D.; Finer, Neil; Gantz, Marie
Cc: Starlett Williams; Martinez, Fernando; Archer, Stephanie (NIH/NICHD) [E]
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9/15, Th, 12:30 PM – 2:00 PM ET
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Thanks,
Jenna

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, September 12, 2011 9:57 AM
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Cc: Gabrio, Jenna
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301-496-3790 (FAX)
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Great job, Yvonne.

I have added more comments.

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Cc: Vaucher, Yvonne
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All,

Thanks for all your excellent suggestions, revisions, editing! Here is next draft. I incorporated most of the comments from Wally and Abhik and left the comments that are still in discussion/have questions.

Yvonne

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Subject: RE: SUPPORT paper draft: CPAP vs Surf

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Clinical Professor of Pediatrics
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tele: 619-543-3759
FAX: 619-543-3812

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "jgabrio@rti.org"
Subject: Re: SUPPORT paper draft: CPAP vs Surf -- Availability
Date: Tuesday, September 13, 2011 11:20:13 AM

Ok for the 15th and 16th. Note- RTI (abhik, Kris 9allie + jenny) have a meeting on 9/14 from 10-11 using the regular call-in number

---

From: Gabrio, Jenna <jgabrio@rti.org>
To: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik <adas@rti.org>; Wally Carlo, M.D. <WCarlo@peds.uab.edu>; Vaucher, Yvonne <yvaucher@ucsd.edu>; Myriam Peralta, M.D. <MPeralta@peds.uab.edu>; Finer, Neil <nfiner@ucsd.edu>; Gantz, Marie <mgantz@rti.org>
Cc: Starlett Williams <StWilliams@peds.uab.edu>; fmartinez@ucsd.edu <fmartinez@ucsd.edu>; Archer, Stephanie (NIH/NICHD) [E]
Sent: Tue Sep 13 11:04:59 2011
Subject: RE: SUPPORT paper draft: CPAP vs Surf -- Availability

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I have added more comments.

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Subject: RE: SUPPORT paper draft: CPAP vs Surf
Date: Monday, September 12, 2011 11:19:59 AM

Rose,

I will be OOT Wed, Thurs and Fri. Could we do the call next Monday?

Yvonne

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]
Sent: Monday, September 12, 2011 6:56 AM
To: 'Das, Abhik'; Wally Carlo, M.D.; Vaucher, Yvonne; Myriam Peralta, M.D.; Finer, Neil; Gantz, Marie
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Cc: Vaucher, Yvonne
Subject: RE: SUPPORT paper draft: CPAP vs Surf
Date: Monday, September 12, 2011 9:51:07 AM

Good idea. Let's do this after I incorporate Marie's edits.

Yvonne

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Sent: Monday, September 12, 2011 6:39 AM
To: Das, Abhik; Wally Carlo, M.D.; Vaucher, Yvonne; Myriam Peralta, M.D.; Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]
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I will be sending my edits today.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255
From: Das, Abhik
Sent: Monday, September 12, 2011 9:39 AM
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From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]
Sent: Sunday, September 11, 2011 12:22 PM
To: Das, Abhik; Wally Carlo, M.D.; Myriam Peralta, M.D.; Finer, Neil; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Vaucher, Yvonne
Subject: RE: SUPPORT paper draft: CPAP vs Surf

All,

Thanks for all your excellent suggestions, revisions, editing! Here is next draft. I incorporated most of the comments from Wally and Abhik and left the comments that are still in discussion/have questions.

Yvonne

From: Das, Abhik [mailto:adas@rti.org]
Sent: Saturday, September 10, 2011 12:31 PM
To: Wally Carlo, M.D.; Vaucher, Yvonne; Myriam Peralta, M.D.; Finer, Neil; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT paper draft: CPAP vs Surf

My comments are attached. I think we need as much consistency as possible between the two follow up papers.

Thanks

Abhik

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Tuesday, September 06, 2011 7:14 PM
To: Vaucher, Yvonne; Myriam Peralta, M.D.; Finer, Neil; Gantz, Marie; Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT paper draft: CPAP vs Surf

Forgot to copy Rose.

Wally Carlo, M.D.
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From: Wally Carlo, M.D.

Sent: Tuesday, September 06, 2011 6:13 PM
To: 'Vaucher, Yvonne'; Myriam Peralta, M.D.; Finer, Neil; Gantz, Marie; Das, Abhik
Subject: RE: SUPPORT paper draft: CPAP vs Surf

Hi Yvonne, Neil, Myriam, Marie, Abhik and Rose:

Yvonne: Great job on the draft. I really liked the format of Table 1 as suggested by Abhik.

All: I am enclosing comments and tracked suggestions. I think we need to be careful with exploratory analyses and other subgroup analyses. We may want to keep separate the prespecified analyses as the original tables were drafted and add to that selected exploratory analyses.

Wally

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From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]
Sent: Tuesday, September 06, 2011 3:40 PM
To: Wally Carlo, M.D.; Myriam Peralta, M.D.; Finer, Neil; Gantz, Marie; Das, Abhik
Subject: FW: SUPPORT paper draft: CPAP vs Surf

All,
Here is the most recent draft of Early CPAP vs. Surfactant. There are significant differences between the GA strata which I included since the results for the entire cohort were sometimes misleading, particularly when the results were in opposite directions for the GA strata. The 24 0/7-25 6/7 wk gestation are quite different from the 26 0/7 to 27 6/7 wk gestation group. I still need some data.
I would appreciate your comments, ideas, etc. Thanks.

Yvonne

Yvonne E. Vaucher, M.D., M.P.H.
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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Wally Carlo, M.D."; "Myriam Peralta, M.D."; "nfiner@ucsd.edu"; "Vaucher, Yvonne"; "Das, Abhik"; "mgantz@rti.org"
Subject: Support NDI_09-02-2011_ver 2 0
Date: Monday, September 12, 2011 9:49:00 AM
Attachments: Support NDI_09-02-2011_ver 2 0.doc

HI,

I have looked at this and my comments are in track changes. We need tohave the primary outcome (and predefined secondary outcomes) match the written protocol exactly. NEJM will ask for the original protocol. I would remove "severe" in front of NDI. We also were not doing the Bayleyy III motor during the entire course of the FU, so I think we should remove it. NEJM will ask why all the children don't have this data. Also, I did not recall seeing the growth data as of yet and I thought this was going into the Growth paper?? I agree with the suggestion for Yvonne's paper to make the methods sections match between the two papers.

Thanks for all the hard work – once we have the discussion, we can send to the subcommittee

Rose

Neurodevelopmental Outcome of Extremely Preterm Infants in a Trial of Different Oxygen Saturation Targets

Myriam Peralta-Carcelen, M.D., M.P.H.[1];

[1]University of Alabama at Birmingham, Birmingham, Alabama, United States; the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), Bethesda, Maryland, United States.

Comment [bb1]: Additional authors?

Comment [bb2]: the NICHD?

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Word Count

Abstract: 248

Text: 1,148

ABSTRACT

Comment [WC3]: I had to cut so much to get the abstract under 250 words as required for NEJM

BACKGROUND

Targeting lower oxygen saturations in the SUPPORT Trial decreased severe retinopathy of prematurity while targeting higher oxygen saturations increased survival by discharge. We hypothesized that the long term neurodevelopmental effects of different oxygen saturation levels were not significant between both groups.

METHODS

We followed 1211 of 1316 (92.0) 24 to 27 week infants who had been randomized to higher (91-95%) or lower oxygen saturation targets (85-89%) starting at birth and up to 36 weeks corrected age. The primary outcome of this study was a composite of death or severe [outcome also includes moderate CP, so need to adhere strictly to protocol – recommend removing the word "Severe"] neurodevelopment impairment at 18 to 22 months corrected age. ~~Severe~~ nNeurodevelopmental impairment was defined as a cognitive composite score of less than 70, motor score less than 70[this was added after protocol was final and not for all patients, so I would leave out], modified Gross Motor Function Classification System >1, presence of moderate to severe cerebral palsy, permanent hearing loss, and/or bilateral blindness.

RESULTS

Death or severe neurodevelopmental impairment occurred in 185 (30.2%) infants in the lower oxygen saturation group and 171 (27.5%) infants of the higher oxygen saturation group (relative risk 1.11; confidence interval 0.94, 1.32; p=0.227). Death occurred in 140 (22.3%) of the children in the lower oxygen saturation group and in 118 (18.4%) in the higher oxygen saturation group (relative risk 1.24; confidence interval 1, 1.54, p=0.053). [If there is room, protocol had NDI and CP in survivors as a predefined secondary outcome]

CONCLUSIONS

Among extremely preterm infants exposed to different levels of oxygen saturation, there is no difference in the combined death or NDI outcome. The increased mortality at discharge time in the lower oxygen target group remains significant at 18-22 months. [is partially offset by a trend for increased ~~severe~~ neurodevelopmental impairment at 18 to 22 months in this group. NEJM doesn't like the use of the word "trend" so this should be stated as a fact, not a trend].

Oxygen supplementation is a vital therapy for survival of many preterm infants with respiratory disorders. However, oxygen supplementation may increase the risk of retinopathy of prematurity, bronchopulmonary dysplasia,[Tin et al, 2001] periventricular leukomalacia,[Chow et al, 2003] and cerebral palsy.[Anderson et al, 2004] Restrictive oxygen therapy decreases retinopathy but has resulted in increased deaths in randomized controlled trials.[Bolton DP et al, 1997; Askie et al, 2009; Carlo et al, 2010; Stenson et al, 2011]

Comment [WC4]: These references are quoted in my NEJM paper

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development SUPPORT Trial demonstrated no significant difference in a composite outcome including retinopathy of prematurity and death between a lower oxygen saturation group (85-89%) and the higher saturation group (91-95%). However, mortality was increased and severe retinopathy of prematurity was reduced in the lower oxygen saturation group compared to the higher saturation group. A recent meta-analysis that included the SUPPORT Trial and two other subsequently done multi-center randomized controlled trials with a total of 3631 infants showed that infants randomized to an oxygen saturation of 91-95% % had a lower mortality rate than infants randomized to oxygen saturation targets of 85-89% (17.3% versus 14.4%, P=0.015).[Stenson, NEJM 2011] There has been keen interest to determine if oxygen supplementation can reduce neurodevelopmental impairment. However, in two non randomized studies of different oxygen saturation targeting,[Tin et al, 2001; Bradley et al, 1993] neurodevelopmental outcome did not differ by oxygen targets.

Comment [WC5]: Spell out

This study evaluated the composite primary outcome of death or ~~severe~~ neurodevelopmental impairment at 18 to 22 months corrected age in the subjects enrolled in the two groups of extremely preterm infants randomized to lower (85-89%) or higher oxygen saturation targets (91-95%) from birth to 36 weeks corrected age.

METHODS

Extremely preterm infants (24 weeks 0 days to 27 weeks 6 days) born between February 2005 and February 2009 at participating sites of the Neonatal Research Network of the Eunice Kennedy Shriver National Institute of Child Health and Human Development enrolled in the SUPPORT trial were eligible for this study. Each center's institutional review board approved the study. Enrollment, intervention, data collection, and hospital outcomes have been previously reported. (Carlo NEJM)

Assessments

The composite of death or ~~major neurosensory~~developmental impairment at 18 to 242 months of age corrected for prematurity was the primary outcome. This composite outcome was selected because infants who died before 18 months could not be classified as having neurodevelopmental impairment. Neurodevelopmental impairment was defined as having any of the following: BISD III scales cognitive composite score less than 70, GMFCS > 2, presence of cerebral palsy moderate or severe, permanent hearing loss that does not permit the child to understand directions of the examiner and communicate despite amplification, or bilateral visual impairment (vision < 20/200).

Outcomes at 18-22 months of corrected age were assessed by neurologic examiners and neurodevelopmental testers who had been trained yearly for reliability of assessments during a yearly 2-day workshop and were unaware of the treatment assignments.

The Bayley Scales for Infant Development III (BSID III) was administered. Cognitive Composite Scores are reported in a standardized score of 100 ± 15. The composite Language Score is a sum of the receptive and expressive language scores and are based on a scale of 1 to 19, the overall language composite score is converted to a standardized score of 100 ± 15. The Motor section was added to the evaluation after January 1, 2010. Two scores are calculated: the fine motor and gross motor score. ~~These are added and converted to an overall motor composite score with a mean of 100 ± 15.~~ [delete motor outcomes as this was not part of the original prptocol]

The modified Gross Motor Function Classification System (GMFCS) describes the gross motor performance and has a range from 0 (normal) to 5 (most impaired). Examiners also recorded the presence of cerebral palsy defined as a nonprogressive disorder of the central nervous system characterized by abnormal muscle tone in at least one arm or leg and abnormal control of movement or posture with delayed attainment of motor milestones. Cerebral palsy was classified depending on severity into mild (GMFCS ≤1), moderate (GMFCS 2 or 3) or severe (GMFCS ≥ 4). [Anthropometrics measures included weight, height and head circumference. Z scores using

the Center for Disease Control growth charts were calculated for weight, height, and head circumference – is this part of the original proposal??? I don't recall seeing these data}.

~~Severe neurodevelopmental impairment was defined as having any of the following: BISD III scales cognitive composite score less than 70, motor score less than 70, GMFCS ≥ 2, presence of cerebral palsy moderate or severe, permanent hearing loss that does not permit the child to understand directions of the examiner and communicate despite amplification, or bilateral visual impairment (vision < 20/200).~~

Socioeconomic data was updated during the 18-224 month visit and if not available, data during the neonatal period was included. Medical information included the number of rehospitalizations.

Analysis

Data was entered in standard forms and was transmitted to RTI International which stored, managed and analyzed the data for this study. Comparisons of primary and secondary outcomes were done between infants in the lower saturation group and the higher oxygen saturation group. In addition comparisons were done between two gestational age stratification categories:. Categorical outcomes were compared with the use of chi-square tests for trends and appropriate or Fisher's exact test.

RESULTS

Characteristics of the Study Sample

The SUPPORT trial enrolled 1316 study in the study (Figure 1). Five hundred twenty four infants in the lower oxygen saturation group and 555 in the higher oxygen saturation group survived to discharge from the hospital. The baseline characteristics of the entire group have been reported previously[Carlo NEJM] Ten children in the lower oxygen saturation group and 11 children in the higher oxygen saturation group died after discharge from the nursery prior to the 18 to 22 month adjusted age follow up visit. The baseline characteristics of the eligible infants for follow up are presented in Table 1. There were no significant differences in the baseline characteristics of the follow up group who received lower oxygen saturation versus higher oxygen saturation.

Comment [bbf1]: Figures ?

Primary Outcome

The rate of composite outcome, neurodevelopmental impairment plus death was not significantly different between the lower oxygen saturation group and the high oxygen saturation group. (Table 2) Death prior to the 18 to 22 month adjusted age visit occurred in infant in the lower oxygen saturation group and infants in the higher saturation group. Similar results were observed for both gestational age strata.

The rate of neurodevelopmental impairment on among survivors followed to the 18 to 22 month adjusted age visit was similar between the low oxygen saturation group and the high oxygen saturation group. The rate of retinopathy of prematurity was higher in the high oxygen group compared to the low oxygen group however the rate of blindness was not significantly at the 18 to 22 month adjusted age visit on the follow up group.

Secondary Outcomes

The mean scores of the Bayley Scales of Cognitive Impairment were not significantly different in the low oxygen saturation group and the high oxygen saturation group. There were also no significant differences in rates of cerebral palsy between both groups (Table 3). ~~On the follow up group.~~ At patient follow up at 18-22 months, the rate of infants who required eye surgery was higher in the high oxygenation group compared to the low oxygen saturation group.

DISCUSSION

REFERENCES

Anderson CG, Benitz We, Madan A. Retinopathy of prematurity and pulse oximetry: a national survey of recent practices. J Perinatol. 2004;24:164-168.

Askie LM, Henderson-Smart DJ, Ko H. Restricted versus liberal oxygen exposure for preventing morbidity and mortality in preterm or low birth weight infants. Cochran Database Syst Rev. 2009;1:CD001077.

Bolton DP, Cross KW. Further observations on cost of preventing retrolental fibroplasias. Lancet. 1974;303:445-448.

Bradley S, Anderson K and Tin W, et al.: Early oxygen exposure and outcome at 10 years in babies of less than 29 weeks. Pediatr Res. 55:2004;A373.

Chow LC, Wright KW, Sola A. Can changes in clinical practice decrease the incidence of sever retinopathy of prematurity in very low birth weight infants? Pediatrics. 2003;111:330-345.

Stenson B, Brocklehurst P, Tarnow-Mordi W; U.K. BOOST II trial; Australian BOOST II trial; New Zealand BOOST II trial. Increased 36-week survival with high oxygen saturation target in extremely preterm infants. N Engl J Med. 2011;364:1680-1682.

SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network, Carlo WA, Finer NN, Walsh MC, Rich W, Gantz MG, Laptook AR, Yoder BA, Faix RG, Das A, Poole WK, Schibler K, Newman NS, Ambalavanan N, Frantz ID 3rd, Piazza AJ, Sánchez PJ, Morris BH, Laroia N, Phelps DL, Poindexter BB, Cotten CM, Van Meurs KP, Duara S, Narendran V, Sood BG, O'Shea TM, Bell EF, Ehrenkranz RA, Watterberg KL, Higgins RD. Target Ranges of Oxygen Saturation in Extremely Preterm Infants. N Engl J Med 2010; 362:1959-1969.

Comment [bb7]: check references

Tin W, Milligan DW, Pennefather P, Hey E. Pulse oximetry, severe retinopathy, and outcome at one year in babies of less than 28 weeks gestation. Arch Dis Child Fetal Neonatal. 2001;84:F106-F110.

Table 1. Baseline characteristics of the SUPPORT group

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Characteristics	Trial Cohort		Cohort with Follow-up Visit	
	Lower Oxygen Saturation	Higher Oxygen Saturation	Lower Oxygen Saturation	Higher Oxygen Saturation
			N=479	N=510
Birth weight – g			857.8 ± 186.3	843.9± 191.6
Gestational age – wk			26.3 ± 1.1	26.2 ± 1
Small for gestational age – no./total no. (%)			17/479 (3.5)	38/510 (7.5)
Male sex – no./total no. (%)			240/479 (50.1)	281/510 (55.1)
Race or ethnic group – no./total no. (%)				
Non Hispanic Black			201/479 (42)	176/510 (34.5)
Non Hispanic White			178/479 (37.2)	217/510 (42.5)

Hispanic	86/479 (18)	97/510 (19)
Other or unknown	14/479 (2.9)	20/510 (3.9)
Multiple births – no./total no. (%)	124/479 (25.9)	128/510 (25.1)
Maternal educational level <high school no./total no. (%)	115/471 (24.4)	128/503 (25.4)
Cesarean section – no./total no. (%)	332/479 (69.3)	334/510 (65.5)
Antenatal steroids – no./total no. (%)	462/479 (96.5)	486/510 (95.3)
Retinopathy of prematurity – no./total no. (%)	38/442 (8.6)	82/471 (17.4)
Bronchopulmonary dysplasia – no./total no. (%)	177/479 (37)	202/510 (39.6)
Intraventricular hemorrhage grade 3 or 4 or Periventricular leukomalacia – no./total no. (%)	56/478 (11.7)	60/509 (11.8)
Necrotizing enterocolitis – no./total no. (%)	42/479 (8.8)	44/510 (8.6)
Bronchopulmonary dysplasia no./total no. (%)	177/479 (37)	202/510 (39.6)

Table 2. Primary and Secondary Outcomes at 18-22 Months

	Lower Oxygen Saturation	Higher Oxygen Saturation	Adjusted Relative Risk	p value
Died or had follow-up – no./total no. (%)				
Died by 18-22 months – no./total no. (%)				
Neurodevelopmental impairment or death – no./total no. (%)				
Survivors at follow-up				
Severe neurodevelopmental impairment – no./total no. (%)				
Bayley III cognitive composite score < 70 – no./total no. (%)				
Gross motor function level ≥ 2 – no./total no. (%)				
Moderate/severe cerebral palsy – no./total no. (%)				
Blindness – no./total no. (%)				
Unilateral blindness – no./total no. (%)				
Deafness – no./total no. (%)				
Profound neurodevelopmental impairment – no./total no. (%)				

Table 3. Secondary Outcomes by Group

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Outcome	Low SpO2 (N=479)	High SpO2 (N=510)	Relative Risk for Low SpO2 vs. High SpO2 (95% CI)	Adjusted difference in means (95% CI)	Adjusted P-value
Bayley Scales of Infant Development III					
Cognitive composite <85	105/471 (22.3)	131/502 (26.1)	0.86 (0.69, 1.07)		0.1831
Bayley III composite language score <70	69/462 (14.9)	84/497 (16.9)	0.85 (0.64, 1.15)		0.2940
Bayley III composite language score <85	203/462 (43.9)	224/497 (45.1)	1 (0.99, 1)		0.8121
Bayley III composite motor score <70	18/134 (13.4)	16/142 (11.3)	1.37 (0.76, 2.47)		0.3016
Bayley III composite motor score <85	41/134 (30.6)	44/142 (31.0)	1.02 (0.71, 1.48)		0.8948
Mild cerebral palsy vs. none	23/459 (5.0)	21/490 (4.3)	1.16 (0.66, 2.02)		0.6105
Moderate cerebral palsy vs. none	11/447 (2.5)	10/479 (2.1)	1.19 (0.52, 2.71)		0.6873
Severe cerebral palsy	9/445 (2.0)	10/479 (2.1)	0.95 (0.39, 2.27)		0.9026

Any cerebral palsy	43/479 (9.0)	41/510 (8.0)	1.12 (0.76, 1.65)	0.5766
Abnormal neuro/motor score	108/479 (22.5)	114/510 (22.4)	1.02 (0.82, 1.27)	0.8606
Hypotonia	22/479 (4.6)	20/510 (3.9)	1.24 (0.67, 2.28)	0.4973
Hypertonia	6/479 (1.3)	11/510 (2.2)	0.59 (0.22, 1.58)	0.2962
Diplegia	18/479 (3.8)	16/510 (3.1)	1.21 (0.63, 2.32)	0.5651
Hemiplegia	7/479 (1.5)	6/510 (1.2)	1.28 (0.44, 3.74)	0.6557
Quadriplegia or triplegia	9/479 (1.9)	13/510 (2.5)	0.66 (0.27, 1.61)	0.3585
Strabismus	46/478 (9.6)	41/509 (8.1)	1.2 (0.7, 1.8)	0.3845
Nystagmus	22/479 (4.6)	12/509 (2.4)	1.95 (0.94, 4.07)	0.0737
Tracks 180 degrees	462/476 (97.1)	492/506 (97.2)	1 (0.98, 1.02)	0.9330
Corrective lenses both eyes vs. normal both eyes	21/468 (4.5)	20/492 (4.1)	1.14 (0.62, 2.08)	0.6774
Blind, some function, both eyes vs. normal both eyes	3/450 (0.7)	2/474 (0.4)	1.56 (0.27, 8.95)	0.6151
Blind, no useful vision, both eyes vs. normal both eyes	2/449 (0.4)	4/476 (0.8)	0.54 (0.1, 2.95)	0.4789
Other abnormal vision vs. normal both eyes	6/453 (1.3)	12/484 (2.5)	0.55 (0.21, 1.46)	0.2301
Hearing impairment, no hearing aids vs. no impairment	5/472 (1.1)	6/504 (1.2)	0.91 (0.29, 2.92)	0.8777
Hearing impairment, both hearing aids vs. no impairment	7/474 (1.5)	6/504 (1.2)	1.27 (0.44, 3.7)	0.6595

Eye surgery	31/477 (6.5)	67/508 (13.2)	0.52 (0.35, 0.78)		0.0014
PDA ligation	48/477 (10.1)	39/508 (7.7)	1.33 (0.9, 1.95)		0.1519
Any surgery	210/477 (44.0)	241/509 (47.3)	0.95 (0.83, 1.08)		0.4314
Bronchodilators	159/475 (33.5)	185/505 (36.6)	0.92 (0.78, 1.09)		0.3583
Steroids	95/475 (20.0)	108/505 (21.4)	0.92 (0.72, 1.18)		0.5016
Diuretics	15/475 (3.2)	14/505 (2.8)	1.16 (0.58,2.34)		0.6717
High calorie formula	90/475 (18.9)	102/505 (20.2)	0.92 (0.71, 1.2)		0.5353
Anticonvulsants	12/478 (2.5)	12/510 (2.4)	1.08 (0.49, 2.37)		0.8514
Readmission for respiratory reason	110/470 (23.4)	127/503 (25.2)	0.93 (0.74, 1.16)		0.5114
Readmission for growth/nutrition	12/470 (2.6)	13/503 (2.6)	1.05 (0.49, 2.25)		0.8953
Any hospital readmission	210/478 (43.9)	238/510 (46.7)	0.94 (0.82, 1.08)		0.4111
Weight (kg)	10.87 ± 0.09	10.91 ± 0.09		-0.05(-0.27, 0.17)	0.6581
Weight-for-age z-score	-0.20 ± 0.06	-0.24 ± 0.06		0.04 (-0.12, 0.19)	0.6374
Weight-for-age z-score	-0.20 ± 0.06	-0.24 ± 0.06		0.04 (-0.12, 0.19)	0.6374
Recumbent length (cm)	81.38 ± 0.25	81.49 ± 0.24		-0.11(-0.72, 0.51)	0.7285
Length-for-age z-score	-0.70 ± 0.08	-0.75 ± 0.07		0.05 (-0.13, 0.24)	0.5729

Length-for age z-score	-0.69 ± 0.07	-0.73 ± 0.07	0.04 (-0.13, 0.21)	0.6270
Weight-for-length z-score	0.18 ± 0.07	0.14 ± 0.06	0.04 (-0.12, 0.20)	0.6136
Weight-for-length z-score	0.17 ± 0.06	0.15 ± 0.06	0.03 (-0.13, 0.18)	0.7356
Occipital-frontal circumference (cm)	46.98 ± 0.11	41.06 ± 0.10	-0.08 (-0.34,0.18)	0.5544
Head circumference-for-age z-score	-0.11 ± 0.08	-0.11 ± 0.07	-0.01 (-0.19,0.18)	0.9367
Head circumference-for-age z-score	-0.07 ± 0.07	-0.02 ± 0.07	-0.04 (-0.22,0.13)	0.6278

From: Vaucher, Yvonne
To: Das, Abhik; Wally Carlo, M.D.; Myriam Peralta, M.D.; Finer, Neil; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Vaucher, Yvonne
Subject: RE: SUPPORT paper draft: CPAP vs Surf
Date: Sunday, September 11, 2011 1:22:19 PM
Attachments: SUPPPORT_CPAP_FUPNF_Rev_Sept_06_2011_WC_adYEVrev1[1]091111.docx

All,

Thanks for all your excellent suggestions, revisions, editing! Here is next draft. I incorporated most of the comments from Wally and Abhik and left the comments that are still in discussion/have questions.

Yvonne

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My comments are attached. I think we need as much consistency as possible between the two follow up papers.

Thanks

Abhik

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Forgot to copy Rose.

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Subject: RE: SUPPORT paper draft: CPAP vs Surf

Hi Yvonne, Neil, Myriam, Marie, Abhik and Rose:

Yvonne: Great job on the draft. I really liked the format of Table 1 as suggested by Abhik.

All: I am enclosing comments and tracked suggestions. I think we need to be careful with exploratory analyses and other subgroup analyses. We may want to keep separate the prespecified analyses as the original tables were drafted and add to that selected exploratory analyses.

Wally

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From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]
Sent: Tuesday, September 06, 2011 3:40 PM
To: Wally Carlo, M.D.; Myriam Peralta, M.D.; Finer, Neil; Gantz, Marie; Das, Abhik
Subject: FW: SUPPORT paper draft: CPAP vs Surf

All,
Here is the most recent draft of Early CPAP vs. Surfactant. There are significant differences between the GA strata which I included since the results for the entire cohort were sometimes misleading, particularly when the results were in opposite directions for the GA strata. The 24 0/7-25 6/7 wk gestation are quite different from the 26 0/7 to 27 6/7 wk gestation group. I still need some data. I would appreciate your comments, ideas, etc. Thanks.

Yvonne

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Early CPAP versus Surfactant in Extremely Preterm Infants: Neurodevelopmental Outcomes in Early Childhood

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ABSTRACT

BACKGROUND

The SUPPORT trial demonstrated that early CPAP is an alternative to surfactant after intubation, and is associated with similar rates of death or BPD in infants born at 24 to 27 weeks gestation. We hypothesized that long term neurodevelopmentally intact survival ~~, compared to treatment with surfactant administration after intubation, treatment with early CPAP would result in decreased mortality or neurodevelopmental impairment~~would be increased by CPAP treatment.

METHODS

We followed ~~1108 infants,~~ 24 to 27 weeks gestation infants randomized in the SUPPORT trial to receive either CPAP with limited ventilation after delivery or intubation with surfactant administration within one hour after birth~~. A standardized neurodevelopmental assessment was performed~~ at 18-22 months corrected age. The pre-specified primary outcome was death or neurodevelopmental impairment (NDI). NDI was defined as Bayley III cognitive score < 70, Gross Motor Function Classification score ≥ 2, moderate/severe cerebral palsy, bilateral blindness or permanent hearing impairment.

RESULTS

Death or NDI was determined for 1233/1316 (93.7%) of infants enrolled in SUPPORT and 93.5% of known survivors (989/1058) were evaluated at 18-22 months corrected age. Death or NDI occurred in 28% (174/621) of the CPAP group and in 29.7% (182/612) of the Surfactant -group (p=0.44). Rates of death and NDI alone (CPAP-11.1 vs. Surf-8.9%, p=0.32) were similar in both treatment arms. In the most immature stratum (24 -25-weeks gestation), there were fewer deaths

Comment [ad1]: NEJM requires this to be 250 words. I tried to cut down to get to that number.

Comment [yev 2]: As I read the protocol (pgs 10-11) the secondary hypotheses were " CPAP...and or a lower SPO2...will result in....a decreased mortality/NDI...NDI...cerebral palsy...at 18-22 months corrected age." So I have used this in the paper. How can we change it now to "no effect"?

Comment [yev 3]: Isn't it helpful to have the total number (1108) in the abstract esp. as it is a very impressive number in ELGA infants. We can cut somewhere else to make the word limit.

Comment [y4]: Is this primary because the study was powered for it? The Mortality/NDI and related outcomes are listed as secondary hypotheses in the protocol (pg 10)

Comment [yev 5]: See above-the protocol actually specifies cerebral palsy without differentiating severity (pg 31) though the definition of NDI is moderate/severe CP

[CPAP-26.5% (73/276) vs. Surf-35.7% (117/264), p=0.02] ~~but a higher rate of hearing impairment [CPAP-5.5% (11/201) vs. Surf-1.2% (2/171), p=0.043]~~ in the CPAP arm.

CONCLUSION

We found no significant differences in the composite outcome of death or NDI, ~~NDI only, or moderate/severe cerebral palsy~~ at 18-22 months corrected age between extremely premature infants who were randomized to receive either early CPAP with a limited ventilation strategy or early intubation with surfactant administration followed by conventional ventilation.

Comment [yce3]: As it read before it looked like death or NDI individually rather than as a composite outcome of death/NDI. How should we best express and make clear the composite outcome?

BACKGROUND

There is emerging evidence that CPAP is an effective strategy to support preterm infants with respiratory distress syndrome that may also improve outcomes (Morley, Finer, Others?). The recent, multicenter, randomized, controlled (SUPPORT) trial demonstrated that treatment with non-invasive CPAP shortly after birth may be considered as an alternative to surfactant administration after intubation and is associated with similar rates of death or BPD at 36 weeks corrected age in extremely premature infants born at 24 0/7 to 27 6/7 weeks gestation (REF Finer). Early CPAP was also associated with less frequent need for postnatal steroids, shorter duration of mechanical ventilation, and similar rates of air leak and IVH compared with surfactant, all factors associated with adverse neurodevelopmental outcomeoutcome in ~~ELBW/ELGA~~extremely low birthweight and extremely premature infants. In addition, mortality before discharge was lower in the most immature, 24-25 week gestation stratum.

The SUPPORT study was designed and powered to evaluate early childhood neurodevelopmental outcome of enrolled infants. We hypothesized that compared to treatment with surfactant administration after intubation, treatment with early, non-invasive CPAP and a limited ventilation strategy would result in decreased mortality or neurodevelopmental impairment at 18-22 months corrected age.

METHODS

Study design

1316 infants, 24 0/7 to 27 6/7 weeks gestation, born at 20 participating NICHD Neonatal Research Network sites between February 2005 through February 2009, from whom antenatal consent had been obtained were enrolled immediately following delivery in the prospective, randomized, controlled SUPPORT trial. ~~The study randomized~~ Infants were randomized within each study site and gestational age strata (24 0/7 to 25 6/7 or 26 0/7 to 27 6/7 weeks) to receive either CPAP immediately following delivery and a limited ventilation strategy if subsequent intubation was required or surfactant within an hour after birth. In addition, using

Comment [WC7]: The background is succinct. You may want to add high rates of NDI in survivors following ventilation as neonates, high after DC mortality, uncertainty about outcomes after surf vs no surf.

Comment [yev 8]: Yes, we will spell out. I left the abbrev for our internal review only.

Comment [ad9]: Do we need to spell out these abbreviations? NEJM doesn't like acronyms very much.

Comment [yev 10]: Again the clarity issue of how to best express the composite outcome of death or NDI. Not clear here.

Comment [ad11]: The 2 papers seem to express this differently. The saturation paper states this in terms of the null hypothesis of no effect, whereas we have the reverse here. We need to be consistent between the 2 papers.

Comment [y12]: See comment in abstract

a 2X2 factorial design, all infants were randomly assigned to either higher (91-95%) or lower (85-89%) oxygen saturation target ranges ~~of pulse modified pulse oximeters~~ until supplemental oxygen was no longer needed or the infant reached 36 weeks corrected age. (REF NEJM Finer,Carlo) Details of the SUPPORT Trial protocol have been previously described. (REF NEJM Finer,Carlo) In addition to the primary outcome of death or neurodevelopmental impairment (NDI) at 18-22 months corrected age, other pre-specified follow up outcomes included incidence of cerebral palsy, NDI, and the components thereof (Bayley III cognitive score, Gross Motor Function Classification score, bilateral blindness or permanent hearing impairment). The study was approved by the human subjects committee at each participating site and at RTI International, the Data Coordinating Center (DCC) for the Neonatal Research Network. Data collected at participating centers were transmitted to RTI International which stored, managed and analyzed the data for this study.

Comment [y13]: Were these actually pre-specified? Not in the protocol list separately from NDI.

Study population

From February 2005-February 2009, 1316 infants at 20 neonatal tertiary care centers in the United States participating in the NICHD Neonatal Research Network (NRN) were enrolled in the SUPPORT Trial. ~~Surviving infants were enrolled at 36 weeks adjusted age in the prospective follow-up cohort.~~ A comprehensive neurodevelopmental assessment was performed at 18-22 months corrected age (CA) by examiners unaware of study intervention assignment (CPAP vs. Surfactant). Developmental function was assessed using the Bayley Scales of Infant Development-III (BSID III) (REF); neurologic function was assessed using a standardized neurologic exam, motor function was determined using the Gross Motor Function Classification Scale (GMFCS)(REF); neurosensory outcome was determined based on parental history and examination. Examiners from each center were centrally trained and certified annually to assure standardization in psychometric and neurologic test administration.

The initial 2/3 of the cohort (N=713) were administered only the cognitive and language scales of the BSID-III; the composite motor scale of the BSID-III was included for the final one third of the participants (N=275). BISD-III cognitive,

language and motor standardized scores are presented as composite scores with a mean of 100 and a standard deviation of 15.

Study definitions

Neurodevelopmental impairment (NDI) was defined by the presence of at least one of the following: BSID III cognitive composite score < 70; a GMFCS of ≥ 2, the presence of moderate/severe CP, blindness (< 20/200 bilaterally), or permanent hearing loss interfering with the ability to understand or communicate despite amplification with hearing aids or cochlear implants.

Moderate/severe cerebral palsy was determined by a neurologic examination compatible with cerebral palsy and a GMFCS or ≥2.

Comment [y14]: Are we defining hearing impairment as "permanent" or not for inclusion in the NDI? We do not know the "permanent" status of 11 children with "hearing impairment" but no amplification. They are included in the 7/29/11 NDI analyses so at present we are including any hearing impairment, permanent or not, amplification or not. Either way will not change the significance since the predominance is in the CPAP arm but we need to be consistent in our description/inclusion either way.

Statistical analysis:

Details regarding sample size calculations for the SUPPORT trial have been previously reported (REF Finer). All analyses were performed according to the intention-to-treat principle. The denominator that was used to calculate the rate of each outcome was the number of infants for whom that outcome was known. The primary analyses focused on the percentage of infants in each group for whom the primary outcome of death or NDI at 18-22 months corrected age could be assigned. Analysis of this and all other categorical outcomes was performed with the use of robust Poisson regression in a generalized-estimating-equation model to obtain adjusted relative risks with 95% confidence intervals. Continuous outcomes were analyzed with the use of mixed-effects linear models to obtain adjusted means and standard errors.

In the analysis of all outcomes, the results were adjusted, as prespecified, for gestational-age strata, center, and familial clustering. Two-sided P values of less than 0.05 were considered to indicate statistical significance, and no adjustments have been made for multiple comparisons.

For the xx planned analyses of secondary outcomes according to treatment, we would expect no more than tests to have p values of less than 0.05 on the basis of chance alone. Subgroup analyses were conducted within prespecified gestational-

age strata for zz predefined outcomes. Although these tests have not been adjusted for multiple comparisons, we would expect no more than n tests per stratum to have p values of less than 0.05 on the basis of chance alone.

Comment [y15]: Thanks!

Comment [ad16]: This is lifted straight from the NEJM paper because we used the same approach here as well.

RESULTS

All survivors at 36 weeks adjusted age (1108/1316) were enrolled at discharge in the prospective SUPPORT follow-up cohort. (See Figure 1) Sixty-nine children (6.2%) were lost to follow up. Fifty (4.5%) children died after 36 weeks adjusted age and before 18-22 months. The survival status of 48/69 children who were lost to follow-up LTFU was unknown. A neurodevelopmental assessment at 18-22 months corrected age was performed for 989/1079 (91.7%) children known to be alive during the assessment interval. Of those who were seen for their 18-22 mo ND exam, NDI was determined for 975 children; 16 children were seen but had an incomplete evaluation that precluded assigning a NDI status. Ultimately, the pre-specified outcome, death or NDI, was determined for 93.6% of the randomized infants(see Figure 1 for flow chart). There was no difference in the FUP rate between the CPAP and Surfactant arms (93.4 vs 93.4%) of the trial.

Comment [WC17]: As we have reported hosp mort already, should this be limited to after DC mort?

Comment [y18]: This # will change with new data)

Compared with mothers of the 989 children who had a ND assessment at 18-22 months, mothers of 69 children LTFU were less likely to be married (30 vs 47%, p=0.01), and more likely to have public insurance (70 vs 52%, p=0.00601), and less likely to have completed high school (75 vs 63%, p=0.04). No other demographic variables or neonatal characteristics were significantly different between the groups.

Comment [yev 19]: Fine with me to use only 2 decimal places for significance, but does this p take into account the number of comparisons?

Demographics and neonatal characteristics:

Comment [ad20]: Why do we need this section for a randomized trial? Randomization should take care of such differences and we have reported on most of these in the previous papers anyway. I suggest we briefly refer to a table and move on.

Comment [y21]: Mmk, Do we need a table at all if we can refer to the original paper? However, several of the factors do independently predict outcome so I think it is important to reiterate the similarities and differences here also esp for readers/FUP people who may not have read the original paper and since there were some differences in the FUP cohort.

Trial Cohort: There were no significant differences between the CPAP and Surfactant trial arms in the incidence of death before discharge, severe IVH/ PVL, sepsis, severe ROP in survivors, medical or surgical NEC, BPD, or late onset sepsis. BW, GA, gender, race/ethnicity, multiple birth, mode of delivery, insurance status, maternal education, English as the primary language, and household income were also similar in the both groups. Compared to the Surfactant arm, infants in the in

Comment [WC22]: It may be best to delete this sentence and rather say they were comparable demographic characteristics between the enrolled babies but specify the differences in the FU cohort.

the CPAP arm were less likely to be SGA (5.6 vs 9%, unadjusted p=0.016) and less likely to have been exposed to postnatal steroids (7.2 vs 13.2 %, unadjusted p=0.0005). There was a trend towards fewer deaths before 18-22 months corrected age in the CPAP arm (18.5 vs. 22.2%, adjusted p=0.1). This difference reached significance in the lower 24 0/7 to 25 6/7 weeks gestation stratum (26.4 vs. 35.7%, unadjusted p=0.02), but not in the higher gestational age stratum 12.4 vs. 12%). The 24 0/7 to 25 6/7 weeks gestation stratum of the CPAP arm also had less ROP compared to the Surfactant arm (22.2 vs. 31.6%, unadjusted p=0.042) whereas the reverse occurred in the 26 0/7 to 27 6/7 weeks gestation stratum (7.3 vs. 10.2%, unadjusted p=0.044).

Follow-Up Cohort: (Table 1)There were no significant differences between the CPAP and Surfactant trial arms among surviving babies followed at 18-22 months corrected age in the incidence of death before discharge, SGA status, sepsis, ROP in survivors, or LOS. BW, GA, gender, race/ethnicity, multiple birth, mode of delivery, insurance status, maternal education, English as the primary language, household income were also similar in the both groups. Compared to the Surfactant arm, infants in the in the CPAP arm were more likely to be have Grade 3-4 IVH or cystic PVL (13.7 vs 9.6%, unadjusted p=0.05) and more likely to have modified Bell's Stage ≥ 2, medical or surgical NEC (11 vs 6.3%, unadjusted p=0.009). Infants in the CPAP arm were less likely to have been exposed to postnatal steroids (6.7 vs 11.4%, unadjusted p=0.01.)

~~Pre-specified~~Primary outcome: The mean corrected age at neurodevelopmental assessment was similar for both treatment arms (CPAP ~~20~~ 19.9 ± 2.4 mo, Surf 20.1 ± 2.7 mo, unadjusted p=0.34,). There was no significant difference in the composite outcome of *death or NDI* at 18-22 month corrected age between the CPAP and surfactant arms in the entire cohort (28.8 vs. 29.8%) or for the either of the two gestational age strata (40.1 vs. 44.3% for 24 0/7-25 6/7 weeks gestation; 18.6 vs. 18.7% for 26 0/7 to 27 6/7 weeks gestation).

Pre-specified secondary outcomes: (Tables 2 and 3) For the entire surviving cohort or within either gestational age stratum followed up at 18-22 months corrected age, there was there were no significant difference between the CPAP

Comment [yev 23]: Can we eliminate the 0/7 and 6/7 throughout the paper as long as it is in the methods?

Comment [y24]: I think so. We did look at IVH/PVL and NEC for hearing impairment-not related

Comment [ad25]: So, should we have adjusted for these factors when looking at the secondary outcomes among survivors?

Comment [ad26]: Also report adjusted RR and 95% CI here and below

Comment [yev 27]: No RR here in Data table 1b

and Surfactant arms in the incidence of *NDI* or *moderate/severe cerebral palsy*. ~~for the entire cohort (4.1 vs. 4%, adjusted p=0.82) or for either of the two gestational age strata (7 vs. 4.7, p=0.52 for 24 0/7-25 6/7 weeks gestation; 6.6 vs. 7.2%, p=0.93 for 26 0/7 to 27 6/7 weeks gestation).~~

~~Components of NDI:~~ (Table 2) ~~The incidence of~~ Cognitive impairment (BSID-III cognitive composite score < 70), gross motor function level ≥ 2, moderate/severe CP, or blindness were similar in both the CPAP and Surfactant treatment groups. The incidences of NDI, cognitive impairment, moderate to severe cerebral palsy and blindness were higher in the lower gestational age compared to the higher gestational age group (Table 3). Infants in the CPAP arm of 24-25 week gestational age group had a lower risk of death or bilateral blindness and a trend towards lower risk of combined death or cognitive impairment and death or moderate/severe cerebral palsy.

Overall 24 surviving infants assessed at 18-22 months corrected age had hearing impairment, 13 of whom had bilateral hearing aids. Compared to Surfactant treated infants, those treated with early CPAP had a significantly increased incidence of hearing impairment (3.5 vs. 1.3%, adjusted p=.03). The incidence of hearing impairment differed in the two gestational age strata, being significantly higher in the CPAP arm among the 24 0/7 to 25 6/7 gestation group (5.5 vs.1.2%, adjusted p=.04) but not among the 26 0/7 to 27 6/7 gestation group (2.3 vs. 1.3%, p=0.36). There was no association between hearing impairment and severe IVH/PVL or NEC, which had a higher incidence in the CPAP arm.

~~There were no significant differences in the risk of death or individual NDI composite outcomes between the CPAP and Surfactant arms for the entire trial cohort. (Table 4) However, in the lower gestational age stratum there was a higher risk of death or bilateral blindness in the Surfactant arm and a trend towards lower risk in the CPAP treatment arm for death or cognitive impairment and death or moderate to severe cerebral palsy.~~

Other outcomes (Table 4): Mean BSID-III composite *cognitive scores* and *composite language scores* were similar in both CPAP and Surfactant arms for the entire follow-up cohort and between CPAP and Surfactant arms in both

Comment [yev28]: The outcomes below were not pre-specified to be part of NDI

Comment [yev29]: Do we need to cite Table 3 again as it is cited at the beginning of this para?

Comment [yev30]: I moved this up and think it is clearer.

Comment [y31]: Marie: Is this true for both higher and lower GA strata? Is there any interaction for hearing impairment between the CPAP/Surf and high/low oxygen saturation groups).

Comment [yev32]: Abhik: Check with Marie re Tables. She looked at models after usual adjustments for CPAP/x hearing impairment with and without NEC and IVH/PVL. When IVH and NEC were added to the model, NEC just missed significance p=.07 as did CPAP p=.059. When both GA strata for CPAP vs Surf were used with NEC, IVH in the model results were NEC p=07, IVH p=.67, CPAP 24-25 wk p=.38, CPAP 26-27 p=.06 So there was a suggestion that NEC contributed but in the higher GA strata.

Comment [ad33]: This statement is unclear. Are you trying to say that the higher incidence could not be explained by these additional factors, i.e., their addition to the model did not change the results?

Comment [ad34]: It may be less confusing to present these results right after the primary outcome for the entire trial cohort, before jumping into outcomes among survivors.

gestational age strata. Mean BSID-III composite *motor scores* , available only on a smaller subgroup (N=276), were likewise similar for the entire follow up cohort and for both gestation strata. Scaled BSID-III scores were also similar in both treatment arms for receptive and expressive language subtests and for fine and gross motor function motor subtests. Median BSID-III composite scores were virtually identical to the mean composite scores for all groups. Composite cognitive, language and motor scores were lower in the 24-25 weeks gestation group compared to the 26-27 week gestation group.

Marie: Need #/% completely Normal [i.e. Cognitive composite score ≥85, GMFCS Normal (B 6=1), Neuro exam normal C 9a=Y), no hearing impairment (B 2b=1) , vision normal (B 1e= 1)] for CPAP/SURF arms of entire cohort and for both GA strata

There were no significant differences between the CPAP and Surfactant arms or within the two gestational age strata in any growth parameter including weight, length, head circumference, weight for age z-score, length for age z-score and head circumference for age z or weight for length z-score.

Readmission rates were also similar (44.7% for CPAP vs. 46% for Surfactant treated children). There were no there significant differences in the use of diuretics, bronchodilators, steroids after discharge between the two groups.

DISCUSSION:

The SUPPORT Trial is the first large multicenter trial that assessed neurodevelopmental outcomes following the use of early CPAP and a limited ventilator strategy with early intubation, surfactant administration, and conventional ventilation in extremely premature (24 0/7 to 26 6/7 week gestational age) infants.

We found no significant difference in the primary, composite outcome of death or NDI at 18-22 months corrected age between those extremely premature infants treated with early CPAP vs. those treated early intubation and surfactant administration. Neither were there differences between the CPAP and Surfactant arms in individual outcomes among survivors assessed at follow up, including NDI,

Comment [y35]: Agree. I put exact scores in first draft so we could all see them.

Comment [WC36]: I would just mention the exact results in the tables.

Abhik: Agree

Comment [ad37]: Do we really need these? Since we don't have significant differences on the big ticket items, should we bother, and do we have space?

Comment [y38]: I think so as neonatologists and ND FUP people will be looking at this paper to see the outcomes in this very vulnerable group and the status of overall "normal" is as important as overall "impaired" in these high risk children. Also normality at 18-22 months is the best predictor of normality later in childhood. The other children are much more likely to change groups between 22 mo and later childhood.

Comment [yev 39]: We could put table in Appendix
Marie:It would be helpful to know what proportion of cohort and GA strata were <10th centile for age for head, length and weight

Comment [y40]: These growth outcomes were in the original tables but I am happy to put them in the growth paper instead.

Comment [ad41]: Does this belong to Tina's secondary?

Comment [WC42]: Morley's trial was also multicenter and copared CPAP vs surf

severe mental impairment (cognitive score < 70), moderate/severe CP, moderate/severe motor impairment (GMFSC ≥2), bilateral blindness, or in mean composite cognitive, language or motor BSID-III scores.

The only significant difference between the CPAP and Surfactant arms was in hearing impairment among survivors assessed at follow up, which was more frequent in the CPAP arm, especially in the lower gestational age stratum. The reasons for this are unclear but possible mechanisms contributing to hearing dysfunction may include changes in middle ear pressure and noise damage to the cochlea. However, the number of affected children was small and there were no differences between the two groups in the incidence of death or hearing impairment among the entire trial cohort.

As reported in previous studies, compared to the more mature infants (26 0/7 to 27 6/7 weeks gestation), the most immature infants (24 0/7 to 25 6/7 weeks gestation) in both CPAP and Surfactant arms were at higher risk for adverse neurodevelopmental outcomes in early childhood including death before 18-22 months, severe cognitive impairment, abnormal gross motor function, moderate/severe cerebral palsy and hearing impairment. (REF)

The strengths of this study include the large number of extremely premature infants enrolled in this national, multicenter trial; the very high percentage of participants who were followed and evaluated in early childhood; as well as the comprehensive and standardized neurodevelopmental evaluation performed. The generalizability of this study may be somewhat limited by the need for antenatal consent which resulted in a trial cohort with higher socioeconomic status than the entire eligible cohort (Ref Wade's paper).

CONCLUSIONS:

We found no significant differences in the incidence death or NDI, NDI only, or moderate/severe cerebral palsy at 18-22 months corrected age between extremely premature infants who were randomized to either early CPAP with a limited ventilation strategy or early intubation with surfactant administration

followed by conventional ventilation. Early CPAP is an effective management strategy for the ELGA infant and is associated with increased survival without increased NDI in the most immature infants.

Figure 1: Patient Flow diagram-CPAP vs. Surfactant

Table 1: Demographic and neonatal characteristics of trial and FUP cohorts-Early CPAP vs. Surfactant treatment arms

Table 2: Pre-specified outcomes and components of NDI for entire cohort and by gestational age strata for Early CPAP vs. Surfactant treatment arms

Table 3: Death and components of NDI for entire cohort and by gestational age strata for Early CPAP vs. Surfactant treatment arms

Table 4: Developmental outcome for entire cohort and by gestational age strata for Early CPAP vs. Surfactant treatment arms

From: Vaucher, Yvonne
To: Wally Carlo, M.D.; Das, Abhik; Myriam Peralta, M.D.; Finer, Neil; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT paper draft: CPAP vs Surf
Date: Sunday, September 11, 2011 2:22:45 AM

Agree re methods.

Yvonne

From: Wally Carlo, M.D. [WCarlo@peds.uab.edu]
Sent: Saturday, September 10, 2011 4:03 PM
To: Das, Abhik; Vaucher, Yvonne; Myriam Peralta, M.D.; Finer, Neil; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT paper draft: CPAP vs Surf

I agree. Much of the methods should be very similar. We can use previous NRN NEJM papers as models in part to solve differences between our two current papers.

Wally

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From: Das, Abhik [mailto:adas@rti.org]
Sent: Saturday, September 10, 2011 2:31 PM
To: Wally Carlo, M.D.; Vaucher, Yvonne; Myriam Peralta, M.D.; Finer, Neil; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT paper draft: CPAP vs Surf

My comments are attached. I think we need as much consistency as possible between the two follow up papers.

Thanks

Abhik

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Tuesday, September 06, 2011 7:14 PM
To: Vaucher, Yvonne; Myriam Peralta, M.D.; Finer, Neil; Gantz, Marie; Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT paper draft: CPAP vs Surf

Forgot to copy Rose.

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From: Wally Carlo, M.D.
Sent: Tuesday, September 06, 2011 6:13 PM
To: 'Vaucher, Yvonne'; Myriam Peralta, M.D.; Finer, Neil; Gantz, Marie; Das, Abhik
Subject: RE: SUPPORT paper draft: CPAP vs Surf

Hi Yvonne, Neil, Myriam, Marie, Abhik and Rose:

Yvonne: Great job on the draft. I really liked the format of Table 1 as suggested by Abhik.

All: I am enclosing comments and tracked suggestions. I think we need to be careful with exploratory analyses and other subgroup analyses. We may want to keep separate the prespecified analyses as the original tables were drafted and add to that selected exploratory analyses.

Wally

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From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]
Sent: Tuesday, September 06, 2011 3:40 PM
To: Wally Carlo, M.D.; Myriam Peralta, M.D.; Finer, Neil; Gantz, Marie; Das, Abhik
Subject: FW: SUPPORT paper draft: CPAP vs Surf

All,
Here is the most recent draft of Early CPAP vs. Surfactant. There are significant differences between the GA strata which I included since the results for the entire cohort were sometimes misleading, particularly when the results were in opposite directions for the GA strata. The 24 0/7-25 6/7 wk gestation are quite different from the 26 0/7 to 27 6/7 wk gestation group. I still need some data.
I would appreciate your comments, ideas, etc. Thanks.

Yvonne

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From: Finer, Neil
To: Gantz, Marie; Wally Carlo, M.D.
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Vaucher, Yvonne; Das, Abhik
Subject: RE: SUPPORT OUTCOMES
Date: Friday, September 09, 2011 2:25:19 PM

Thanks Marie
Can we see these analyses please
The previous analyses still I assume are correct that there is an interaction between Low SpO2 group and Death/ROP in the small strata. Your current analysis would then say that there is no increase in NDI. Thus If I have understood this, there is a significant benefit to Death/ROP in the CPAP/Low SpO2 group?
I would like to see all these analyses
Thanks again
Neil

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Friday, September 09, 2011 10:06 AM
To: Wally Carlo, M.D.; Finer, Neil
Cc: higginsr@mail.nih.gov; Vaucher, Yvonne; Das, Abhik
Subject: RE: SUPPORT OUTCOMES

Neil,

I have looked at the interaction between CPAP, SpO2 target and GA group for survival without NDI and the interaction is not significant (p=.29) which does not support doing subgroup analyses. However, I looked at the groups anyway because of your concern, and there are not significant differences between the CPAP and surfactant groups for the GA 24-25 group within either of the SpO2 targets (and the same is true for the GA 26-27 group).

I have not had time to do a thorough review of the draft papers that have been sent out, but I plan to work on that this afternoon.

Marie

Marie Gantz, Ph.D.
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mgantz@rti.org
919-254-6255

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Saturday, September 03, 2011 8:42 AM
To: nfiner@ucsd.edu; Gantz, Marie
Cc: higginsr@mail.nih.gov; Vaucher, Yvonne; Das, Abhik; wcarlo@peds.uab.edu
Subject: RE: SUPPORT OUTCOMES

Marie, Neil and all.

I have not seen the raw numbers. Is death by itself decreased in the low sat CPAP

group or is the effect all due to ROP? This is important as the ROP effect can be much larger yet the long term significance differs markedly for these outcomes (few ROP babies will be handicapped by it. Have you done the follow data analysis for the small babies?

Wally

-----Original message-----
From: "Finer, Neil" <nfiner@ucsd.edu>
To: "Gantz, Marie" <mgantz@rti.org>
Cc: rose higgins <higginsr@mail.nih.gov>, "Vaucher, Yvonne" <yvaucher@ucsd.edu>, "Das, Abhik" <adas@rti.org>, "wcarlo@peds.uab.edu" <wcarlo@peds.uab.edu>
Sent: Sat, Sep 3, 2011 05:04:48 GMT+00:00
Subject: RE: SUPPORT OUTCOMES

Many thanks Marie
The smaller strata infants are very different from the bigger strata. They have greater mortality and morbidity, more severe illness, and more subsequent handicap
Our concern was and is that since the CPAP infants in lower gestational age strata had less death 8% and less ROP, and the overall SpO2 trial had more deaths 4%, with less ROP. I became concerned that this CPAP group in the low strata had better outcomes in both death and ROP, and wondered if the additional benefit of a low SpO2 in these infants would further decrease ROP. In addition since this CPAP group had 8% less death it was possible that the increase in death from the low SpO2 if it did occur, might still result in an improved overall survival without ROP
This is what you have now found
Here is the concern
The world is now moving to increase the SpO2 acceptable range for all very preterm infants including the 24 -25 week infants because of our findings and that reported from UK and Australia NZ
These other studies did not have a respiratory intervention, and did not start the study oximeter till about 18 hrs.
If the use of CPAP and a permissive strategy actually results in improved survival without ROP, then it is possible that using the low SpO2 strategy with CPAP is the very best approach
Since we did not find more NDI , this would stand
We now need the analyses for survival without NDI evaluating the CPAP vs Surf in the strata comparing hi vs low SpO2 range.
This is vital information
I am doubtful that further studies which are as large as our small strata will never be done and thus our data may be as good as is
ever available
Before the others studies publish their data and recommend that we now raise the SpO2 range for all preterms we need to look at this a carefully as possible. The best conclusion at present may be that the combination of early CPAP and a limited vent strategy with a low SpO2 range is in fact the optimal approach for the most immature infants.
Thanks again and I would ask that you run the groups for survival without NDI to ensure that there is no adverse effect of this combination on later outcome
Be well
Neil

-----Original Message-----
From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Friday, September 02, 2011 3:07 PM
To: Finer, Neil
Cc: rose higgins; Vaucher, Yvonne; Das, Abhik
Subject: RE: SUPPORT OUTCOMES

Neil,

Attached are the analyses you requested.

To fill Abhik in, Neil and Yvonne were looking at the tables for the FU papers and were wondering if there was interaction between CPAP, oximeter and GA group for ROP and ROP/death. I did a quick look at ROP last week and found that there was significant interaction (p=.03) and that for infants with GA 24-25 weeks, those with CPAP had lower ROP, and the difference was very significant within the Low SpO2 group (but not significant in the High group). Neil and Yvonne were very interested in whether the combination of CPAP and Low SpO2 target was protective against ROP in the smaller GA stratum. Neil and Rose both called me this week to ask if I would also look at death/ROP to see if the results were similar. For death/ROP, the interaction between CPAP, oximeter and GA had a p value of .10, so I again ran the models separately for each GA group. Similar to the results for ROP, infants with GA 24-25 weeks had less ROP/death in the CPAP group, and that difference was very significant within the Low SpO2 group. I also looked at the interaction for the outcome of death, but it was not significant (p=.44) so I did not do sub-analyses.

I think this is very interesting, but what are the implications given that there was greater death in the Low SpO2 group in both GA strata, regardless of CPAP or surfactant use (although the difference in death was only significant when the SUPPORT population was analyzed as a whole)?

Marie

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-----Original Message-----
From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Friday, September 02, 2011 2:08 PM
To: Gantz, Marie
Cc: rose higgins; Vaucher, Yvonne
Subject: SUPPORT OUTCOMES

Hi Marie
Will you be able to get us any data this week??
I would like to work on this over the long weekend Thanks Neil

From: Stevens, Timothy
To: Higgins, Rosemary (NIH/NICHD) [E]; "Das, Abhik"
Subject: Breathing Outcomes
Date: Wednesday, September 07, 2011 8:47:06 PM

Hi Rose and Abhik,

I hope the analysis of the neurodevelopmental outcome of patients in SUPPORT is going well.

Will you be able to analyze data on the Breathing Outcomes of these patients in time for a PAS submission?

Thanks

Tim

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Cc: "yvaucher@ucsd.edu"; "nfiner@ucsd.edu"
Subject: Fw: SUPPORT paper draft: CPAP vs Surf
Date: Wednesday, September 07, 2011 8:31:45 AM
Attachments: SUPPPORT CPAP FUPNF Rev Sept 06 2011 NFYEVMostrecent revision2.docx
Figure Patient CPAPSurf Flow chartYEV082311.doc
Table 1 CPAPDemo09052011.docx
Table 2 NDIOutcomesALL09052011.docx
Table 2cont GA Comparison NDI Outcomes.docx
Table 3abcDeathNDIComponentsGAComp090511.docx
Table4 ContinNeuromotorALL09052011.docx

Stephanie
Can you fix the boilerplate and title page and send to Yvonne/Neil?
Thanks
Rose

From: Vaucher, Yvonne <yvaucher@ucsd.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tue Sep 06 16:34:37 2011
Subject: SUPPORT paper draft: CPAP vs Surf

Rose,
Here is the most recent draft of Early CPAP vs. Surfactant. There are significant differences between the GA strata which I included since the results for the entire cohort were sometimes misleading, particularly when the results were in opposite directions for the GA strata. The 24 0/7-25 6/7 wk gestation are quite different from the 26 0/7 to 27 6/7 wk gestation group.
Please distribute to subcommittee for comments, ideas, etc. Thanks.

Yvonne

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Early CPAP versus Surfactant in Extremely Preterm Infants: Neurodevelopmental Outcome in Early Childhood

Yvonne E. Vaucher, M.D., M.P.H.[1],.....

[1] University of California San Diego, San Diego, California, United States; Eunice Kennedy Shriver National Institue of Child Health and Human Development (NICHD), Bethesda, Maryland, United States

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ABSTRACT

BACKGROUND

The recent randomized, multicenter SUPPORT trial demonstrated that initial treatment with early, non-invasive CPAP is an alternative to early surfactant administration after intubation and is associated with similar rates of death or BPD in infants born at 24 0/7 to 27 6/7 weeks gestation. We hypothesized that, compared to treatment with surfactant administration after intubation, treatment with early CPAP would result in decreased mortality or neurodevelopmental impairment.

METHODS

We followed 1108 infants, 24 0/7 to 27 6/7 weeks gestation, who had been randomized in the SUPPORT trial to receive either CPAP with limited ventilation after delivery or intubation with surfactant administration within one hour after birth. A standardized neurodevelopmental assessment was performed at 18-22 months corrected age. The pre-specified, composite outcomes were death or neurodevelopmental impairment (NDI), NDI, or moderate/severe cerebral palsy. NDI was defined as a cognitive score < 70, Gross Motor Function Classification score of ≥ 2, moderate/severe cerebral palsy, bilateral blindness or permanent hearing impairment.

RESULTS

Death or NDI was determined for 1233/1316 (93.7%) of infants enrolled in SUPPORT and 93.5% of known survivors (989/1058) were evaluated at 18-22 months corrected age. Death or NDI occurred in 28% (174/621) of the CPAP group and in 29.7% (182/612) of the Surfactant group (p=0.44). Rates of NDI alone (CPAP-11.1 vs. Surf-8.9%, p=0.32), and moderate/severe cerebral palsy (CPAP-4.1

vs. Surf-4.0%, p=0.81) were similar in both treatment arms. In the most immature stratum (24 0/7-25-6/7 weeks gestation) there were fewer deaths [CPAP-26.5% (73/276) vs. Surf-35.7% (117/264), p=0.022] but a higher rate of hearing impairment [CPAP-5.5% (11/201) vs. Surf-1.2% (2/171), p=0.043] in the CPAP treatment arm.

CONCLUSION

We found no significant differences in the incidence death or NDI, NDI only, or moderate/severe cerebral palsy at 18-22 months corrected age between extremely premature infants who were randomized to receive either early CPAP with a limited ventilation strategy or early intubation with surfactant administration followed by conventional ventilation.

BACKGROUND

The recent, multicenter, randomized, controlled (SUPPORT) trial demonstrated that treatment with non-invasive CPAP shortly after birth is an alternative to surfactant administration after intubation and is associated with similar rates of death or BPD in extremely premature infants born at 24 0/7 to 27 6/7 weeks gestation (REF Finer). Early CPAP was also associated with less frequent need for postnatal steroids, shorter duration of mechanical ventilation, and similar rates of air leak and IVH compared with surfactant, all factors associated with adverse ND outcome in ELBW/ELGA infants. In addition, mortality was lower in the most immature, 24-25 week gestation stratum.

The SUPPORT study was in initially designed and powered to evaluate early childhood neurodevelopmental outcome of enrolled infants. We hypothesized that compared to treatment with surfactant administration after intubation, treatment with early, non-invasive CPAP and a limited ventilation strategy would result in decreased mortality or neurodevelopmental impairment at 18-22 months corrected age.

METHODS

Study design

1316 infants, 24 0/7 to 27 6/7 weeks gestation, born at 20 participating NICHD Neonatal Research Network sites between February 2005 through February 2009, from whom antenatal consent had been obtained, were enrolled immediately following delivery in the prospective, randomized, controlled SUPPORT trial. The study randomized infants to receive either CPAP immediately following delivery and a limited ventilation strategy if subsequent intubation was required or surfactant within an hour after birth. There were two gestational age stratum, (24 0/7-25 6/7 or 26 0/7 to 27 6/7 weeks). In addition, using a 2X2 factorial design, all infants were randomly assigned to either higher (91-95%) or lower (85-89%) ranges of pulse modified oximeters until supplemental oxygen was no longer needed or until the infant reached 36 weeks corrected gestational age. (REF NEJM Finer,Carlo) Details of the SUPPORT study protocol have been previously

described. (REF NEJM Finer,Carlo) The pre-specified outcomes of SUPPORT at 18-22 months corrected age were the incidence of cerebral palsy, the incidence of neurodevelopmental impairment (NDI), and the combined incidence of mortality or NDI. The study was approved by the human subjects committee at each participating site and at RTI International which is the data center for the Neonatal Research network. Data collected at participating centers were transmitted to RTI International which stored, managed and analyzed the data for this study.

Study population

From February 2005-February 2009, 1316 infants at 20 neonatal tertiary care centers in the United States participating in the NICHD Neonatal Research Network (NRN) were enrolled in the SUPPORT Trial. Surviving infants were enrolled at 36 weeks adjusted age in the prospective follow-up cohort. A comprehensive neurodevelopmental assessment was performed at 18-22 months corrected age (CA) by examiners unaware of study intervention assignment (CPAP vs. Surfactant). Developmental function was assessed using the Bayley Scales of Infant Development-III (BSID III) (REF); neurologic function was assessed using a standardized neurologic exam, motor function was determined using the Gross Motor Function Classification Scale (GMFCS)(REF); neurosensory outcome was determined based on parental history and examination. Examiners from each center were centrally trained and certified annually to assure standardization in psychometric and neurologic test administration.

The initial 2/3 of the cohort (N=713) were administered only the cognitive and motor scales of the BSID-III; the composite motor scale of the BSID-III was included for the final one third of the participants (N=275). BISD-III cognitive, language and motor standardized scores are presented as composite scores with a mean of 100 and a standard deviation of 15.

Study definitions

Neurodevelopmental impairment (NDI), was defined by the presence of at least one of the following: BSID III cognitive composite score < 70; a GMFCS of ≥ 2, the presence of moderate/severe CP, blindness (< 20/200 bilaterally), or permanent hearing loss interfering with the ability to understand or communicate despite amplification with hearing aids or cochlear implants.

Comment [y1]: Are we defining hearing impairment as "permanent" or not for inclusion in the NDI? We do not know the "permanent" status of 11 children with "hearing impairment" but no amplification. They are included in the 7/29/11 NDI analyses so at present we are including any hearing impairment, permanent or not, amplification or not. Either way will not change the significance since the predominance is in the CPAP arm but we need to be consistent in our description/inclusion either way.

Moderate/severe cerebral palsy was determined by a neurologic examination compatible with cerebral palsy and a GMFCS or ≥2.

Statistical analysis:

The sample size for the pre-specified, composite outcome of death or NDI was based upon NRN outcome data from the year 2000 and assumed a rate of death or survival with NDI at 18-22 months CA of 50%. The study was powered to detect a 10% difference in the pre-specified outcome of Death or NDI. The sample size was increased to allow for multiple births and a 17% loss-to-follow-up rate.

Comment [y2]: Barbara is this power description correctly phrased?

Additional pre-specified outcomes of the SUPPORT study included the incidence of NDI or cerebral palsy at 18-22 mo corrected age.

Bivariate analyses were performed to compare demographic and neonatal characteristics and neurodevelopmental outcomes. Demographic and neonatal variables included gestational age, birthweight, gender, multiple gestation, small for gestational age status, race/ethnicity, insurance status, marital status, maternal education, and household income, English as primary language, living with biologic parents at discharge, severe ROP (Stage3, threshold , ± surgery), BPD (physiologic definition), medical or surgical NEC (modified Bell's ≥ Stage 2), late onset sepsis, severe (Grades 3-4) IVH/cystic PVL, and receipt of antenatal and/or postnatal steroids. (Ref definitions ROP,BPD,NEC,IVH/PVL) Chi square was used for categorical variables and ANOVA for continuous variables. Multiple and logistic regression analyses were performed using_____. A p value of < 0.05 was considered significant. Unless otherwise noted, all p values in this report are adjusted for center, gestational age and familial clustering.

Comment [y3]: Maria please elaborate here as to models, etc.

RESULTS

All survivors at 36 weeks adjusted age (N=1108/1316) were enrolled at discharge in the prospective SUPPORT follow-up cohort. (See Figure 1) Sixty-nine children (6.2%) were lost to FUP. Fifty children were known to have died after 36 weeks adjusted age and before 18-22 months. The survival status of 48/69 children who were LTFU was unknown. A neurodevelopmental assessment at 18-22 months corrected age was performed for 989/1079 (91.7%) children known to be alive during the assessment interval. Of those who were seen for their 18-22 mo ND exam, NDI was determined for 975 children; 16 children were seen but had an incomplete evaluation that precluded assigning a NDI status. Ultimately, the pre-specified outcome, death or NDI, was determined for 93.6% of the eligible cohort. There was no difference in the FUP rate between the CPAP and Surfactant arms (93.4 vs 93.4%) of the trial.

Comment [y4]: this # will change with new data)

Compared with mothers of the 989 children who had a ND assessment at 18-22 months, mothers of 69 children LTFU were less likely to be married (30 vs 47%, p=0.008), and more likely to have public insurance (70 vs 52%, p=0.006) and less likely to have completed high school (75 vs 63%, p=0.04). No other demographic variables or neonatal characteristics were different between the groups.

Demographics and neonatal characteristics:

Trial Cohort: There were no significant differences between the CPAP and Surfactant trial arms in the incidence of death before discharge, severe IVH/ PVL, sepsis, severe ROP in survivors, medical or surgical NEC, BPD or late onset sepsis. BW, GA, gender, race/ethnicity, multiple birth, mode of delivery, insurance status, maternal education, English as the primary language, household income were also similar in the both groups. Compared to the Surfactant arm, infants in the in the CPAP arm were less likely to be SGA (5.6 vs 9%, unadjusted p=0.016) and less likely to have been exposed to postnatal steroids (7.2 vs 13.2 %, unadjusted p=0.0005). There was a trend towards fewer deaths before 18-22 months corrected age in the CPAP arm (18.5 vs. 22.2%, adjusted p=0.1). This difference reached significance in the lower 24 0/7 to 25 6/7 weeks gestation stratum (26.4 vs. 35.7%, unadjusted p=0.02), but not in the higher gestational age stratum 12.4 vs. 12%). The 24 0/7 to 25 6/7 weeks gestation stratum of the CPAP arm also had

less ROP compared to the Surfactant arm (22.2 vs. 31.6%, unadjusted p=0.042) whereas the reverse occurred in the 26 0/7 to 27 6/7 weeks gestation stratum (7.3 vs. 10.2%, unadjusted p=0.044).

Follow-Up Cohort: (Table 1)There were no significant differences between the CPAP and Surfactant trial arms in the incidence of death before discharge, SGA status, sepsis, ROP in survivors, or LOS. BW, GA, gender, race/ethnicity, multiple birth, mode of delivery, insurance status, maternal education, English as the primary language, household income were also similar in the both groups. Compared to the Surfactant arm, infants in the in the CPAP arm were more likely to be have Grade 3-4 IVH or cystic PVL (13.7 vs 9.6%, unadjusted p=0.05) and more likely to have modified Bell's Stage ≥ 2, medical or surgical NEC (11 vs 6.3%, unadjusted p=0.009). Infants in the CPAP arm were less likely to have been exposed to postnatal steroids (6.7 vs 11.4%, unadjusted p=0.01.)

Pre-specified outcomes: (Tables 2 and 3) The mean corrected age at neurodevelopmental assessment was similar for both treatment arms (CPAP 20 ± 2.4 mo, Surf 20.1 ± 2.7 mo, p=0.34). There was no significant difference in the composite outcome of *death or NDI* at 18-22 month corrected age between the CPAP and surfactant arms in the entire cohort (28.8 vs. 29.8%) or for the either of the two gestational age strata (40.1 vs. 44.3% for 24 0/7-25 6/7 weeks gestation; 18.6 vs. 18.7% for 26 0/7 to 27 6/7 weeks gestation).

For the entire cohort there was there were no significant difference between the CPAP and Surfactant arms in the incidence of *NDI* (11.1 vs. 8.9%, adjusted p=0.33) or in either of the two gestational age strata (18.1 vs. 12.0, p=0.16 for 24 0/7-25 6/7 weeks gestation; 6.6 vs. 7.2%, p=0.93 for 26 0/7 to 27 6/7 weeks gestation).

Likewise for the entire cohort there were no significant differences between the CPAP and Surfactant arms in the incidence of *moderate/severe cerebral palsy* for the entire cohort (4.1 vs. 4%, adjusted p=0.82) or for either of the two gestational age strata (7 vs. 4.7, p=0.52 for 24 0/7-25 6/7 weeks gestation; 6.6 vs. 7.2%, p=0.93 for 26 0/7 to 27 6/7 weeks gestation).

Components of NDI: (Table 2) The incidence of cognitive impairment (BSID-III cognitive composite score < 70) (7.2% vs. 7.6%), gross motor function level ≥ 2 (5.1 vs. 4.8%), moderate/severe CP (4.1 vs. 4.0%), or blindness (0.8 vs. 1.5%) were similar in both the CPAP and Surfactant treatment groups. Although the incidences of NDI, cognitive impairment, moderate to severe cerebral palsy and blindness were higher in the lower gestational age compared to the higher gestational age group, there were no significant differences between the trial arms in either group. (Table 3)

Overall 24 infants had hearing impairment, 13 of whom had bilateral hearing aids. Compared to Surfactant treated infants, those treated with early CPAP had a significantly increased incidence of hearing impairment (3.5 vs. 1.3%, adjusted p=.027). The incidence of hearing impairment differed in the two gestational age strata, being significantly higher in the CPAP arm of the 24 0/7 to 25 6/7 gestation group (5.5 vs.1.2%, adjusted p=.043) but not in 26 0/7 to 27 6/7 gestation group (2.3 vs. 1.3%, p=0.36). There was no association between hearing impairment and severe IVH/PVL or NEC, which had a higher incidence in the CPAP arm.

Comment [y5]: Marie: is this true for both higher and lower GA strata? Is there any interaction for hearing impairment between the CPAP/Surf and high/low oxygen saturation groups).

There were no significant differences in the risk of death or individual NDI composite outcomes between the CPAP and Surfactant arms for the entire cohort. (Table 4) However, in the lower gestational age stratum there was a higher risk of death or bilateral blindness in the Surfactant arm and a trend towards lower risk in the CPAP treatment arm for cognitive composite score < 70 and moderate to severe cerebral palsy.

Other outcomes (Table 5): Mean BSID-III composite *cognitive scores* were similar in both CPAP and Surfactant arms for the entire FUP cohort (91.3 ± 0.74 vs. 90.4 ± 0.75) as well as for the 24 0/7 to 25 6/7 week (89.2 ± 1.1 vs. 88.2 ± 1.2) and 26 0/7 to 27 6/7 week (93.4 ± 0.9 vs. 92.6 ± 0.9) gestational age strata. Mean BISD-III composite *language scores* were likewise similar between the CPAP and Surfactant groups for the entire cohort (86.1 ± 0.9 vs 85.6 ± 0.9); for the 24 0/7 to 25 6/7 week gestation stratum (84.3 ± 1.3 vs 83 ± 1.4) and for the 26 0/7 to 27 6/7 week gestation stratum (88 ± 1.1 vs 87.9 ± 1). Mean BSID-III composite *motor scores* obtained for the smaller cohort (N=276) were also similar for the entire

cohort (88.2 ± 1.5 vs 88.5 ± 1.4); for the 24 0/7 to 25 6/7 week gestation stratum (82.8 ± 2.2 vs 83 ± 2.2); and for the 26 0/7 to 27 6/7 week gestation stratum (93.4 ± 1.8 vs 92.2 ± 1.7). Scaled BSID-III scores were also similar for receptive and expressive language subtests and for fine and gross motor function motor subtests. Median BSID-III composite scores were virtually identical to the mean composite scores for all groups.

Marie: Need #/% completely Normal [i.e. Cognitive composite score ≥85, GMFCS Normal (B 6=1), Neuro exam normal C 9a=Y), no hearing impairment (B 2b=1) , vision normal (B 1e= 1)] for CPAP/SURF arms of entire cohort and for both GA strata

There were no significant differences between the CPAP and Surfactant arms or within the two gestational age strata in any growth parameter including weight, length, head circumference, weight for age z-score, length for age z-score and head circumference for age z or weight for length z-score.

Comment [yev 6]: We could put table in Appendix
Marie It would be helpful to know what proportion of cohort and GA strata were <10th centile for age for head, length and weight.

Readmission rates were also similar (44.7% for CPAP vs. 46% for Surfactant treated children). There were no there significant differences in the use of diuretics, bronchodilators, steroids after discharge between the two groups.

DISCUSSION:

The SUPPORT Study is the first large multicentered trial comparing the use of early CPAP and a limited ventilator strategy with early intubation, surfactant administration and conventional ventilation in extremely premature (24 0/7 to 26 6/7 week gestational age) infants.

We found no significant difference in the pre-specified, composite outcome of death or NDI at 18-22 months corrected age between those extremely premature infants treated with early CPAP vs. those treated early intubation and surfactant administration. Neither were there differences between the CPAP and Surfactant arms in individual outcomes including NDI, severe mental impairment (cognitive score < 70), moderate/severe CP, moderate/severe motor impairment (GMFSC ≥2), bilateral blindness, or in mean composite cognitive, language or motor BSID-III scores.

The only significant difference between the CPAP and Surfactant arms was in hearing impairment which was more frequent in the CPAP arm, especially in the lower gestational age stratum. The reasons for this are unclear but possible mechanisms contributing to hearing dysfunction may include changes in middle ear pressure and noise damage to the cochlea. However, the number of affected children was small and this finding needs to be further explored and confirmed by other large RCT comparing these alternative treatments.

As reported in previous studies, compared to the more mature infants (26 0/7 to 27 6/7 weeks gestation), the most immature infants (24 0/7 to 25 6/7 weeks gestation) in both CPAP and Surfactant arms were at higher risk for adverse neurodevelopmental outcomes in early childhood including death before 18-22 months, severe cognitive impairment, abnormal gross motor function, moderate/severe cerebral palsy and hearing impairment. (REF)

The strengths of this study include the large number of extremely premature infants enrolled in this national, multicenter trial; the very high percentage of participants who were followed and evaluated in early childhood; as well as the comprehensive and standardized neurodevelopmental evaluation performed. The generalizability of this study may be somewhat limited by the need for antenatal consent which resulted in a trial cohort with higher socioeconomic status than the entire eligible cohort (Ref Wade's paper).

CONCLUSIONS:

We found no significant differences in the incidence death or NDI, NDI only, or moderate/severe cerebral palsy at 18-22 months corrected age between extremely premature infants who were randomized to either early CPAP with a limited ventilation strategy or early intubation with surfactant administration followed by conventional ventilation. Early CPAP is an effective management strategy for the ELGA infant and is associated with increased survival without increased NDI in the most immature infants.

Figure 1: Patient Flow diagram-CPAP vs. Surfactant

Table 1: Demographic and neonatal characteristics of trial and FUP cohorts-Early CPAP vs. Surfactant treatment arms

Table 2: Pre-specified outcomes and components of NDI for entire cohort and by gestational age strata for Early CPAP vs. Surfactant treatment arms

Table 3: Death and components of NDI for entire cohort and by gestational age strata for Early CPAP vs. Surfactant treatment arms

Table 4: Developmental outcome for entire cohort and by gestational age strata for Early CPAP vs. Surfactant treatment arms

Figure: Patient Flow Diagram: CPAP vs. Surfactant

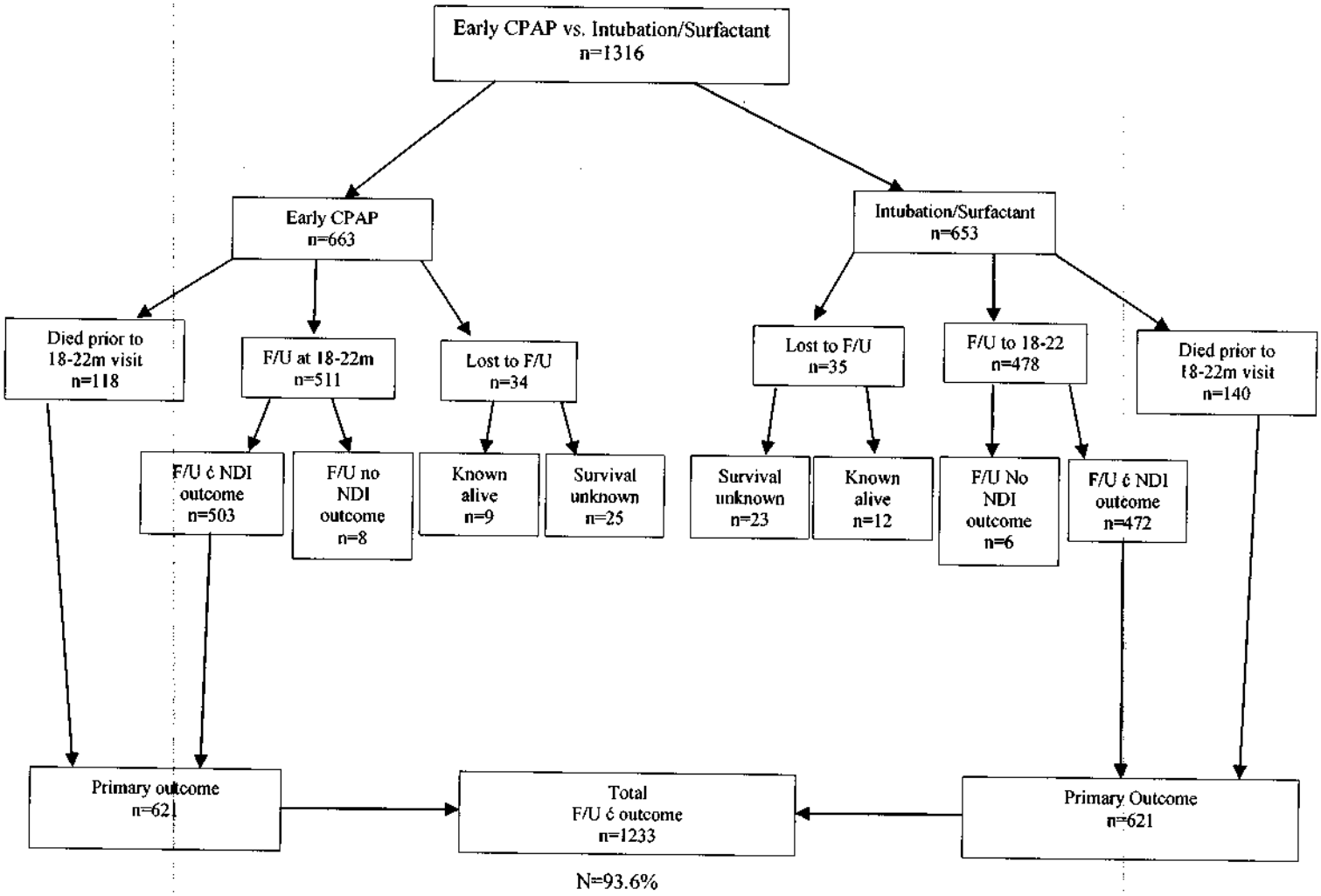

Table 1: Demographics and Characteristics of Trial Cohort and Follow-up Cohorts

	Trial Cohort		Follow-up Cohort	
	CPAP	SURFACTANT	CPAP	SURFACTANT
Total enrollment	N=663	N=653	N=511	N=478
Birth weight (grams)*	835±188	825±198	849±186	853±193
Gestational age (weeks)*	26.2±1.1	26.2±1.1	26.3±1.1	26.3±1.1
Small for gestational age < 10, #./total # (%)	37/663(5.6)	59/653(9)**	23/511(4.5)	32(478(6.7)
Male, #/total # (%)	342/663(51.6)	370/653(56.7)	256/511(50.1)	265/478(55.4)
Race				
Non-Hispanic White, #/total # (%)	250/663(39.1	271/653(41.5)	196/511(38.4)	199/478(41.6)
Non-Hispanic Black, #/total # (%)	254/663(38.3)	235/653(36)	200/511(39.1)	177/478(37)
Hispanic, #/total # (%)	138/663(20.8)	121/653(18.5)	98/511(19.2)	85/478(17.8)
Other or unknown, #/total # (%)	21/663(3.2)	26/653(4)	17/511(3.3)	17/478(3.6)
Multiples, #/total # (%)	178/663(26.8)	159/653(24.3)	138/511(27)	114/478(23.8)
Antenatal steroids(any), #/total # (%)	642/663(96.8)	623/652(95.6)	493/511(96.5)	455/478(95.2)

Cesarean section, #/total # (%)	449/663(67.7)	434/653(66.5)	352/511(68.9)	314/478(65.7)
Public health insurance only, #/total # (%)	351/661(53.1)	353/649(54.4)	262/511(51.3)	256/478(53.6)
Mother married, #/total # (%)	305/662(46.1)	287/651(44.1)	244/511(47.7)	221/478(46.2)
With both biological parents, #/total # (%)	365/539(67.7)	353/516(68.4)	348/510(68.2)	328/478(68.6)
Maternal education < 12, #/total # (%)	161/616(26.1)	152/590(25.8)	128/506(25.3)	115/468(24.6)
Income < $30,000/year†, #/total # (%)	270/514(52.5)	268/488(54.9)	260/493(52.7)	250/460(54.3)
English as primary language, #/total # (%)	427/511(83.6)	403/478(84.3)	426/510(83.5)	402/477(84.3)
Severe ROP, #/total # (%)no. (%)	67/511(13.1)	65/473(13.7)	62/479(12.9)	58/434(13.4)
Bronchopulmonary dysplasia§, #/total # (%)	223/569(39.2)	219/539(40.6)	193/511(37.8)	186/478(38.9)
IVH grade 3-4/PVL¶, #/total # (%)	111/642(17.3)	87/628(13.9)	70/510(13.7)	46/477(9.6)*
NEC-stage ≥2 ,#/total # (%)	83/654(12.7)	63/636(9.9)	56/511(11)	30/478(6.3)***
Late onset sepsis/meningitis,#/total # (%)	224/634(35.3)	230/624(36.9)	167/511(32.1)	153/478(32)
Postnatal steroids, #/total # (%)	47/649(7.2)	83/631(13.2)***	34/508(6.7)	54/475(11.4)**
Died before discharge, #/total # (%)	109/663(16.4)	128/653(19.6)		
Died before 18-22 months, #/total # (%)			118/638(18.5)	140/630(22.2)

*Plus-minus values are used for mean ±SD

†Not available for trial cohort at time of discharge

*p<0.05, **p<0.02,***p,0.001

*Results presented as number/total number (%); All values adjusted for stratification factors (study center and gestational-age group) and familial clustering.

Table 2: SUPPORT Death and NDI Outcomes at 18-22 Months Corrected Age*

	CPAP	SURFACTANT	aRR	p
a. Entire cohort:CPAP vs. Surfactant				
Death before 18-22 mo CA	118/638(18.5)	140/630(22.2)	0.83(0.67,1.03)	0.10
Outcome determined for death or NDI	621/663(93.7)	612/653(93.7)	1(0.97,1.03)	0.92
Death or NDI	174/621(28)	182/612(29.7)	0.94(0.79,1.11)	0.44
NDI	56/503(11.1)	42/472(8.9)	1.21(0.82,1.78)	0.33
BSID-III cognitive composite score < 70	36/502(7.2)	36/471(7.6)	0.95(0.61,1.49)	0.83
Gross motor function level ≥ 2	26/511(5.1)	23/478(4.8)	0,98(0.57,1.69)	0.95
Moderate/severe cerebral palsy	21/511(4.1)	19/478(4)	0.93(0.51,1.71)	0.82
Blindness, bilateral	4/511*0.8)	7/478(1.5)	0.53(0.16,1.78)	0.3
Hearing impairment	18/511(3.5)	6/478(1.3)	2.8(1.1-6.9)	0.03

*Results presented as, number/total number (%); Relative risk adjusted for stratification factors (study center and gestational-age group) and familial clustering.

**Mean ± SD (N=989)

Table 2(cont): NDI Outcomes at 18-22 Months Corrected Age* for 24 0/7 to 25 6/7 weeks GA

	CPAP	SURFACTANT	aRR	p
b. 24 0/7-25 6/7 weeks Gestational Age				
Death before 18-22 mo CA	73/276(26.4)	97/272(35.7)	0.74(0.57,0.96)	0.02
Death/NDI determined	272/285(95.4)	264/280(94.3)	1.01(0.97,1.05)	0.55
NDI or death	109/272(40.1)	117/264(44.3)	0.9 (0.74,1.1)	0.33
NDI	36/199(18.1)	20/167(12)	1.44(0.86,2.39)	0.16
BSID-III cognitive composite score < 70	23/198(11.6)	16/166(9.6)	1.16(0.64,2.11)	0.63
Gross motor function level ≥ 2	17/201(8.5)	9/171(5.3)	1.51(0.7,3.28)	0.30
Moderate/severe cerebral palsy	14/201(7.0)	8/171(4.7)	1.32(0.57,3.03)	0.52
Blindness, bilateral	2/201(1.0)	2/171(1.2)	0.85(0.12,5.99)	0.87
Hearing impairment	11/201(5.5)	2/171(1.2)	4.83(1.05,2.21)	0.04

	CPAP	SURFACTANT	aRR*	p
c. <u>26 0/7-27 6/7 weeks Gestational Age</u>				
Death before 18-22 mo CA	45/362(12.4)	43/358(12.0)	1.04(0.7,1.54)	0.85
Death/NDI determined	349/378(92.3)	348/373(93.3)	.99(0.95,1.03)	0.58
NDI or death	65/349(18.6)	65/848(18.7)	1 (0.73,1.37)	0.99
NDI	20/304(6.6)	22/305(7.2)	0.97(0.53,1.79)	0.93
BSID-III cognitive composite score < 70	13/304(4.3)	20/305(6.6)	0.74(0.36,1.51)	0.41
Gross motor function level ≥ 2	9/310(2.9)	14/307(4.6)	0.61(0.27,1.4)	0.24
Moderate/severe cerebral palsy	7/310(2.3)	11/307(3.6)	0.62(0.24,1.58)	0.31
Blindness, bilateral	2/310(0.6)	5/307(1.6)	0.39(0.08,1.99)	0.23
Hearing impairment	7/310(2.3)	4/307(1.3)	1.75(0.53,5.79)	0.36

*adjusted for familial clustering, center(except for blindness due to small N)

Table 3:

CPAP vs. Surfactant- Death and Components of NDI for entire cohort and gestational age strata

a. Entire cohort: CPAP vs. Surfactant

Death or cognitive composite<70	154/620(24.8)	176/611(28.8)	0.86(0.72,1.03)	0.11
Death or GMF level ≥2	144/629(22.9)	163/618(26.4)	0.87(0.72,1.05)	0.15
Death or moderate/severe CP	139/629(22.1)	159/618(25.7)	0.86(0.71,1.04)	0.13
Death or blind in both eyes	122/629(19.4)	147/618(23.8)	0.82(0.67,1.01)	0.07
Death or hearing impairment	136/629(21.6)	146/618(23.8)	0.84(0.68,1.03)	0.09

b. <u>24 0/7-25 6/7 weeks Gestational Age</u>

Death or cognitive composite<70	96/271(35.4)	113/263(43.0)	0.82(0.67,1.02)	0.071
Death or GMF level ≥2	90/274(32.8)	106/268(39.6)	0.83(0.67,1.04)	0.108
Death or moderate/severe CP	75/274(27.4)	105/268(36.9)	0.81(0.65,1.02)	0.074
Death or blind in both eyes	75/274(27.4)	99/268(36.9)	0.75(0.58,0.96)	0.023
Death or hearing impairment	84/274(30.7)	99/368(36.9)	0.83(0.65,1.06)	0.134

c. 26 0/7-27 6/7 weeks Gestational Age

Death or cognitive composite<70	58/349(16.6)	63/348(18.1)	0.93(0.67,1.29)	0.670
Death or GMF level ≥2	54/355(15.2)	57/350(16.3)	0.94(0.67,1.33)	0.738
Death or moderate/severe CP	52/355(14.6)	54/350(25.7)	0.96(0.68,1.36)	0.816
Death or blind in both eyes	47/355(13.2)	48/350(13.7)	0.97(0.67,1.42)	0.889
Death or hearing impairment	52/355(14.6)	47/350(13.4)	1.09(0.76,1.58)	0.632

Table 4: Developmental Outcomes at 18-22 months Corrected Age

	CPAP	SURF	RR	p
Cognitive Composite score (mean±SEM)	91±0.74	90±0.75	0.88(-0.98, 2.75)	0.35
Language composite score (mean±SEM)	86±0.87	86±0.88	0.49(-1.71, 2.69)	0.66
Composite motor score (mean±SEM)	88±1.45	88±1.38	0.67(-321, 4.54)	0.72
Cognitive Composite score < 70*	36/502(7.2)	36/471(7.6)	0.95(0.61, 1.49)	0.83
Language composite score <70*	73/479(14.7)	80/462(17.3)	0.84 (0.63, 1.13)	0.26
Composite motor score < 70*	16/135(11.9)	18/141(12.8)	0.91(0.5, 1.65)	0.76

* number/total number (percent)

From: Vaucher, Yvonne
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: SUPPORT paper draft: CPAP vs Surf
Date: Tuesday, September 06, 2011 7:17:28 PM
Attachments: SUPPPORT CPAP FUPNF Rev Sept 06 2011 NFYEVMostrecent revision2.docx
Figure Patient CPAPSurf Flow chartYEV082311.doc
Table 1 CPAPDemo09052011.docx
Table 2 NDIOutcomesALL09052011.docx
Table 2cont GA Comparison NDI Outcomes.docx
Table 3abcDeathNDIComponentsGAComp090511.docx
Table4 ContinNeuromotorALL09052011.docx

Since you were OOT I sent the draft directly to the subcommittee.

Yvonne

From: Vaucher, Yvonne
Sent: Tuesday, September 06, 2011 1:40 PM
To: Wally Carlo, M.D.; Myriam Peralta, M.D.; Finer, Neil; 'Gantz, Marie'; Das, Abhik
Subject: FW: SUPPORT paper draft: CPAP vs Surf

All,

Here is the most recent draft of Early CPAP vs. Surfactant. There are significant differences between the GA strata which I included since the results for the entire cohort were sometimes misleading, particularly when the results were in opposite directions for the GA strata. The 24 0/7-25 6/7 wk gestation are quite different from the 26 0/7 to 27 6/7 wk gestation group. I still need some data. I would appreciate your comments, ideas, etc. Thanks.

Yvonne

Yvonne E. Vaucher, M.D., M.P.H.
Division of Neonatal/Perinatal Medicine
Clinical Professor of Pediatrics
UCSD School of Medicine

tele: 619-543-3759
FAX: 619-543-3812

From: Finer, Neil
To: Gantz, Marie; Wally Carlo, M.D.
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Vaucher, Yvonne; Das, Abhik
Subject: RE: SUPPORT OUTCOMES
Date: Tuesday, September 06, 2011 1:39:42 PM

Thanks Marie
Neil

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Tuesday, September 06, 2011 6:15 AM
To: Wally Carlo, M.D.; Finer, Neil
Cc: higginsr@mail.nih.gov; Vaucher, Yvonne; Das, Abhik
Subject: RE: SUPPORT OUTCOMES

Neil and Wally, I am in meetings most of today, but I will look into your questions as soon as I am able and get back to you in the next couple of days.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Saturday, September 03, 2011 8:42 AM
To: nfiner@ucsd.edu; Gantz, Marie
Cc: higginsr@mail.nih.gov; Vaucher, Yvonne; Das, Abhik; wcarlo@peds.uab.edu
Subject: RE: SUPPORT OUTCOMES

Marie, Neil and all.

I have not seen the raw numbers. Is death by itself decreased in the low sat CPAP group or is the effect all due to ROP? This is important as the ROP effect can be much larger yet the long term significance differs markedly for these outcomes (few ROP babies will be handicapped by it. Have you done the follow data analysis for the small babies?

Wally

-----Original message-----
From: "Finer, Neil" <nfiner@ucsd.edu>
To: "Gantz, Marie" <mgantz@rti.org>
Cc: rose higgins <higginsr@mail.nih.gov>, "Vaucher, Yvonne" <yvaucher@ucsd.edu>, "Das, Abhik" <adas@rti.org>, "wcarlo@peds.uab.edu" <wcarlo@peds.uab.edu>
Sent: Sat, Sep 3, 2011 05:04:48 GMT+00:00
Subject: RE: SUPPORT OUTCOMES

Many thanks Marie

The smaller strata infants are very different from the bigger strata. They have greater mortality and morbidity, more severe illness, and more subsequent handicap
Our concern was and is that since the CPAP infants in lower gestational age strata had less death 8% and less ROP, and the overall SpO2 trial had more deaths 4%, with less ROP. I became concerned that this CPAP group in the low strata had better outcomes in both death and ROP, and wondered if the additional benefit of a low SpO2 in these infants would further decrease ROP. In addition since this CPAP group had 8% less death it was possible that the increase in death from the low SpO2 if it did occur, might still result in an improved overall survival without ROP
This is what you have now found
Here is the concern
The world is now moving to increase the SpO2 acceptable range for all very preterm infants including the 24 -25 week infants because of our findings and that reported from UK and Australia NZ
These other studies did not have a respiratory intervention, and did not start the study oximeter till about 18 hrs.
If the use of CPAP and a permissive strategy actually results in improved survival without ROP, then it is possible that using the low SpO2 strategy with CPAP is the very best approach
Since we did not find more NDI , this would stand
We now need the analyses for survival without NDI evaluating the CPAP vs Surf in the strata comparing hi vs low SpO2 range.
This is vital information
I am doubtful that further studies which are as large as our small strata will never be done and thus our data may be as good as is
ever available
Before the others studies publish their data and recommend that we now raise the SpO2 range for all preterms we need to look at this a carefully as possible. The best conclusion at present may be that the combination of early CPAP and a limited vent strategy with a low SpO2 range is in fact the optimal approach for the most immature infants.
Thanks again and I would ask that you run the groups for survival without NDI to ensure that there is no adverse effect of this combination on later outcome
Be well
Neil
-----Original Message-----
From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Friday, September 02, 2011 3:07 PM
To: Finer, Neil
Cc: rose higgins; Vaucher, Yvonne; Das, Abhik
Subject: RE: SUPPORT OUTCOMES

Neil,

Attached are the analyses you requested.

To fill Abhik in, Neil and Yvonne were looking at the tables for the FU papers and were wondering if there was interaction between CPAP, oximeter and GA group for ROP and ROP/death. I did a quick look at ROP last week and found that there was significant interaction (p=.03) and that for infants with GA 24-25 weeks, those with CPAP had lower ROP, and the difference was very significant within the Low SpO2 group (but not significant in the High group). Neil and Yvonne were very interested in whether the combination of

CPAP and Low SpO2 target was protective against ROP in the smaller GA stratum. Neil and Rose both called me this week to ask if I would also look at death/ROP to see if the results were similar. For death/ROP, the interaction between CPAP, oximeter and GA had a p value of .10, so I again ran the models separately for each GA group. Similar to the results for ROP, infants with GA 24-25 weeks had less ROP/death in the CPAP group, and that difference was very significant within the Low SpO2 group. I also looked at the interaction for the outcome of death, but it was not significant (p=.44) so I did not do sub-analyses.

I think this is very interesting, but what are the implications given that there was greater death in the Low SpO2 group in both GA strata, regardless of CPAP or surfactant use (although the difference in death was only significant when the SUPPORT population was analyzed as a whole)?

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

-----Original Message-----
From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Friday, September 02, 2011 2:08 PM
To: Gantz, Marie
Cc: rose higgins; Vaucher, Yvonne
Subject: SUPPORT OUTCOMES

Hi Marie
Will you be able to get us any data this week??
I would like to work on this over the long weekend Thanks Neil

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Wally Carlo, M.D."; "nfiner@ucsd.edu"; "mgantz@rti.org"
Cc: "Vaucher, Yvonne"; "adas@rti.org"
Subject: RE: SUPPORT OUTCOMES
Date: Tuesday, September 06, 2011 11:41:00 AM
Attachments: RE SUPPORT OUTCOMES.msg

Here is the email with the analysis results

Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
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301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

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Marie

Marie Gantz, Ph.D.
Research Statistician
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mgantz@rti.org
828-254-6255

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Cc: rose higgins; Vaucher, Yvonne
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I would like to work on this over the long weekend Thanks Neil

From: Juliann Di Fiore
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Archer, Stephanie (NIH/NICHD) [E]; mcw3@cwru.edu
Subject: Re: FW: Draft effect of low target range on the incidence of IH
Date: Tuesday, September 06, 2011 9:25:02 AM

I was thinking of Pediatrics but I am open to suggestions.

Julie

On 9/6/2011 8:53 AM, Higgins, Rosemary (NIH/NICHD) [E] wrote:

> Stephanie
> Can you do a boilerplate?
>
> JULIE- where will this be submitted?

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Juliann Di Fiore [mailto:jmd3@case.edu]
Sent: Friday, September 02, 2011 9:19 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Fwd: Draft effect of low target range on the incidence of IH

Hi Rose,

I sent a draft of the *Effect of low target range on the incidence of IH* manuscript out on Wednesday and, not knowing Network protocol, it just occurred to me that you and Abhik may need to be on the recipient list with these exchanges. Please let me know what you would like me to do.

Thanks!

Julie

-------- Original Message --------
Subject: Draft effect of low target range on the incidence of IH

Date: Wed, 31 Aug 2011 16:35:21 -0400
From: Juliann Di Fiore <jmd3@case.edu>
Reply-To: jmd3@case.edu
To: Richard Martin <rxm6@case.edu>, Michele Walsh <Michele.Walsh@UHhospitals.org>, Wade Rich <wrich@ucsd.edu>, Neil Finer <nfiner@ucsd.edu>, Wally Carlo <WCarlo@peds.uab.edu>, "Wrage, Lisa Ann" <wrage@rti.org>

Hi Everyone,

Attached is the first draft of the *Effect of low target range on the incidence of IH* manuscript for your review.

Thanks!

Julie

--
Juliann Di Fiore
Research Engineer
Case Western Reserve University
Rainbow Babies & Children's Hospital
Division of Neonatology, room 3100
11100 Euclid Ave
Cleveland, OH 44106
(216) 844-1478

--
Juliann Di Fiore
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Federal and Ohio law protect patient medical information, including

psychiatric disorders, (H.I.V) test results, A.I.Ds-related conditions, alcohol, and/or drug dependence or abuse disclosed in this email. Federal regulation (42 CFR Part 2) and Ohio Revised Code section 5122.31 and 3701.243 prohibit disclosure of this information without the specific written consent of the person to whom it pertains, or as otherwise permitted by law.

From: Pablo Sanchez
To: Barbara Stoll
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Luc Brion; JACLYN LEVAN; Cheryl Motta; Christina Stine; JACLYN LEVAN; Ja"Near Anderson; Jenitha Jeyaraj; Joshua Frankfurt; Katherine Stumpf; Michel Mikhael; Olutoye Osunbunmi; Reina Mayor; Vivek Dalal
Subject: RE: Changes in Therapy post SUPPORT-- PAS
Date: Tuesday, September 06, 2011 12:53:53 AM

certainly, barbara--I have cc'd her and Luc who is the mentor and PI --her e-mail is jaclyn.levan@phhs.org --hope you had a nice labor day weekend! --pablo

From: Barbara Stoll [Barbara.Stoll@oz.ped.emory.edu]
Sent: Monday, September 05, 2011 10:55 PM
To: Pablo Sanchez
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Changes in Therapy post SUPPORT-- PAS

Pablo

Hope all is well

I do not have Dr LeVan's email
Would like to help with this presentation/paper for PAS-- when enough post SUPPORT data available to do this

Regards

BJS

UT Southwestern Medical Center
The future of medicine, today.

Blansfield, Earl (NIH/NICHD) [E]

From: Gantz, Marie <mgantz@rti.org>
Sent: Friday, September 02, 2011 6:07 PM
To: Finer, Neil
Cc: rose higgins; Vaucher, Yvonne; Das, Abhik
Subject: RE: SUPPORT OUTCOMES
Attachments: CPAP vs death-ROP by SpO2 and GA - 02SEP11.doc

Neil,

Attached are the analyses you requested.

To fill Abhik in, Neil and Yvonne were looking at the tables for the FU papers and were wondering if there was interaction between CPAP, oximeter and GA group for ROP and ROP/death. I did a quick look at ROP last week and found that there was significant interaction (p=.03) and that for infants with GA 24-25 weeks, those with CPAP had lower ROP, and the difference was very significant within the Low SpO2 group (but not significant in the High group). Neil and Yvonne were very interested in whether the combination of CPAP and Low SpO2 target was protective against ROP in the smaller GA stratum. Neil and Rose both called me this week to ask if I would also look at death/ROP to see if the results were similar. For death/ROP, the interaction between CPAP, oximeter and GA had a p value of .10, so I again ran the models separately for each GA group. Similar to the results for ROP, infants with GA 24-25 weeks had less ROP/death in the CPAP group, and that difference was very significant within the Low SpO2 group. I also looked at the interaction for the outcome of death, but it was not significant (p=.44) so I did not do sub-analyses.

I think this is very interesting, but what are the implications given that there was greater death in the Low SpO2 group in both GA strata, regardless of CPAP or surfactant use (although the difference in death was only significant when the SUPPORT population was analyzed as a whole)?

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

-----Original Message-----
From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Friday, September 02, 2011 2:08 PM
To: Gantz, Marie
Cc: rose higgins; Vaucher, Yvonne
Subject: SUPPORT OUTCOMES

Hi Marie
Will you be able to get us any data this week??
I would like to work on this over the long weekend Thanks Neil

CPAP vs. ROP among survivors, by GA and SpO2 group

The FREQ Procedure

Table 1 of cpap by rop

Controlling for gagrp=24-25 oximeter=High SpO2

cpap(CPAP or surfactant)	rop(ROP)		
Frequency Row Pct	Y	N	Total
CPAP	33 32.04	70 67.96	103
Surfactant	33 34.74	62 65.26	95
Total	66	132	198

Frequency Missing = 91

Table 2 of cpap by rop

Controlling for gagrp=24-25 oximeter=Low SpO2

cpap(CPAP or surfactant)	rop(ROP)		
Frequency Row Pct	Y	N	Total
CPAP	11 11.58	84 88.42	95
Surfactant	21 27.63	55 72.37	76
Total	32	139	171

Frequency Missing = 105

Table 3 of cpap by rop

Controlling for gagrp=26-27 oximeter=High SpO2

cpap(CPAP or surfactant)	rop(ROP)		
Frequency Row Pct	Y	N	Total
CPAP	15 9.38	145 90.63	160
Surfactant	10 6.62	141 93.38	151
Total	25	286	311

Frequency Missing = 62

CPAP vs. ROP among survivors, by GA and SpO2 group

The FREQ Procedure

Table 4 of cpap by rop			
Controlling for gagrp=26-27 oximeter=Low SpO2			
cpap(CPAP or surfactant)	rop(ROP)		
Frequency Row Pct	Y	N	Total
CPAP	8 5.23	145 94.77	153
Surfactant	1 0.66	150 99.34	151
Total	9	295	304
Frequency Missing = 74			

Model for ROP among survivors adjusting for center, familial clustering and interaction between CPAP and SpO2 target (In a separate model including all factors, P value for interaction between CPAP, SpO2 target and GA group was .03) (GA 24-25 weeks)

Predictor	RR	RR Lower 95% Confidence Limit	RR Upper 95% Confidence Limit	Adjusted P-value
CPAP vs. Surf within Low SpO2	0.4183	0.2155	0.8119	0.0100
CPAP vs. Surf within High SpO2	0.9256	0.6178	1.3868	0.7078

Model for ROP among survivors adjusting for center, familial clustering and interaction between CPAP and SpO2 target (In a separate model including all factors, P value for interaction between CPAP, SpO2 target and GA group was .03) (GA 26-27 weeks)

Predictor	RR	RR Lower 95% Confidence Limit	RR Upper 95% Confidence Limit	Adjusted P-value
CPAP vs. Surf within Low SpO2	8.7561	1.1072	69.2485	0.0397
CPAP vs. Surf within High SpO2	1.5076	0.6821	3.3320	0.3103

CPAP vs. death or ROP, by GA and SpO2 group

The FREQ Procedure

Table 1 of cpap by ropdeath

Controlling for gagrp=24-25 oximeter=High SpO2

cpap(CPAP or surfactant)	ropdeath(ROP or death)		
Frequency Row Pct	Y	N	Total
CPAP	64 47.76	70 52.24	134
Surfactant	75 54.74	62 45.26	137
Total	139	132	271

Frequency Missing = 18

Table 2 of cpap by ropdeath

Controlling for gagrp=24-25 oximeter=Low SpO2

cpap(CPAP or surfactant)	ropdeath(ROP or death)		
Frequency Row Pct	Y	N	Total
CPAP	48 36.36	84 63.64	132
Surfactant	69 55.65	55 44.35	124
Total	117	139	256

Frequency Missing = 20

Table 3 of cpap by ropdeath

Controlling for gagrp=26-27 oximeter=High SpO2

cpap(CPAP or surfactant)	ropdeath(ROP or death)		
Frequency Row Pct	Y	N	Total
CPAP	31 17.61	145 82.39	176
Surfactant	28 16.57	141 83.43	169
Total	59	286	345

Frequency Missing = 28

CPAP vs. death or ROP, by GA and SpO2 group

The FREQ Procedure

Table 4 of cpap by ropdeath			
Controlling for gagrp=26-27 oximeter=Low SpO2			
cpap(CPAP or surfactant)	ropdeath(ROP or death)		
Frequency Row Pct	Y	N	Total
CPAP	33 18.54	145 81.46	178
Surfactant	21 12.28	150 87.72	171
Total	54	295	349
Frequency Missing = 29			

Model for death or ROP adjusting for center, familial clustering and interaction between CPAP and SpO2 target (In a separate model including all factors, P value for interaction between CPAP, SpO2 target and GA group was .10) (GA 24-25 weeks)

Predictor	RR	RR Lower 95% Confidence Limit	RR Upper 95% Confidence Limit	Adjusted P-Value
CPAP vs. Surf within Low SpO2	0.6243	0.4744	0.8216	0.0008
CPAP vs. Surf within High SpO2	0.8722	0.6849	1.1108	0.2678

Model for death or ROP adjusting for center, familial clustering and interaction between CPAP and SpO2 target (In a separate model including all factors, P value for interaction between CPAP, SpO2 target and GA group was .10) (GA 26-27 weeks)

Predictor	RR	RR Lower 95% Confidence Limit	RR Upper 95% Confidence Limit	Adjusted P-value
CPAP vs. Surf within Low SpO2	1.4946	0.8963	2.4924	0.1235
CPAP vs. Surf within High SpO2	1.0490	0.6458	1.7039	0.8468

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Archer, Stephanie (NIH/NICHD) [E]
Subject: FW: SUPPORT FU PAPERS??
Date: Tuesday, September 06, 2011 11:41:00 AM
Attachments: Support NDI 09-02-2011 ver 2 0.doc

Can you add the title page and boilerplate?
Thanks
Rose

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From: Becky Brazeel [mailto:bbrazeel@peds.uab.edu] **On Behalf Of** Wally Carlo, M.D.
Sent: Friday, September 02, 2011 1:36 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Yvonne Vaucher; Myriam Peralta, M.D.
Cc: nfiner@ucsd.edu; Wally Carlo, M.D.; Gantz, Marie; Wallace, Dennis; Das, Abhik; brazeel@uab.edu
Subject: SUPPORT FU PAPERS??

Hi,
Myriam and I have worked on this oxygen saturation follow-up paper. It is still a work in progress, but we wanted to share this so we can start getting some feed back. Myriam is out of the country and may have limited email access.

We look forward to hearing your comments,
Thanks,
Wally

SUPPORT NDI_09/02/2011 ver 2.0

Neurodevelopmental Outcome of Extremely Preterm Infants in a Trial of Different Oxygen Saturation Targets

Myriam Peralta-Carcelen, M.D., M.P.H.[1];

[1]University of Alabama at Birmingham, Birmingham, Alabama, United States; the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), Bethesda, Maryland, United States.

Comment [bb1]: Additional authors?

Comment [bb2]: Site NICHD?

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Word Count

Abstract: 248

Text: 1,148

ABSTRACT

Comment [WC3]: I had to cut so much to get the abstract under 250 words as required for NEJM

BACKGROUND

Targeting lower oxygen saturations in the SUPPORT Trial decreased severe retinopathy of prematurity while targeting higher oxygen saturations increased survival by discharge. We hypothesized that the long term neurodevelopmental effects of different oxygen saturation levels were not significant between both groups.

METHODS

We followed 1211 of 1316 (92.0) 24 to 27 week infants who had been randomized to higher (91-95%) or lower oxygen saturation targets (85-89%) starting at birth and up to 36 weeks corrected age. The primary outcome of this study was a composite of death or severe neurodevelopment impairment at 18 to 22 months corrected age. Severe neurodevelopmental impairment was defined as a cognitive composite score of less than 70, motor score less than 70, modified Gross Motor Function Classification System >1, presence of moderate to severe cerebral palsy, permanent hearing loss, and/or bilateral blindness.

RESULTS

Death or severe neurodevelopmental impairment occurred in 185 (30.2%) infants in the lower oxygen saturation group and 171 (27.5%) infants of the higher oxygen saturation group (relative risk 1.11; confidence interval 0.94, 1.32; p=0.227). Death occurred in 140 (22.3%) of the

children in the lower oxygen saturation group and in 118 (18.4%) in the higher oxygen saturation group (relative risk 1.24; confidence interval 1, 1.54, p=0.053).

CONCLUSIONS

Among extremely preterm infants exposed to different levels of oxygen saturation the increased mortality at discharge time in the lower oxygen target group is partially offset by a trend for increased severe neurodevelopmental impairment at 18 to 22 months in this group.

Oxygen supplementation is a vital therapy for survival of many preterm infants with respiratory disorders. However, oxygen supplementation may increase the risk of retinopathy of prematurity, bronchopulmonary dysplasia,[Tin et al, 2001] periventricular leukomalacia,[Chow et al, 2003] and cerebral palsy.[Anderson et al, 2004] Restrictive oxygen therapy decreases retinopathy but has resulted in increased deaths in randomized controlled trials.[Bolton DP et al, 1997; Askie et al, 2009; Carlo et al, 2010; Stenson et al, 2011)

Comment [WC4]: These references are quoted in my NEJM paper

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development SUPPORT Trial demonstrated no significant difference in a composite outcome including retinopathy of prematurity and death between a lower oxygen saturation group (85-89%) and the higher saturation group (91-95%). However, mortality was increased and severe retinopathy of prematurity was reduced in the lower oxygen saturation group compared to the higher saturation group. A recent meta-analysis that included the SUPPORT Trial and two other subsequently done multi-center randomized controlled trials with a total of 3631 infants showed that infants randomized to an oxygen saturation of 91-95% % had a lower mortality rate than infants randomized to oxygen saturation targets of 85-89% (17.3% versus 14.4%, P=0.015).[Stenson, NEJM 2011] There has been interest to determine if oxygen supplementation can reduce neurodevelopmental impairment. However, in two non randomized studies of different oxygen saturation targeting,[Tin et al, 2001; Bradley et al, 1993] neurodevelopmental outcome did not differ by oxygen targets.

Comment [WC5]: Spell out

This study evaluated the composite primary outcome of death or severe neurodevelopmental impairment at 18 to 22 months corrected age in the subjects enrolled in the two groups of extremely preterm infants randomized to lower (85-89%) or higher oxygen saturation targets (91-95%) from birth to 36 weeks corrected age.

METHODS

Extremely preterm infants (24 weeks 0 days to 27 weeks 6 days) born between February 2005 and February 2009 at participating sites of the Neonatal Research Network of the Eunice Kennedy Shriver National Institute of Child Health and Human Development enrolled in the SUPPORT trial were eligible for this study. Each center's institutional review board approved the study. Enrollment, intervention, data collection, and hospital outcomes have been previously reported. (Carlo NEJM)

Assessments

The composite of death or major neurosensory impairment at 18 to 24 months of age corrected for prematurity was the primary outcome. This composite outcome was selected because infants who died before 18 months could not be classified as having neurodevelopmental impairment. Outcomes at 18-22 months of corrected age were assessed by neurologic examiners and neurodevelopmental testers who had been trained yearly for reliability of assessments during a 2-day workshop and were unaware of the treatment assignments.

The Bayley Scales for Infant Development III (BSID III) was administered. Cognitive Composite Scores are reported in a standardized score of 100 ± 15. The composite Language Score is a sum of the receptive and expressive language scores and are based on a scale of 1 to 19, the overall language composite score is converted to a standardized score of 100 ± 15. The Motor section was added to the evaluation after January 1, 2010. Two scores are calculated: the fine motor and gross motor score. These are added and converted to an overall motor composite score with a mean of 100 ± 15.

The modified Gross Motor Function Classification System (GMFCS) describes the gross motor performance and has a range from 0 (normal) to 5 (most impaired). Examiners also recorded the presence of cerebral palsy defined as a nonprogressive disorder of the central nervous system characterized by abnormal muscle tone in at least one arm or leg and abnormal control of movement or posture with delayed attainment of motor milestones. Cerebral palsy was classified depending on severity into mild (GMFCS ≤1), moderate (GMFCS 2 or 3) or severe (GMFCS ≥ 4). Anthropometrics measures included weight, height and head circumference. Z scores using the Center for Disease Control growth charts were calculated for weight, height, and head circumference.

Severe neurodevelopmental impairment was defined as having any of the following: BISD III scales cognitive composite score less than 70, motor score less than 70, GMFCS ≥ 2, presence of cerebral palsy moderate or severe, permanent hearing loss that does not permit the child to

understand directions of the examiner and communicate despite amplification, or bilateral visual impairment (vision < 20/200).

Socioeconomic data was updated during the 18-24 month visit and if not available, data during the neonatal period was included. Medical information included the number of rehospitalizations.

Analysis

Data was entered in standard forms and was transmitted to RTI International which stored, managed and analyzed the data for this study. Comparisons of primary and secondary outcomes were done between infants in the lower saturation group and the higher oxygen saturation group. In addition comparisons were done between two gestational age stratification categories: Categorical outcomes were compared with the use of chi-square tests for trends and appropriate or Fisher's exact test.

RESULTS

Characteristics of the Study Sample

The SUPPORT trial enrolled 1316 study in the study (Figure 1). Five hundred twenty four infants in the lower oxygen saturation group and 555 in the higher oxygen saturation group survived to discharge from the hospital. The baseline characteristics of the entire group have

Comment [bb6]: Figures ?

been reported previously.[Carlo NEJM] Ten children in the lower oxygen saturation group and 11 children in the higher oxygen saturation group died after discharge from the nursery prior to the 18 to 22 month adjusted age follow up visit. The baseline characteristics of the eligible infants for follow up are presented in Table 1. There were no significant differences in the baseline characteristics of the follow up group who received lower oxygen saturation versus higher oxygen saturation.

Primary Outcome

The rate of composite outcome, neurodevelopmental impairment plus death was not significantly different between the lower oxygen saturation group and the high oxygen saturation group. (Table 2) Death prior to the 18 to 22 month adjusted age visit occurred in infant in the lower oxygen saturation group and infants in the higher saturation group. Similar results were observed for both gestational age strata.

The rate of neurodevelopmental impairment on among survivors followed to the 18 to 22 month adjusted age visit was similar between the low oxygen saturation group and the high oxygen saturation group. The rate of retinopathy of prematurity was higher in the high oxygen group compared to the low oxygen group however the rate of blindness was not significantly at the 18 to 22 month adjusted age visit on the follow up group.

Secondary Outcomes

The mean scores of the Bayley Scales of Cognitive Impairment were not significantly different in the low oxygen saturation group and the high oxygen saturation group. There were also no significant differences in rates of cerebral palsy between both groups (Table 3). On the follow up group the rate of infants who required eye surgery was higher in the high oxygenation group compared to the low oxygen saturation group.

DISCUSSION

REFERENCES

Anderson CG, Benitz We, Madan A. Retinopathy of prematurity and pulse oximetry: a national survey of recent practices. J Perinatol. 2004;24:164-168.

Askie LM, Henderson-Smart DJ, Ko H. Restricted versus liberal oxygen exposure for preventing morbidity and mortality in preterm or low birth weight infants. Cochran Database Syst Rev. 2009;1:CD001077.

Bolton DP, Cross KW. Further observations on cost of preventing retrolental fibroplasias. Lancet. 1974;303:445-448.

Comment [bb7]: Check references

Bradley S, Anderson K and Tin W, et al.: Early oxygen exposure and outcome at 10 years in babies of less than 29 weeks. Pediatr Res. 55:2004;A373.

Chow LC, Wright KW, Sola A. Can changes in clinical practice decrease the incidence of sever retinopathy of prematurity in very low birth weight infants? Pediatrics. 2003;111:330-345.

Stenson B, Brocklehurst P, Tarnow-Mordi W; U.K. BOOST II trial; Australian BOOST II trial; New Zealand BOOST II trial. Increased 36-week survival with high oxygen saturation target in extremely preterm infants. N Engl J Med. 2011;364:1680-1682.

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Tin W, Milligan DW, Pennefather P, Hey E. Pulse oximetry, severe retinopathy, and outcome at one year in babies of less than 28 weeks gestation. Arch Dis Child Fetal Neonatal. 2001;84:F106-F110.

Table 1. Baseline characteristics of the SUPPORT group

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Characteristics	Trial Cohort		Cohort with Follow-up Visit	
	Lower Oxygen Saturation	Higher Oxygen Saturation	Lower Oxygen Saturation	Higher Oxygen Saturation
			N=479	N=510
Birth weight – g			857.8 ± 186.3	843.9± 191.6
Gestational age – wk			26.3 ± 1.1	26.2 ± 1
Small for gestational age – no./total no. (%)			17/479 (3.5)	38/510 (7.5)
Male sex – no./total no. (%)			240/479 (50.1)	281/510 (55.1)
Race or ethnic group – no./total no. (%)				
Non Hispanic Black			201/479 (42)	176/510 (34.5)
Non Hispanic White			178/479 (37.2)	217/510 (42.5)

Hispanic	86/479 (18)	97/510 (19)
Other or unknown	14/479 (2.9)	20/510 (3.9)
Multiple births – no./total no. (%)	124/479 (25.9)	128/510 (25.1)
Maternal educational level <high school no./total no. (%)	115/471 (24.4)	128/503 (25.4)
Cesarean section – no./total no. (%)	332/479 (69.3)	334/510 (65.5)
Antenatal steroids – no./total no. (%)	462/479 (96.5)	486/510 (95.3)
Retinopathy of prematurity – no./total no. (%)	38/442 (8.6)	82/471 (17.4)
Bronchopulmonary dysplasia – no./total no. (%)	177/479 (37)	202/510 (39.6)
Intraventricular hemorrhage grade 3 or 4 or Periventricular leukomalacia – no./total no. (%)	56/478 (11.7)	60/509 (11.8)
Necrotizing enterocolitis – no./total no. (%)	42/479 (8.8)	44/510 (8.6)
Bronchopulmonary dysplasia no./total no. (%)	177/479 (37)	202/510 (39.6)

Table 2. Primary and Secondary Outcomes at 18-22 Months

	Lower Oxygen Saturation	Higher Oxygen Saturation	Adjusted Relative Risk	p value
Died or had follow-up – no./total no. (%)				
Died by 18-22 months – no./total no. (%)				
Neurodevelopmental impairment or death – no./total no. (%)				
Survivors at follow-up				
Severe neurodevelopmental impairment – no./total no. (%)				
Bayley III cognitive composite score < 70 – no./total no. (%)				
Gross motor function level ≥ 2 – no./total no. (%)				
Moderate/severe cerebral palsy – no./total no. (%)				
Blindness – no./total no. (%)				
Unilateral blindness – no./total no. (%)				
Deafness – no./total no. (%)				
Profound neurodevelopmental impairment – no./total no. (%)				

Table 3. Secondary Outcomes by Group

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Outcome	Low SpO2 (N=479)	High SpO2 (N=510)	Relative Risk for Low SpO2 vs. High SpO2 (95% CI)	Adjusted difference in means (95% CI)	Adjusted P-value
Bayley Scales of Infant Development III					
Cognitive composite <85	105/471 (22.3)	131/502 (26.1)	0.86 (0.69, 1.07)		0.1831
Bayley III composite language score <70	69/462 (14.9)	84/497 (16.9)	0.85 (0.64, 1.15)		0.2940
Bayley III composite language score <85	203/462 (43.9)	224/497 (45.1)	1 (0.99, 1)		0.8121
Bayley III composite motor score <70	18/134 (13.4)	16/142 (11.3)	1.37 (0.76, 2.47)		0.3016
Bayley III composite motor score <85	41/134 (30.6)	44/142 (31.0)	1.02 (0.71, 1.48)		0.8948
Mild cerebral palsy vs. none	23/459 (5.0)	21/490 (4.3)	1.16 (0.66, 2.02)		0.6105
Moderate cerebral palsy vs. none	11/447 (2.5)	10/479 (2.1)	1.19 (0.52, 2.71)		0.6873
Severe cerebral palsy	9/445 (2.0)	10/479 (2.1)	0.95 (0.39, 2.27)		0.9026

Any cerebral palsy	43/479 (9.0)	41/510 (8.0)	1.12 (0.76, 1.65)	0.5766
Abnormal neuro/motor score	108/479 (22.5)	114/510 (22.4)	1.02 (0.82, 1.27)	0.8606
Hypotonia	22/479 (4.6)	20/510 (3.9)	1.24 (0.67, 2.28)	0.4973
Hypertonia	6/479 (1.3)	11/510 (2.2)	0.59 (0.22, 1.58)	0.2962
Diplegia	18/479 (3.8)	16/510 (3.1)	1.21 (0.63, 2.32)	0.5651
Hemiplegia	7/479 (1.5)	6/510 (1.2)	1.28 (0.44, 3.74)	0.6557
Quadriplegia or triplegia	9/479 (1.9)	13/510 (2.5)	0.66 (0.27, 1.61)	0.3585
Strabismus	46/478 (9.6)	41/509 (8.1)	1.2 (0.7, 1.8)	0.3845
Nystagmus	22/479 (4.6)	12/509 (2.4)	1.95 (0.94, 4.07)	0.0737
Tracks 180 degrees	462/476 (97.1)	492/506 (97.2)	1 (0.98, 1.02)	0.9330
Corrective lenses both eyes vs. normal both eyes	21/468 (4.5)	20/492 (4.1)	1.14 (0.62, 2.08)	0.6774
Blind, some function, both eyes vs. normal both eyes	3/450 (0.7)	2/474 (0.4)	1.56 (0.27, 8.95)	0.6151
Blind, no useful vision, both eyes vs. normal both eyes	2/449 (0.4)	4/476 (0.8)	0.54 (0.1, 2.95)	0.4789
Other abnormal vision vs. normal both eyes	6/453 (1.3)	12/484 (2.5)	0.55 (0.21, 1.46)	0.2301
Hearing impairment, no hearing aids vs. no impairment	5/472 (1.1)	6/504 (1.2)	0.91 (0.29, 2.92)	0.8777
Hearing impairment, both hearing aids vs. no impairment	7/474 (1.5)	6/504 (1.2)	1.27 (0.44, 3.7)	0.6595

Eye surgery	31/477 (6.5)	67/508 (13.2)	0.52 (0.35, 0.78)		0.0014
PDA ligation	48/477 (10.1)	39/508 (7.7)	1.33 (0.9, 1.95)		0.1519
Any surgery	210/477 (44.0)	241/509 (47.3)	0.95 (0.83, 1.08)		0.4314
Bronchodilators	159/475 (33.5)	185/505 (36.6)	0.92 (0.78, 1.09)		0.3583
Steroids	95/475 (20.0)	108/505 (21.4)	0.92 (0.72, 1.18)		0.5016
Diuretics	15/475 (3.2)	14/505 (2.8)	1.16 (0.58,2.34)		0.6717
High calorie formula	90/475 (18.9)	102/505 (20.2)	0.92 (0.71, 1.2)		0.5353
Anticonvulsants	12/478 (2.5)	12/510 (2.4)	1.08 (0.49, 2.37)		0.8514
Readmission for respiratory reason	110/470 (23.4)	127/503 (25.2)	0.93 (0.74, 1.16)		0.5114
Readmission for growth/nutrition	12/470 (2.6)	13/503 (2.6)	1.05 (0.49, 2.25)		0.8953
Any hospital readmission	210/478 (43.9)	238/510 (46.7)	0.94 (0.82, 1.08)		0.4111
Weight (kg)	10.87 ± 0.09	10.91 ± 0.09		-0.05(-0.27, 0.17)	0.6581
Weight-for-age z-score	-0.20 ± 0.06	-0.24 ± 0.06		0.04 (-0.12, 0.19)	0.6374
Weight-for-age z-score	-0.20 ± 0.06	-0.24 ± 0.06		0.04 (-0.12, 0.19)	0.6374
Recumbent length (cm)	81.38 ± 0.25	81.49 ± 0.24		-0.11(-0.72, 0.51)	0.7285
Length-for-age z-score	-0.70 ± 0.08	-0.75 ± 0.07		0.05 (-0.13, 0.24)	0.5729

Length-for age z-score	-0.69 ± 0.07	-0.73 ± 0.07	0.04 (-0.13, 0.21)	0.6270
Weight-for-length z-score	0.18 ± 0.07	0.14 ± 0.06	0.04 (-0.12, 0.20)	0.6136
Weight-for-length z-score	0.17 ± 0.06	0.15 ± 0.06	0.03 (-0.13, 0.18)	0.7356
Occipital-frontal circumference (cm)	46.98 ± 0.11	41.06 ± 0.10	-0.08 (-0.34,0.18)	0.5544
Head circumference-for-age z-score	-0.11 ± 0.08	-0.11 ± 0.07	-0.01 (-0.19,0.18)	0.9367
Head circumference-for-age z-score	-0.07 ± 0.07	-0.02 ± 0.07	-0.04 (-0.22,0.13)	0.6278

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "vkumar3@buffalo.edu"
Subject: Re: PAS Speaker Invitation
Date: Saturday, September 03, 2011 12:22:34 PM

Hi
Thank you for thinking of me. I will need to get permission to participate as an official duty of Federal Employment. Is there a number I can reach you at on Tuesday am? I am traveling and in meetings most of next week.
Best regards,

Rose

----- Original Message -----
From: vkumar3@buffalo.edu <vkumar3@buffalo.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Sat Sep 03 10:29:08 2011
Subject: Re: PAS Speaker Invitation

Dear Dr. Rosemary Higgins,

This is Vasanth Kumar from Buffalo, NY. I work with Rita Ryan (now she is at Charleston, SC).

My proposal 'Oxygen Saturation Targets in Premature Neonates: The Dilemma & The Debate' has been accepted by the PAS committee for the State of the Art Plenary Session at PAS Meeting in Boston April/May 2012. This proposal was put together by me and accepted for presentation by the committee (see below).

The following are tht topics that I choose for the 2 hour session.

The Role of Oxygen & Its Monitoring in Development. 20 minutes (Vasanth Kumar)

Oxygen Saturations in Premature Infants at Resuscitation: Lessons from New NRP Guidelines. 20 minutes (Ola Saugstad) - Accepted

Oxygen Saturations in ELBW Infants < 32 weeks Postmenstrual Age - What do we know? 20 minutes (Neil Finer) - Awaiting confirmation

Saturation Targets and Clinical Outcomes in ELBW Infants >32 weeks Postmenstrual Age. 20 minutes (Cynthia Cole) - Awaiting confirmation

Oxygen Administration and the Art of "Age Appropriate Oxygen Saturations" - Do we know what we are doing? 20 minutes

Questions & Answers . 20 minutes

I am honored to invite you to give the presentation on Oxygen Administration and the Art of "Age Appropriate Oxygen Saturations' during this session. The following is the presentation title -

PRESENTATION TITLE:
Oxygen Administration and the Art of "Age Appropriate Oxygen Saturations" - Do we know what we are doing? OR "Where are we now' OR 'Opportunities for future research'

The above title can be changed a little to make it more palatable for you; I am not finding the right words!

PLEASE let me know as soon as possible your acceptance to speak at this extremely good interactive session. Your

expertise and input is needed to make this session a great success. I am honored to have you in this session and hoping to receive your positive reply. Please do not disappoint me!

I will call you after labor day week end.

I have received confirmation from Saugstad.

I also have some great data from the randomized study of 21%, 40% and 100% oxygen in infants < 32 week gestation (small study) and also some long term gene expression data in mice resuscitated in varying concentrations of oxygen.
Thanking you,

Vasanth Kumar, MD
Assistant Professor of Pediatrics
Director of Neonatal-Perinatal Medicine Fellowship Program
State University of New York at Buffalo

On Tue 08/23/11 10:32 AM , "Kumar, Vasanth" vkumar@upa.chob.edu sent:
> FW: PAS Invited Session Confirmation Received - 12SOA09
> ---
> FROM: Product Support[SMTP:DONOTREPLY@MARATHONMULTIMEDIA.COM]
> SENT: Tuesday, August 23, 2011 10:32:08 AM
> TO: Kumar, Vasanth
> SUBJECT: PAS Invited Session Confirmation Received - 12SOA09
> AUTO FORWARDED BY A RULE
>
> Dear Dr. Kumar:
>
> We successfully received the final submission of your invited
> science program "Oxygen Saturation Targets in Premature Neonates: The
> Dilemma & The Debate." for the 2012 Pediatric Academic Societies'
> Annual Meeting. We understand that all participants have accepted the
> invitation to participate and the program is considered approved and
> acceptable for all meeting publications or promotions.
>
> Participation details regarding housing and meeting registration,
> conflict of interest disclosure and resolution processing, audiovisual
> requirements, and final session details will be distributed to the
> session participants from the PAS Program Office prior to the meeting.
>
>
> We thank you for your contributions to an exciting 2012 PAS meeting
> and look forward to seeing you in Boston next spring!
>
> Technical Support can be reached at support@marathonmultimedia.com
> or 1-866-759-5440 (507-333-1000 if Outside the U.S.).
>
> Invited program or speaker questions should be directed to Linda
> Baker at the PAS Program Office at lindab@aps-spr.org or 281-419-0052.
>
>
> Sincerely,
>
> Marathon Multimedia
> for the Pediatric Academic Societies

From: Juliann Di Fiore
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Fwd: Draft effect of low target range on the incidence of IH
Date: Friday, September 02, 2011 9:19:10 AM
Attachments: Draft effect of low target range on the incidence of IH.docx

---

Hi Rose,

I sent a draft of the *Effect of low target range on the incidence of IH* manuscript out on Wednesday and, not knowing Network protocol, it just occurred to me that you and Abhik may need to be on the recipient list with these exchanges. Please let me know what you would like me to do.

Thanks!

Julie

-------- Original Message --------
Subject: Draft effect of low target range on the incidence of IH
Date: Wed, 31 Aug 2011 16:35:21 -0400
From: Juliann Di Fiore <jmd3@case.edu>
Reply-To:jmd3@case.edu
To: Richard Martin <rxm6@case.edu>, Michele Walsh <Michele.Walsh@UHhospitals.org>, Wade Rich <wrich@ucsd.edu>, Neil Finer <nfiner@ucsd.edu>, Wally Carlo <WCarlo@peds.uab.edu>, "Wrage, Lisa Ann" <wrage@rti.org>

Hi Everyone,

Attached is the first draft of the *Effect of low target range on the incidence of IH* manuscript for your review.

Thanks!

Julie

--
Juliann Di Fiore
Research Engineer
Case Western Reserve University
Rainbow Babies & Children's Hospital
Division of Neonatology, room 3100
11100 Euclid Ave
Cleveland, OH 44106
(216) 844-1478

alcohol, and/or drug dependence or abuse disclosed in this email. Federal regulation (42 CFR Part 2) and Ohio Revised Code section 5122.31 and 3701.243 prohibit disclosure of this information without the specific written consent of the person to whom it pertains, or as otherwise permitted by law.

Low oxygen saturation target range is associated with increased incidence of intermittent hypoxemia

Juliann M. Di Fiore, Michele Walsh, Lisa Wrage, Wade Rich, Neil Finer, Waldemar Carlo, Richard J. Martin and the SUPPORT Study Group of the NICHD Neonatal Network

Background:

There is increasing evidence that intermittent hypoxemia (IH) may be associated with perinatal morbidity. In newborn animal models, administered IH paradigms have been shown to impair dopamine signaling [Decker 2002], contribute to neurological handicap [Ratner 2007, Decker 2002, Gozal 2001], and exacerbate retinal neovascularization [Coleman]. Although it is known that IH events are common in preterm infants, data relating to the prevalence of these events has been limited. Pulse oximetry technology has enabled us to non-invasively record spontaneous intermittent hypoxemic events in preterm infants over prolonged periods of time. This has allowed for accurate documentation of the temporal changes in the incidence of IH events over the first few months of life. Recent data in preterm infants of 24-28 weeks gestation have shown relatively few IH events over the first week of life, a progressive increase in events until approximately 5 weeks post natal age followed by a decline thereafter[Di Fiore 2010]. In contrast, a sustained increase in the incidence of IH events was shown to be associated with severe retinopathy of prematurity. [Di Fiore 2010].

Low baseline oxygen saturation levels may exacerbate the occurrence of IH events in preterm infants. The multi-center SUPPORT trial previously examined the role of high and low O_2 saturation target ranges on retinopathy of prematurity. Following randomization to low (85-89%) or high (91-95%) oxygen saturation target ranges, infants in the low target group were found to have a lower incidence of severe ROP and a higher mortality [SUPPORT 2010]. However, the effect of these oxygenation target ranges on the occurrence of intermittent hypoxemia (IH) is unknown. Therefore, the purpose of this study was to test the hypothesis that infants randomized to a low compared to high O_2 saturation target range would have an increase in the incidence of intermittent hypoxemia.

Methods:

The study population included a subcohort of 115 preterm infants enrolled in the multi-center SUPPORT study from two sites: Rainbow Babies & Children's Hospital, Cleveland, and University of California San Diego. The study was approved by the institutional review board at each site and by RTI Internatinal, which is the independent data coordinating center for the Neonatal Research Network. Written informed consent was obtained from the parent or guardian of each child before delivery.

Enrollment criteria included infants who were born between 24 weeks 0 days and 27 weeks 6 days of gestation for whom a decision had been made to provide full resuscitation. Infants born in other hospitals and those known to have major anomalies were excluded. Using a permuted-block randomization design, with stratification according to study center and gestational age (24 weeks 0 days to 25 weeks 6 days or 26 weeks 0 days to 27 weeks 6 days), infants were randomized to a low (85-89%) or high (91-95%) oxygen saturation target group. Infants who were part of multiple births were randomly assigned to the same group.

Electronically altered pulse oximeters (Masimo Radical) were used to blind the staff to the randomization group. The clinical staff was instructed to maintain infants in a oxygen saturation range of 88-92%, with altered monitors for both target ranges showing levels of 88-92% with a maximum offset of 3%. For example a displayed value of 90% corresponded to an actual oxygen saturation value of 87% in the low target group and 93% in the high target group. [SUPPORT 2010]. Actual values were displayed when the oxygen saturation values were <84% or higher than 95% in both treatment groups.

Targeting of oxygen saturation and high resolution (2 sec sample rate and 2 sec time averaging) data collection began within 2 hours after birth and continued until 36 wks PMA or until the infant was breathing air without respiratory support (high frequency ventilation, conventional mechanical ventilation, Nasal SIMV, CPAP, nasal canula, or hood) for ≥ 72 hours, whichever came first. Infants weaned to room air but re-administered supplemental oxygen were returned to the original randomization group. As previous studies have suggested that the timing of IH events may play a role in morbidity [Coleman], the number of IH (≤80% for ≥10sec and ≤3min), the duration of IH events and the time interval between events (Figure 1a,b) were documented daily.

A GEE regression model assuming a negative binomial distribution was utilized to model counts of intermittent hypoxemia events. This type of model provides robust standard error estimates which take into account the correlations within multiple-birth clusters. Variables included in the final model were treatment group, linear and quadratic terms for postnatal age, interactions between treatment group and postnatal age variables, gestational age group, and respiratory support (yes or no, per day). Gestational age group was included to adjust for the fact that randomization was stratified by GA (24-25 weeks and 26-27 weeks). An additional quadratic term which allowed the quadratic relationship of postnatal age and IH events to vary before and after 28 days was also included; this spline regression approach provided a better fit than simpler models [Marsh]. Also considered were interactions between GA group and postnatal age, between GA group and treatment group, and between the additional quadratic term and treatment group, as well as variables for gender, race, center, CPAP versus surfactant treatment group (an additional randomization of the main SUPPORT trial protocol), and

caffeine use. Each of these additional terms considered were not significant and thus were not included in the final model. The models for the < 1minute and 1 to 20 minute interval subsets were run with the same final set of variables as the overall model. [Lisa- Where do I reference the Fitzmaurice study?]

Results:

The population of 115 infants had a mean birth weight of 827±181gm and gestational age of 26.2 ±1.0wks. There were 50 infants in the gestational age range of 24 to 25 weeks 6 days and 65 infants in the gestational age range of 26 to 27 weeks 6 days range. Fifty one percent of the infants were male and 35% were non-Hispanic white. Characteristics of infants randomized to the high (n=62) and low (n=53) target group are presented in Table 1. There were no differences between groups in birth weight, gestational age, or incidence of bronchopulmonary dysplasia. There was a trend towards a higher mortality in the low target group (p=.10) which did not reach statistical significance. Caffeine use was common with approximately 80% of days during the monitoring period on caffeine in both infant groups.

The model based estimates showed an increase in IH events over the first 3 weeks of life in both infant groups followed by a decrease in IH events in the high target group compared to a plateau in the low target group (Figure 2a). The relative rate of IH events (RR), (the ratio of the number of IH events in the low target group/ the number of IH events in the high target group), revealed a significantly higher rate of IH events from <12 days, and >57 days of age in the low target group ($p<0.05$, Figure 2b). Within treatment groups, higher relative rates of IH events were associated with lower gestational age, RR 1.24 (95% CI 1.01-1.5, p=.032), and respiratory support, RR 1.85 (95% CI 1.52-2.49, p<.0001). Infants in the low target group received respiratory support for 86% of the monitoring period infants compared with 91.6% in the high target group (RR low versus high target, .93 (95% CI 0.86-0.99, p=.031).

The mean duration of IH events shortened (p<.01) and the severity worsened (p<.01) with increasing day of life (Figure 3). However, there were no differences in duration or severity between infant groups.

There was a wide range in the time between sequential IH events both within and between infants. To address the association between the timing of IH events and the oxygen saturation target group, the number of IH events was documented for three time interval ranges 1) <1 minute, 2) 1-20 minutes and, 3) >20 minutes between IH events. The highest incidence of events occurred with a time interval between events of <1 min, followed by a time interval of 1-20 minutes. There were relatively few IH events that occurred with a time interval of >20 minutes between events. (Figure 4). IH events occurring with a time interval between events of <1 minute were associated with a significantly higher relative rate of IH events in the low target

group at <15 and >54 days of life ($p<0.05$). This was consistent with events that occurred 1-20 minutes apart at >65 days of life ($p<.05$) with no differences between groups with a time interval of >20 minutes between events.

The above analysis examined the characteristics of IH events with increasing postnatal age. In addition, the effect of post menstrual age on the occurrence of IH events was also assessed. While the number of IH events varied with post menstrual age, the number of IH events was not significantly different by treatment group, at any post menstrual age.

Conclusion:

This study showed an association between a low oxygen saturation target range and an escalation in the incidence of intermittent hypoxemia that changed with increasing day of life. Infants in the low target range had a higher number if IH events during the first two weeks and after 57 days of life but followed a similar trajectory as the high saturation target group in between these time periods. Intermittent hypoxemic events became shorter and more severe with increasing post natal age, however, there were no differences in duration or severity between infant groups. Lastly, the higher incidence of IH events in the low target group was predominantly associated with a time interval between IH events of <1minute in duration.

Intermittent hypoxemic episodes are ubiquitous in preterm infants, both ventilated [Dimaguila 1997] and spontaneously breathing [Hunt]. Nonetheless, the precise incidence of these events has not been well documented. Although the mechanism of these events is unknown they are thought to be a consequence of immature respiratory control. This study and previous data in a similar infant cohort [Di Fiore 2010] suggest that there are developmental phases of maturation. Even with a significantly higher number of IH events in the low target group, similar to healthy term infants [Brockman], there were relatively few IH events during the 1st week of life regardless of the level of oxygen exposure. This early phase was followed by a linear increase in IH events through weeks two to three of life that was not affected by the oxygen saturation target range. These events occurred too early to be attributed to underlying lung disease such as bronchopulmonary dysplasia (BPD). However, during assisted ventilation these episodes may have been secondary to hypoventilation or ineffective ventilation and aggravated by loss of functional residual capacity associated with recruitment of abdominal muscles during expiration [Bolivar 1995]. This, in turn, may have decreased the effectiveness of spontaneous ventilatory efforts [Dimaguila 1997]. The third phase of IH events began after four weeks of age with a plateau in IH events. After this time group differences emerge with a decline in events in the high target group while remaining relatively constant in the low target group. This may be due to a low baseline alveolar PO_2 in the low target group which, in a model based analysis, has been shown to cause early onset of desaturation [Sands]. Why this low

reserve did not consistently result in a higher number of IH events at earlier post natal ages remains unclear.

Caffeine use and respiratory support are the main clinical therapies for apnea and accompanying desaturation. Although caffeine has been shown to decrease apnea [Henderson-Smart], interestingly, it has been shown to have little if any effect on desaturation episodes [Buchner]. Both infant groups spent a high percentage of the monitoring period on caffeine therapy with no significant difference in caffeine usage between infant groups, therefore, it is unlikely that caffeine use affected the results of this study. Respiratory support was associated with a higher incidence of IH events within each treatment group. However, with the low target group having a higher percentage of time receiving respiratory support, this cannot explain the increased incidence of IH in the low target infants.

Both groups showed a comparable decrease in duration and increase in severity of IH events during the first four weeks of life with no further changes throughout the study monitoring period. Previous data have suggested that infants with increased spontaneous apnea have an augmented ventilatory response to acute hypoxia [Nock]. Thus, although infants in the low target group may have been more susceptible to initiation of a hypoxic event, they may have been able to rally a compensatory ventilatory response and recover as well as infants in the high target group.

Previous data in animal models have suggested that the timing of patterns of IH events are important and may affect morbidity. Clustered patterns of IH events have been shown to be associated with enhanced retinal neovascularization when compared to equally dispersed patterns [Coleman]. This may be a result mediated by a hypoxia induced factor (HIF) [Smith] or reactive oxygen species (ROS) cascade known to occur in response to IH [Prabhakar 2011]. In response to hypoxic exposure, measurements of reactive oxygen species have shown an increase in superoxide anion concentration during the recovery phase, with a delayed response of a few minutes [Fabian]. Current preterm infant data from our group suggests that ROP is associated with a time interval between events of 1-20 min [Di Fiore to be submitted] corresponding to timing of the ROS increase. In contrast, the higher number of IH events in the low target group predominantly occurred with a time interval between events of less than 1 minute which may have limited the ROS response. However, the effect of the duration of recovery time on the resultant oxidative stress response has yet to be determined and merits further investigation.

There are limited data on the long term consequences of IH events in preterm infants [Martin &Fanaroff]. A history of apnea of prematurity during hospitalization [Taylor] and cardiorespiratory events in the home [Hunt 2004] have been associated with neurodevelopmental impairment. These studies have focused on apnea rather than the

accompanying hypoxemic events. The only study to address the latter issue is the observation that mean oxygen saturation during apnea has been shown to predict motor scores [Cheung 1999]. Further analysis is ongoing to assess the relationship between IH events and neurodevelopmental outcome in this infant cohort.

This study showed a higher incidence of IH in the low target group which is consistent with McEvoy et al showing a relationship between oxygen levels and IH in former preterm infants with chronic lung disease. However, the lower incidence of severe ROP in the main trial is in contrast to our previous findings of an association between IH and severe ROP [Di Fiore 2010]. This may be due to avoidance of early hyperoxic exposure associated with the first phase of angiogenesis of retinopathy of prematurity or differences in timing patterns of IH events shown to be associated with ROP[Di Fiore to be submitted].

This study was limited by the known challenge of keeping infants in a designated oxygen saturation target range [Laptook, Hagadorn]. The main SUPPORT trial revealed overlap in the median level of oxygen saturation between target groups with actual median oxygen saturation levels slightly higher than targeted levels in both treatment groups. [SUPPORT] This may have affected the number of IH events as lowering the median baseline saturation and increasing the time in the actual low target level may have resulted in an even higher incidence of IH events. In addition, the data used in this analysis were collected via pulse oximeters which remained in use from birth until 36 weeks postmenstrual age (PMA), but only during times when the infants were receiving respiratory support and during the three days after respiratory support was discontinued. Thus, data do not exist for time points four or more days after discontinuation of respiratory support or for time points following death, transfer to a non-study hospital, discharge, or 36 weeks PMA (whichever came first). The GEE models used in this analysis assume that any missing data are missing completely at random. This assumption probably does not hold for these data, because infants who dropped out of the data due to a poor outcome such as death, or a favorable outcome such as discharge or being able to breathe room air without support, are likely to differ from those who remained on respiratory support through 36 weeks PMA. Thus, this should be considered a conditional analysis; that is, it is conditioned upon being alive and on respiratory support, and the results provided by the GEE model for any given point in time should be interpreted as applying only to the subset of infants who were alive and on respiratory support at that time.

In conclusion, a low oxygen saturation target range is associated with an increased incidence of intermittent hypoxemic events that is dependent on post natal age. These events are of comparable duration and severity regardless of level of oxygen exposure. Further studies are needed to assess the contribution of timing of IH events and morbidity. We speculate that, to

minimize episodes of IH, the optimal O_2 saturation target may need to be adjusted by postmenstrual or postnatal age.

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Figure Legends:

Figure 1

A) A raw SaO2 waveform with the duration of the event and the time interval between events denoted by the arrows. B) An example tracing representing the same number of IH events occurring in a equally dispersed (top graph) and clustered (bottom graph) sequence.

Figure 2

A) The model based estimates showed an increase in IH events over the first 3 weeks of life in both infant groups followed by a decrease in IH events in the high target group (- - -)compared to a plateau in the low target group (—) . B) The relative rate of IH events (RR), (the ratio of the number of IH events in the low target group/ the number of IH events in the high target group), revealed a higher rate of IH events from <12 days, and >57 days of age in the low target group (* $p<0.05$).

Figure 3

IH event duration decreased and severity worsened with increasing postnatal age in both the low and high target groups with no differences between groups.

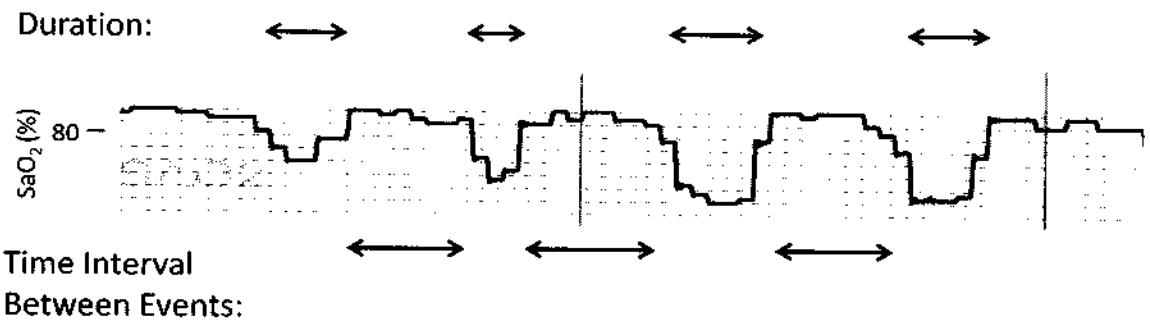
Figure 4

A) The number of IH events was documented for three time interval ranges; <1 minute, 1-20 minutes and, >20 minutes between IH events. The highest incidence of events occurred with a time interval between events of <1 min, followed by a time interval of 1-20 minutes. There were relatively few IH events that occurred with a time interval of >20 minutes between events. B) IH events occurring with a time interval between events of <1 minute were associated with a significantly higher relative rate of IH events in the low target group at <15 and >54 days of life ($p<0.05$). IH events occurring with a time interval of 1-20 minutes between event had a higher relative rate of IH events >65 days of life ($p<0.05$). IH events occurring >20 min apart were comparable between target groups with a relative rate of approximately one throughout the monitoring period.

	Low Target (53)	High Target (62)	p value
Birth Weight (gm)	810±179	846±193	0.29
Gestational Age (wk)	26.2±1.0	26.2±1.1	0.98
BPD (O_2 @ 36 wk)	15 (28%)	23 (38%)	0.36
Death before 36 wk PMA	3 (6%)	0 (0%)	0.10
Caffeine (% of monitoring period)	80±20%	82±20	0.58
Respiratory Support * (% of monitoring period)	86%	92%	0.03

*High frequency jet ventilation, CPAP, conventional ventilation, nasal cannula, Nasal SIMV, or hood

A



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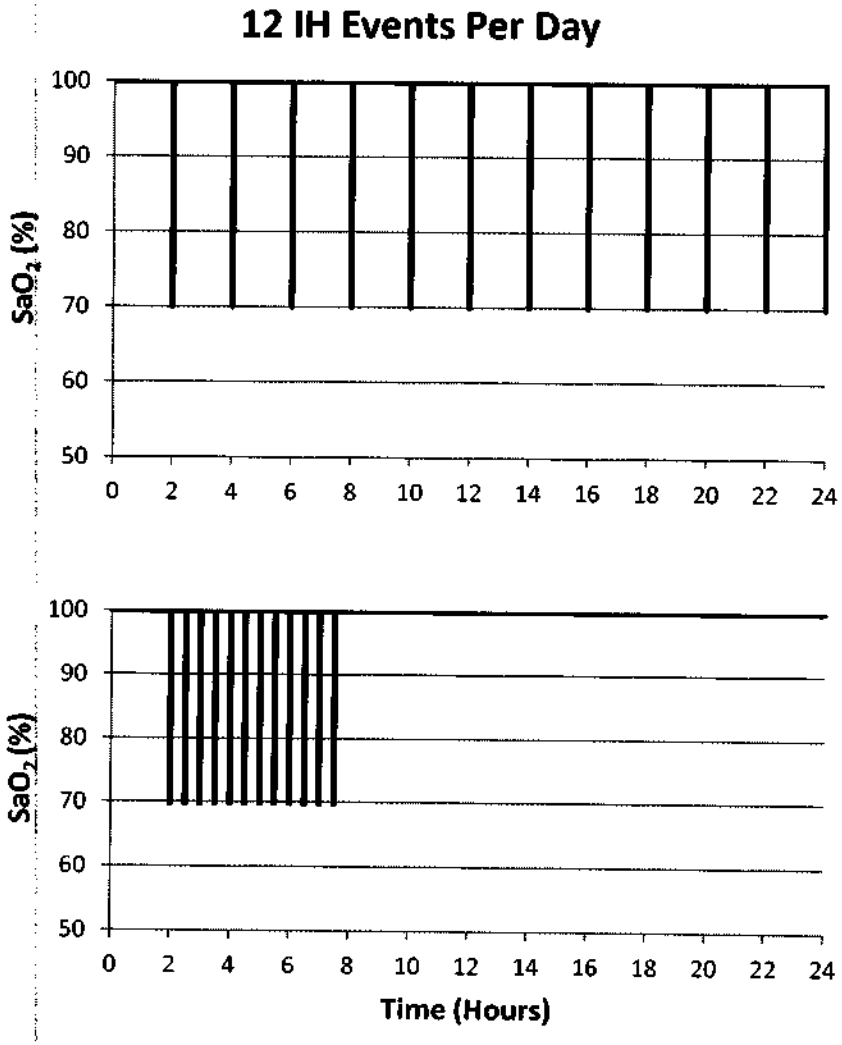
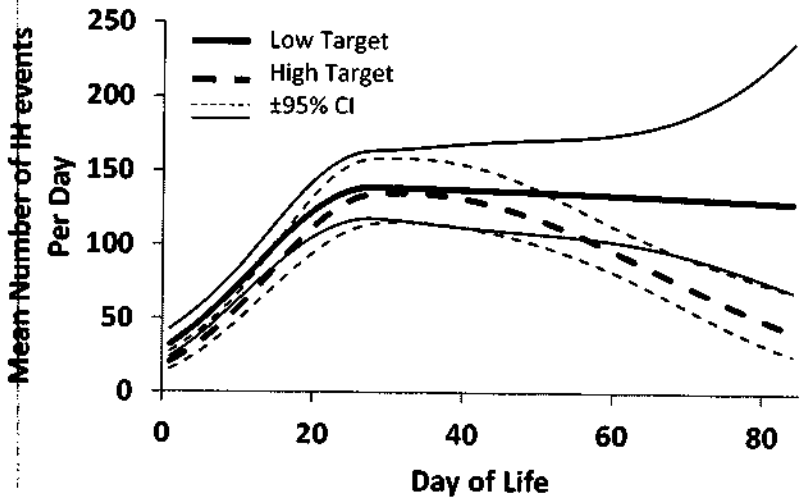


Fig 1

A



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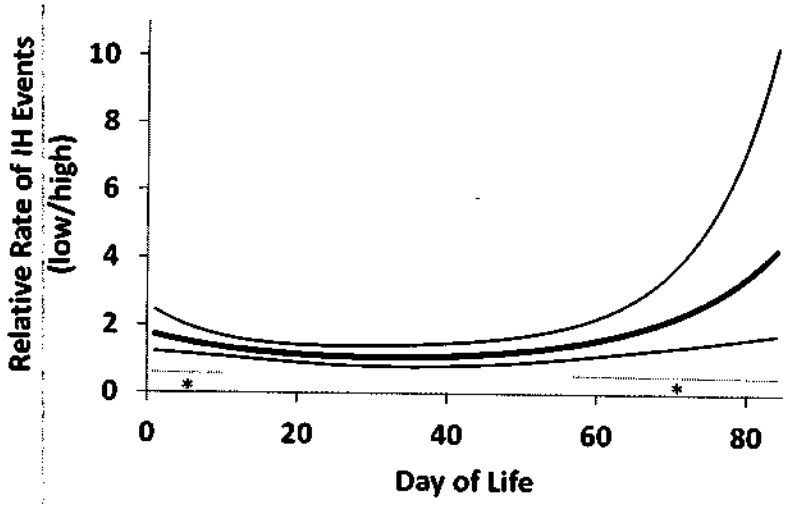
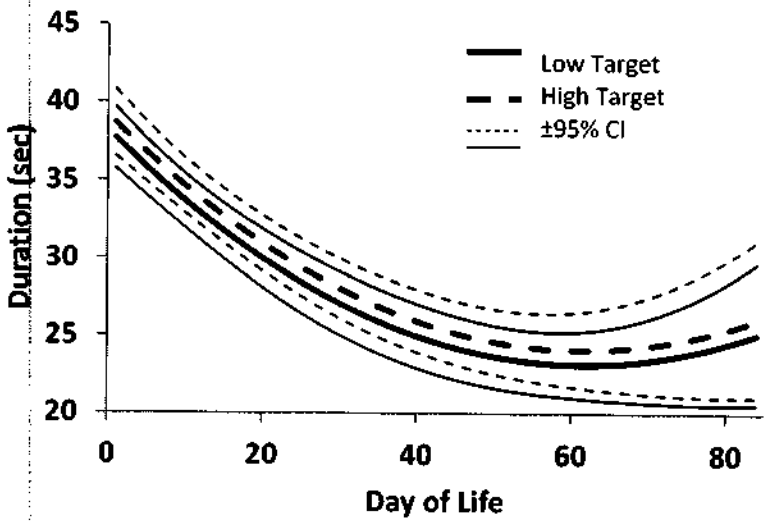


Fig. 2

A



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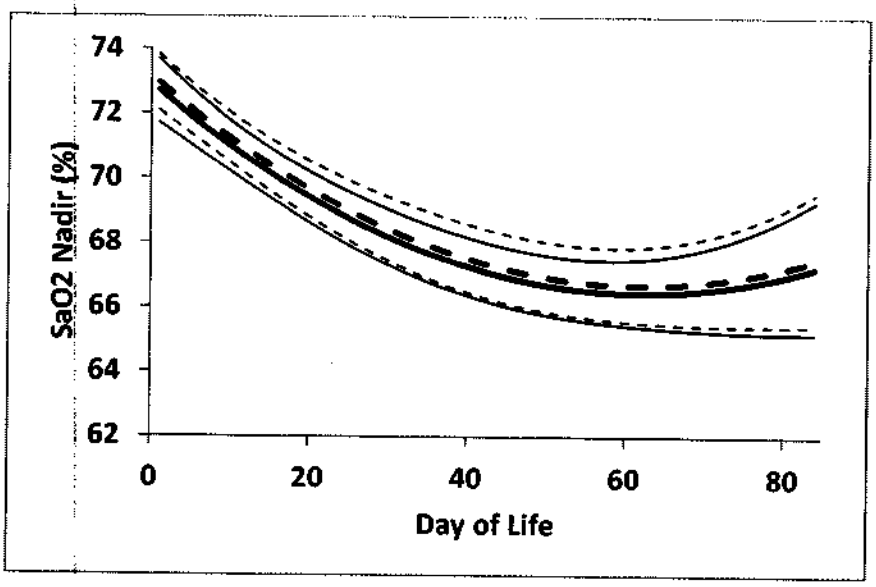

Fig 3

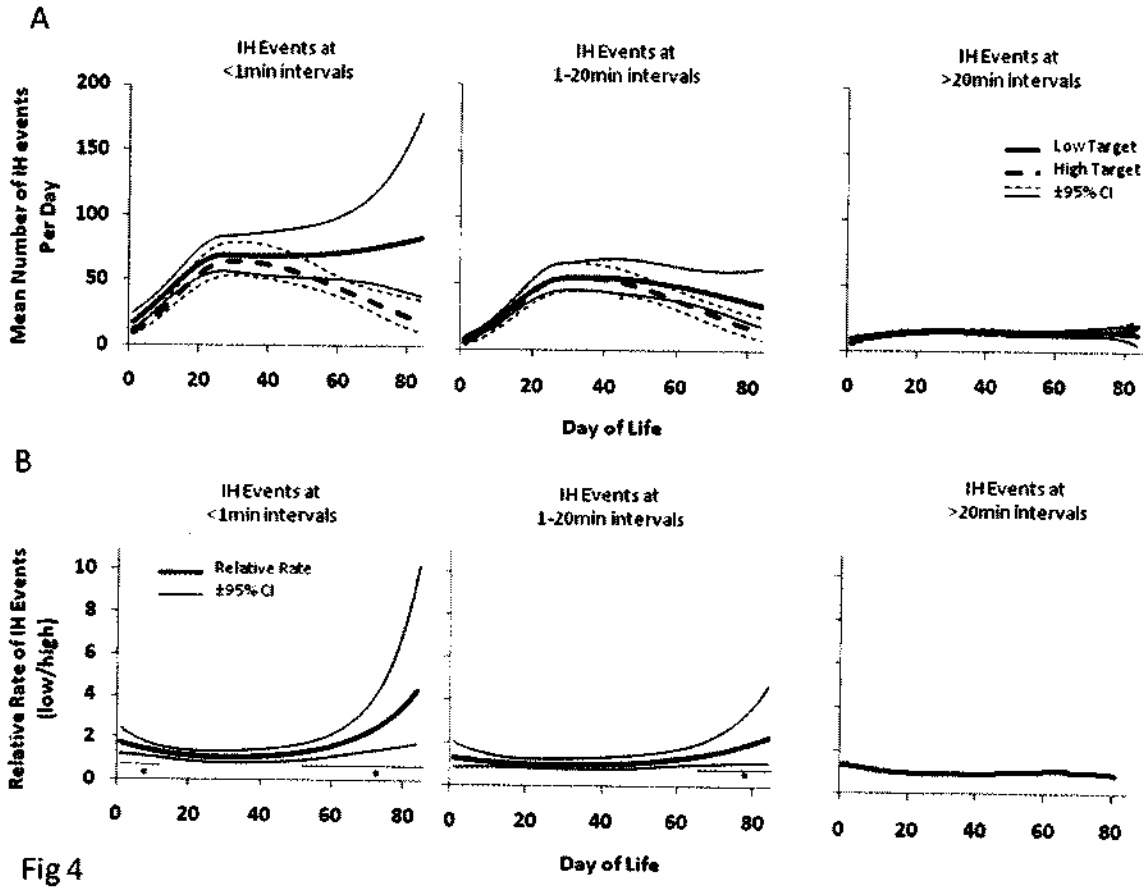

Fig 4

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "wcarlo@peds.uab.edu"; "mperalta@peds.uab.edu"
Cc: "adas@rti.org"
Subject: Re: SUPPORT FU Paper
Date: Thursday, September 01, 2011 2:22:19 PM

Fabulous!
Thanks for all the effort!
Rose

From: Wally Carlo, M.D. <WCarlo@peds.uab.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]; Myriam Peralta, M.D. <MPeralta@peds.uab.edu>
Sent: Thu Sep 01 14:14:58 2011
Subject: RE: SUPPORT FU Paper

Rose:

Myriam sent me a draft yesterday. I have been working on it. I will get a draft to both of you tomorrow.

wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
1700 6th Avenue South
176F Suite 9380R
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From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, September 01, 2011 9:19 AM
To: Myriam Peralta, M.D.
Cc: Wally Carlo, M.D.
Subject: SUPPORT FU Paper

Myriam
Can you please send us the working draft of the SUPPORT follow up paper?
Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
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higginsr@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Wally Carlo, M.D."
Cc: "Kathryn Fallon"
Subject: RE: Safe O2 paper draft 1.1
Date: Wednesday, August 31, 2011 9:51:00 AM
Attachments: Safe and Optimal Oxygen Therapy in Preterm Infants_NA_rdh.doc
Clean copy Safe and Optimal Oxygen Therapy in Preterm Infants_NA_rdh.doc

Wally
I made some changes and am sending the one marked "Clean copy" through NICHD clearance.

Thanks for including me

Rose

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From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Monday, August 29, 2011 5:49 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Kathryn Fallon
Subject: Safe O2 paper draft 1.1

Hi Rose:

I have enclosed Ambal's tracked changes. Please use this draft.

wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
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From: Namasivayam Ambalavanan
Sent: Monday, August 29, 2011 4:43 PM
To: Wally Carlo, M.D.
Subject: RE:

Looks great! I have made some minor suggestions,
Ambal

N. Ambalavanan MD
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Professor, Departments of Pediatrics, Cell Biology, and Molecular and Cellular Pathology
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From: Wally Carlo, M.D.
Sent: Monday, August 29, 2011 4:23 PM
To: Namasivayam Ambalavanan
Subject: FW:

I added MD to your name!!! Sorry.

wally

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From: Kathryn Fallon
Sent: Monday, August 29, 2011 4:07 PM
To: Wally Carlo, M.D.
Subject:

8-29-2011
Rev. 1.10

Safe and Optimal Oxygen Therapy in Preterm Infants

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[1]University of Alabama at Birmingham, Birmingham, Alabama, United States; [2]*Eunice Kennedy Shriver* National Institute of Child Health and Human Development, Bethesda, MD

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Word count: 1,122

4-14108

INTRODUCTION

For many years, there has been an ongoing controversy regarding the optimal levels of oxygenation that should be targeted in preterm infants. When oxygen therapy became widely used in preterm infants in the 1940s, there was an increase in retinopathy and blindness. Randomized trials of restricted versus unrestricted supplementation of oxygen showed that retinopathy was decreased with oxygen restriction in the era preceeding use of pulse oximetry.[1] However, meta-analyses of these trials subsequently showed although retinopathy was reduced, ~~that~~ mortality tended to be increased with oxygen restriction.[1,2] A retrospective study soon after reported an increase in mortality and cerebral palsy with oxygen restriction.[3] In the 1960s, the practice of restricting oxygen supplementation was estimated to result in an increase in 16 deaths per case of ~~blinded~~ blindness prevented.[4]

Oxygen Saturation Targeting Starting Soon After Birth

Availability of pulse oximetry in the mid-late 1980's allowed continuous monitoring of oxygenation both early after birth and late in the neonatal course. In non-randomized studies, several groups of investigators initially reported that the incidence of severe or threshold retinopathy of prematurity could be reduced by targeting oxygen saturations ~~on~~ towards the lower end of the range used clinically. In three before-and-after design studies, target levels of oxygen saturation of about 83 to 95% were associated with ~~a decrease in the incidence of~~ less retinopathy ~~of prematurity,~~ when compared with ~~a retrospective~~ the "before" period ~~before~~ when targeting was done ~~per~~ at clinicians discretion and higher saturations were accepted.[5, 6, 7] In a

survey of clinical practices in 144 neonatal intensive care units (NICUs), the rate of retinal ablation surgery was 5.6% in NICUs using oxygen saturation targets of 98% or higher, 3.1% in NICUs using targets of less than 98%, and 1.4% in NICUs using targets ≤ 92%.[8] In a retrospective study in which outcomes in five NICUs were compared, the incidence of severe retinopathy requiring ablation surgery was 27% in NICUs with oxygen saturations target levels of 88-98% and only 6% in NICUs where the target level was 70 to 90%.[9] However, these studies have major limitations because of lack of or inadequate control groups. Furthermore, in these studies, the major reduction in retinopathy was reported with prevention of very high saturations such as > 98%, which has not been an acceptable practice for years.

Investigators of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Neonatal Research Network designed the SUPPORT Trial to target two ranges of saturations within the range used by most clinicians. Thus, infants were randomized before birth to oxygen saturation targets of 85 to 89% or to 91 to 95%. Infants were included if they were 24 to $27^{6/7}$ weeks gestation, the most premature ones who usually get full support in most NICUs in the United States and other middle-to-high-income countries. Electronically-altered pulse oximeters displayed saturations of 88 to 92% when infants in the lower saturation target groups had saturations of 85 to 89% and when infants in the high saturations group had saturations of 91 to 95% using an offset of 3% in opposite directions. Use of these monitors allowed masking of clinicians and separation of oxygen exposure (Figure 1). Targeting was initiated no later than at 2 hours after birth and continued until the infants were off oxygen supplementation and respiratory support or until they were 36 weeks post-menstrual age.

With 1316 patients randomized (Table 1), the trial showed that targeting oxygen saturations of 85 to 89% decreased the incidence of severe retinopathy (defined as indication for ablation therapy) from 17.9 to 8.6% ($p < 0.05$, Table 2). However, targeting oxygen saturations of 91 to 95% decreased hospital mortality from 19.9 to 16.2% ($p < 0.05$) and the combined outcome of severe retinopathy~~/~~ or death ~~were~~ was not significantly ~~affected~~different between the two saturation target groups. In addition, bronchopulmonary dysplasia and other major outcomes such as intraventricular hemorrhage, periventricular leukomalacia, necrotizing enterocolitis, ~~and~~ patent ductus arteriosus, etc were not significantly impacted. Long term follow-up is planned but because the increase in mortality exceeds the rates of blindness in this population, there are concerns that using low saturation targeting of 85 to 89% ~~or lower can no longer be recommended~~ should be avoided until long-term data are reported.

Other investigators have reproduced the SUPPORT Trial design using the same oxygen saturation targets. Trials similar to the SUPPORT Trial were led by investigators in the United Kingdom, Australia, New Zealand, and Canada. A joint safety analysis of survival was undertaken pooling 2315 infants from three of these four trials together with the 1316 infants in the SUPPORT Trial.[10] This analysis revealed that oxygen saturation targeting in the range of 91 to 95% resulted in an increase in survival from 14.4 to 17.3% ($p < 0.05$). The results of one trial have not been published yet.

These trials indicate that oxygen saturations targeting of 91-95% increase survival by about 3%, which is a large effect in this high risk population and is at least twice as large as the rate of blindness observed in this population in comparable NICUs. Thus, saturation targets of 91 to

95% should be considered for use by clinicians in these infants until further data including follow up are available.

Oxygen Saturation Targets Late in the Neonatal Intensive Care Unit Course

Two randomized controlled trials have been conducted to determine if targeting high saturations in preterm infants after the neonatal period and at home (if necessary) would improve outcomes.[3] The STOP-ROP Trial enrolled infants with confirmed prethreshold retinopathy of prematurity.[11] This trial reported that supplemental oxygen to target oxygen saturations of 96 to 99% did not affect progression of prethreshold retinopathy or use of ablation surgery. However, targeting saturations of 96 to 99% compared to saturations of 89 to 94% resulted in increased risk of adverse pulmonary events including pneumonia and/or exacerbation of bronchopulmonary dysplasia and the need for oxygen and diuretics, hospitalization at three months of corrected age, and oxygen supplementation at home.

A second trial randomized infants to higher (95 to 98%) versus lower oxygen saturation (91 to 94%) at about one month of age in an attempt to improve growth and neurodevelopment as practiced by some. This trial showed that the duration of oxygen supplementation doubled in the higher oxygen saturations group without benefits in growth or neurodevelopment.[12] There were 6 deaths due to pulmonary causes in the high oxygen saturation group and one such death in the lower oxygen saturation group ($p = 0.12$). Thus, in both of these trials targeting of oxygen saturations in the low 90s in the post neonatal period in preterm infants resulted in less adverse pulmonary outcomes compared to targeting of oxygen saturation sin the high 90s.

Best Practice and Conclusions

Recent high level evidence indicates that targeting of oxygen saturation in the low 90s (91-94 or to -95%) results in better outcomes including survival and pulmonary outcomes compared to higher or lower ranges. While follow-up data and data from future trials may modify the conclusions, the current evidence-based medicine approach supports oxygen saturations targeting in the low 90s in extremely preterm infants.

REFERENCES

1. Duc G, Sinclair JC. Oxygen Administration. In: Sinclair JC, Bracken MB, eds. Effective care of the newborn infant. New York: Oxford University Press, 1992:178-194.

2. Askie LM, Henderson-Smart DJ, Ko H. Restricted versus liberal oxygen exposure for preventing morbidity and mortality in preterm or low birth weight infants. Cochrane Database Syst Rev. 2009;1:CD001077.

3. Avery ME, Oppenheimer EH. Recent increase in mortality in hyaline membrane disease. J Pediatr 1960;57:553-559

4 Bolton DP, Cross KW. Further observations on cost of preventing retrolental fibroplasia. Lancet 1974:303-445-448.

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12. Askie LM, Henderson-Smart DJ, Irwing L, Simpson JM, Oxygen-saturation targets and outcomes in extremely preterm infants. N Engl J Med 2003;349:959-967.

Biography:

Waldemar A. Carlo, MD: Professor of Pediatrics and Director of the Division of Neonatology of the University of Alabama at Birmingham. His main interest is in pulmonary disorders in neonates, neonatal mortality, and clinical trials.

Rosemary D. Higgins, MD: Program Scientist for the NICHD Neonatal Research Network. Her main interest is in retinopathy and clinical trials.

Namasivayam Ambalavanan, MD: Professor of Pediatrics and Director of the Division of Neonatology Research at the University of Alabama at Birmingham. His main interest is in lung injury and clinical trials.

Figure 1:

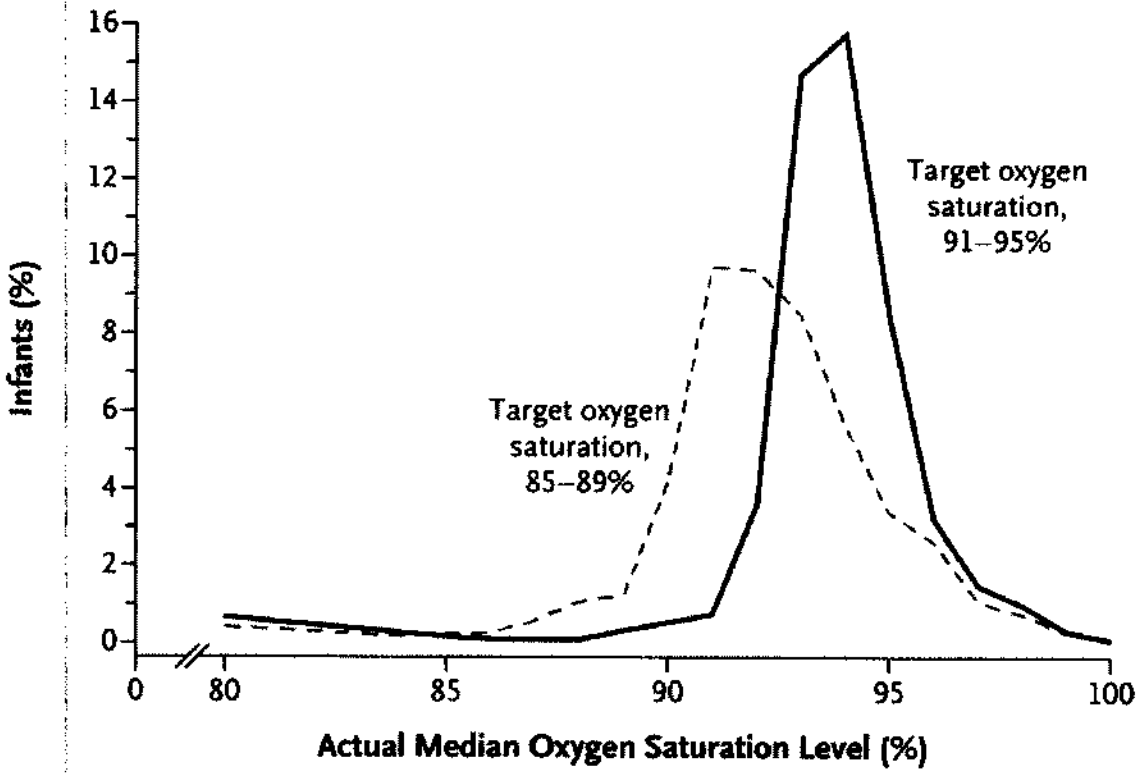

Table 1 Baseline Characteristics of the Patients

Table 1. Baseline Characteristics of the Patients

Characteristic	Lower Oxygen Saturation (N = 654	Higher Oxygen Saturation (N = 662)
Birth weight – g	836±193	825±193
Gestational age – wk	26±1	26±1
Male sex – no./total no. (%)	341/654 (52.1)	371/662 (56.0)
Maternal use of antenatal corticosteroids – no./total no. (%)	633/654 (96.8)	632/661 (95.6)

P>0.05 for all comparisons.

Table 2. Major Outcomes*

Outcome	Lower Oxygen Saturation (N = 654)	Higher Oxygen Saturation (N = 662)	Adjusted Relative Risk (95% CI)
	No./total no. (%)		
Severe retinopathy of prematurity or death before discharge	171/605 (28.3)	198/616 (32.1)	0.90 (0.76-1.06)
Severe retinopathy of prematurity	41/475 (8.6)	91/509 (17.9)	0.52 (0.37-0.73)
Death			
Before discharge	130/654 (19.9)	107/662 (16.2)	1.27 (1.01-1.60)
By 36 wk postmenstrual age	114/654 (17.4)	94/662 (14.2)	1.27 (0.99-1.63)
BPD, physiological definition at 36 wk	205/540 (38.0)	237/568 (41.7)	0.92 (0.81-1.05)
BPD, physiological definition, or death by 36 wk	319/654 (48.8)	331/662 (50.0)	0.99 (0.90-1.10)

8-29-2011
Rev. 1.1

Safe and Optimal Oxygen Therapy in Preterm Infants

Waldemar A. Carlo, M.D.[1] Rosemary D. Higgins, MD[2], Namasivayam Ambalavanan, MD[1]

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Word count: 1,122

4-14120

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higher, 3.1% in NICUs using targets of less than 98%, and 1.4% in NICUs using targets ≤ 92%.[8] In a retrospective study in which outcomes in five NICUs were compared, the incidence of severe retinopathy requiring ablation surgery was 27% in NICUs with oxygen saturations target levels of 88-98% and only 6% in NICUs where the target level was 70 to 90%.[9] However, these studies have major limitations because of lack of or inadequate control groups. Furthermore, in these studies, the major reduction in retinopathy was reported with prevention of very high saturations such as > 98%, which has not been an acceptable practice for years.

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therapy) from 17.9 to 8.6% ($p < 0.05$, Table 2). However, targeting oxygen saturations of 91 to 95% decreased hospital mortality from 19.9 to 16.2% ($p < 0.05$) and the combined outcome of severe retinopathy or death was not significantly different between the two saturation target groups. In addition, bronchopulmonary dysplasia and other major outcomes such as intraventricular hemorrhage, periventricular leukomalacia, necrotizing enterocolitis, patent ductus arteriosus, etc were not significantly impacted. Long term follow-up is planned but because the increase in mortality exceeds the rates of blindness in this population, there are concerns that using low saturation targeting of 85 to 89% should be avoided until long-term data are reported.

Other investigators have reproduced the SUPPORT Trial design using the same oxygen saturation targets. Trials similar to the SUPPORT Trial were led by investigators in the United Kingdom, Australia, New Zealand, and Canada. A joint safety analysis of survival was undertaken pooling 2315 infants from three of these four trials together with the 1316 infants in the SUPPORT Trial.[10] This analysis revealed that oxygen saturation targeting in the range of 91 to 95% resulted in an increase in survival from 14.4 to 17.3% ($p < 0.05$). The results of one trial have not been published yet.

These trials indicate that oxygen saturations targeting of 91-95% increase survival by about 3%, which is a large effect in this high risk population and is at least twice as large as the rate of blindness observed in this population in comparable NICUs. Thus, saturation targets of 91 to 95% should be considered for use by clinicians in these infants until further data including follow up are available.

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Two randomized controlled trials have been conducted to determine if targeting high saturations in preterm infants after the neonatal period and at home (if necessary) would improve outcomes.[3] The STOP-ROP Trial enrolled infants with confirmed prethreshold retinopathy of prematurity.[11] This trial reported that supplemental oxygen to target oxygen saturations of 96 to 99% did not affect progression of prethreshold retinopathy or use of ablation surgery. However, targeting saturations of 96 to 99% compared to saturations of 89 to 94% resulted in increased risk of adverse pulmonary events including pneumonia and/or exacerbation of bronchopulmonary dysplasia and the need for oxygen and diuretics, hospitalization at three months of corrected age, and oxygen supplementation at home.

A second trial randomized infants to higher (95 to 98%) versus lower oxygen saturation (91 to 94%) at about one month of age in an attempt to improve growth and neurodevelopment as practiced by some. This trial showed that the duration of oxygen supplementation doubled in the higher oxygen saturations group without benefits in growth or neurodevelopment.[12] There were 6 deaths due to pulmonary causes in the high oxygen saturation group and one such death in the lower oxygen saturation group ($p = 0.12$). Thus, in both of these trials targeting of oxygen saturations in the low 90s in the post neonatal period in preterm infants resulted in less adverse pulmonary outcomes compared to targeting of oxygen saturation sin the high 90s.

Best Practice and Conclusions

Recent high level evidence indicates that targeting of oxygen saturation in the low 90s (91 to 95%) results in better outcomes including survival and pulmonary outcomes compared to higher or lower ranges. While follow-up data and data from future trials may modify the conclusions, the current evidence-based medicine approach supports oxygen saturations targeting in the low 90s in extremely preterm infants.

REFERENCES

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Biography:

Waldemar A. Carlo, MD: Professor of Pediatrics and Director of the Division of Neonatology of the University of Alabama at Birmingham. His main interest is in pulmonary disorders in neonates, neonatal mortality, and clinical trials.

Rosemary D. Higgins, MD: Program Scientist for the NICHD Neonatal Research Network. Her main interest is in retinopathy and clinical trials.

Namasivayam Ambalavanan, MD: Professor of Pediatrics and Director of the Division of Neonatology Research at the University of Alabama at Birmingham. His main interest is in lung injury and clinical trials.

Figure 1:

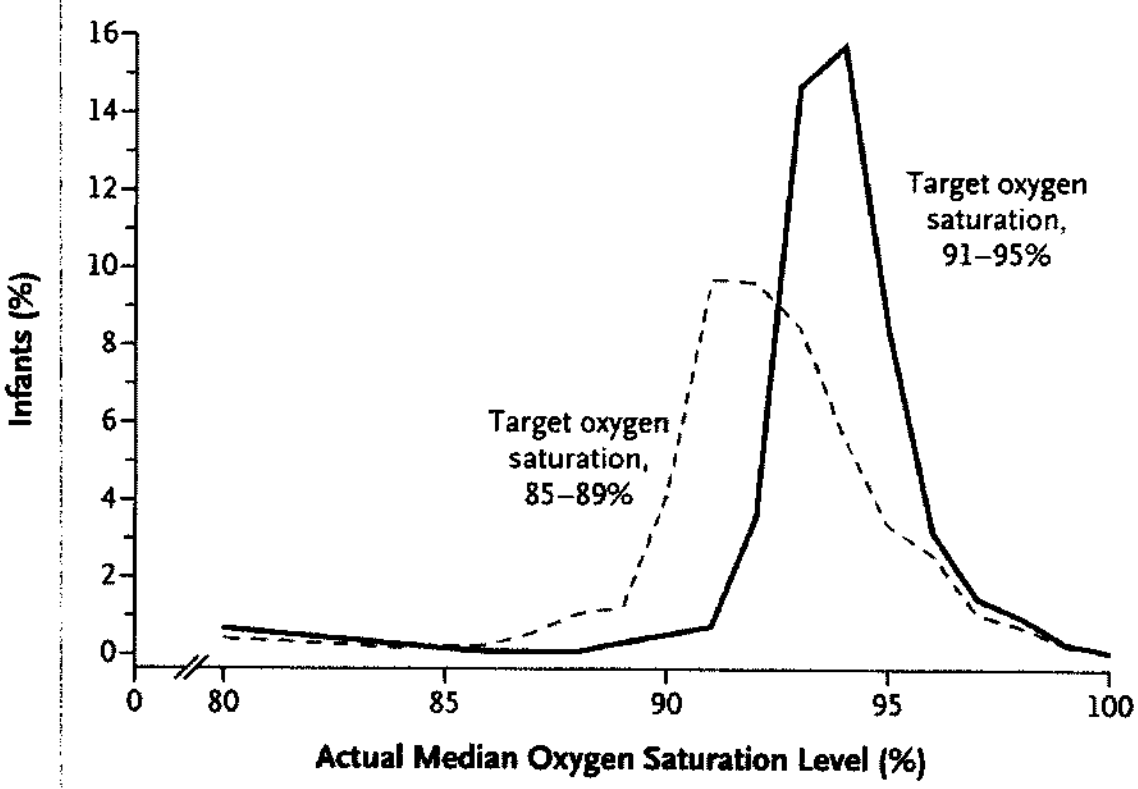

Table 1 Baseline Characteristics of the Patients

Table 1. Baseline Characteristics of the Patients

Characteristic	Lower Oxygen Saturation (N = 654	Higher Oxygen Saturation (N = 662)
Birth weight – g	836±193	825±193
Gestational age – wk	26±1	26±1
Male sex – no./total no. (%)	341/654 (52.1)	371/662 (56.0)
Maternal use of antenatal corticosteroids – no./total no. (%)	633/654 (96.8)	632/661 (95.6)

P>0.05 for all comparisons.

Table 2. Major Outcomes*

Outcome	Lower Oxygen Saturation (N = 654)	Higher Oxygen Saturation (N = 662)	Adjusted Relative Risk (95% CI)
	No./total no. (%)		
Severe retinopathy of prematurity or death before discharge	171/605 (28.3)	198/616 (32.1)	0.90 (0.76-1.06)
Severe retinopathy of prematurity	41/475 (8.6)	91/509 (17.9)	0.52 (0.37-0.73)
Death			
Before discharge	130/654 (19.9)	107/662 (16.2)	1.27 (1.01-1.60)
By 36 wk postmenstrual age	114/654 (17.4)	94/662 (14.2)	1.27 (0.99-1.63)
BPD, physiological definition at 36 wk	205/540 (38.0)	237/568 (41.7)	0.92 (0.81-1.05)
BPD, physiological definition, or death by 36 wk	319/654 (48.8)	331/662 (50.0)	0.99 (0.90-1.10)

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Myriam Peralta, M.D."
Subject: RE: SUPPORT FU PAPERS??
Date: Monday, August 29, 2011 9:26:00 AM

MYRIAM,
I KNOW THIS IS (b)(6) - CAN YOU SEND US THE DRAFT MANUSCRIPT AND WE CAN GET IT MOVING THROUGH THE NRN SYSTEM.
TAKE CARE
ROSE

Rosemary D. Higgins, MD
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higginsr@mail.nih.gov

From: Myriam Peralta, M.D. [mailto:MPeralta@peds.uab.edu]
Sent: Friday, August 26, 2011 11:29 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT FU PAPERS??

Thank you

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Fri 8/26/2011 8:38 AM
To: Myriam Peralta, M.D.
Subject: RE: SUPPORT FU PAPERS??

Myriam
I am (b)(6)

Take care
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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From: Myriam Peralta, M.D. [mailto:MPeralta@peds.uab.edu]
Sent: Thursday, August 25, 2011 12:45 PM
To: Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; Yvonne Vaucher
Cc: nfiner@ucsd.edu; Gantz, Marie; Wallace, Dennis; Das, Abhik
Subject: RE: SUPPORT FU PAPERS??

I apologize for not sending the draft earlier, (b)(6) (b)(6) but I will send a draft by this weekend, thank you.

From: Wally Carlo, M.D.
Sent: Thursday, August 25, 2011 7:51 AM
To: 'Higgins, Rosemary (NIH/NICHD) [E]'; 'Yvonne Vaucher'; Myriam Peralta, M.D.
Cc: nfiner@ucsd.edu; Gantz, Marie; 'Wallace, Dennis'; 'Das, Abhik'
Subject: RE: SUPPORT FU PAPERS??

Could the drafts be circulated soon even if incomplete so we can start giving feedback?

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
1700 6th Avenue South
176F Suite 9380R
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Phone: 205 934 4680
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From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, August 25, 2011 7:44 AM
To: 'Yvonne Vaucher'; Myriam Peralta, M.D.
Cc: nfiner@ucsd.edu; Wally Carlo, M.D.; Gantz, Marie; 'Wallace, Dennis'; 'Das, Abhik'
Subject: SUPPORT FU PAPERS??

Hi,

How are we doing on the manuscript drafts of the SUPPORT FU papers? Please let us know as we would like to get these moving.

Thanks
Rose

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Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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higginsr@mail.nih.gov

From: Finer, Neil
To: Gantz, Marie
Cc: Vaucher, Yvonne; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Wally Carlo, M.D.
Date: Sunday, August 28, 2011 10:31:33 PM

Hi Marie
Can you please send me the actual results of the analyses that you did looking at the small and large strata and comparing the hi and low sat arms with CPAP vs Surf
Many thanks
Neil

Neil N. Finer, M.D.
Professor of Pediatrics
Director, Division of Neonatology
Department of Pediatrics
UC San Diego School of Medicine
UC San Diego Medical Center
402 Dickinson Street, MPF 1-140
San Diego, CA 92103
Telephone: 619-543-3759
Facsimile: 619-543-3812

From: Finer, Neil
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Martinez, Fernando
Subject: RE: Questions:CPAP vs Surfactant
Date: Sunday, August 28, 2011 4:37:03 PM

Hi Rose
Glad to hear that you guys escaped
I will call you at about 12:15 your time - 9:15 here if that is OK
If not let me know a better time
Be well
Neil

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Sunday, August 28, 2011 1:20 PM
To: Finer, Neil
Subject: Re: Questions:CPAP vs Surfactant

I am available except 11-noon and 2-3 ET. Let me know what works best for you.

We are fine from the hurricane!
Thanks for asking - talk to you soon

Rose

----- Original Message -----
From: Finer, Neil <nfiner@ucsd.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Sun Aug 28 13:39:42 2011
Subject: RE: Questions:CPAP vs Surfactant

Hi Rose
I will need to get the Tables as I Yvonne has them
I think we should talk about this
Are you available by phone tomorrow
Please give me a good time to call
Any damage from Irene??
Be well
Neil

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Sunday, August 28, 2011 6:55 AM
To: Finer, Neil; 'mgantz@rti.org'; Vaucher, Yvonne
Cc: 'wcarlo@peds.uab.edu'; Rich, Wade; 'adas@rti.org'
Subject: Re: Questions:CPAP vs Surfactant

Neil-
Which table are you using? The one for the GA strata? This would be post-hoc, right?
I need to think this through.

Thanks
Rose

----- Original Message -----
From: Finer, Neil <nfiner@ucsd.edu>
To: Gantz, Marie <mgantz@rti.org>; Vaucher, Yvonne <yvaucher@ucsd.edu>
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D. <WCarlo@peds.uab.edu>; Rich, Wade <wrich@ucsd.edu>; Das, Abhik <adas@rti.org>
Sent: Fri Aug 26 20:00:52 2011
Subject: RE: Questions:CPAP vs Surfactant

Hi Marie
These are VERY VERY different groups.
ROP is a much lesser issue in the larger strata babies, and they are generally much healthier babies
We need to look into this for any clues
Thanks for sending the data and your analyses
Be well
Neil

-----Original Message-----
From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Friday, August 26, 2011 3:50 PM
To: Finer, Neil; Vaucher, Yvonne
Cc: higginsr@mail.nih.gov; Wally Carlo, M.D.; Rich, Wade; Das, Abhik
Subject: RE: Questions:CPAP vs Surfactant

It is interesting, but there are opposite results in the 24-25 (lower ROP with CPAP) and 26-27 (higher ROP with CPAP) week strata. We would have to think about that carefully.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

-----Original Message-----
From: Finer, Neil [mailto:nfiner@ucsd.edu]
Sent: Friday, August 26, 2011 6:31 PM
To: Gantz, Marie; Vaucher, Yvonne
Cc: higginsr@mail.nih.gov; Wally Carlo, M.D.; Rich, Wade; Das, Abhik
Subject: RE: Questions:CPAP vs Surfactant

Hi Marie and Rose and Abhik
Yvonne and I have been looking very closely at this data
We postulated after looking at the data recently circulated by Marie, that there was likely to be a relationship between CPAP and low SpO2 in the 24-25 week strata.
The 24-25 wk strata is very interesting in that there appears to be an interaction between the SpO2 arm and the CPAP arm
It may be that, in fact, the combination of CPAP with Low SpO2 decreases ROP without increasing the risk of death.
Can we look at this in more depth. However this would need to be a separate paper and should not confuse or delay the follow-up manuscripts. We think that there may be a need to test this hypothesis in such infants
We would appreciate your thoughts
Neil and Yvonne

-----Original Message-----
From: Gantz, Marie [mailto:mgantz@rti.org]

Sent: Friday, August 26, 2011 1:29 PM
To: Vaucher, Yvonne
Cc: Finer, Neil
Subject: RE: Questions:CPAP vs Surfactant

Yvonne,

Please see my responses below. I received answers today to the last of the queries about the survival status of children who were last contacted in or after the FU window. I am working on new versions of the tables, and I will add the variable for no abnormalities to them.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

-----Original Message-----
From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]
Sent: Thursday, August 25, 2011 11:15 PM
To: Gantz, Marie
Cc: Finer, Neil; Vaucher, Yvonne
Subject: FW: Questions:CPAP vs Surfactant

Marie,

The data analyses raise several questions:

1. We are making multiple comparisons. Don't we need to adjust for this statistically? The adjustments given are for GA, familial clustering and center but not for multiple comparisons.

MG: I suggest the approach we used for the primary papers, which was to say that we made x number of comparisons, and we would expect no more than y of them to be statistically significant on the basis of chance alone.

2. The lower strata (24-25 weeks) clearly has different results than the higher strata (26-27 weeks) esp with respect to ROP. There was significantly more ROP in SURF survivors in the lower GA strata but in the reverse occurred in the higher GA strata. Since these were in opposite directions the overall incidence for CPAP and SURF in the combined strata was virtually identical. Although there was no interaction between arms for the entire group, is there an interaction between CPAP/SURF and LOW/High Sat arms in the individual GA strata? For instance would the lowest incidence of ROP in the lower strata be CPAP plus exposure to LowSat?

MG: The ROP results presented in Table 1 are unadjusted results (not adjusted for familial clustering, center, multiples) and are presented as background since ROP is not one of the outcomes for this paper. However, I did look briefly at whether there was interaction between

CPAP and saturation and there is, but only in the sense that the difference between CPAP vs. surfactant is significant (in both GA subsets) within the lower saturation target group and is not significant within the higher saturation target group. The direction of the CPAP effect is the same in both saturation groups as it is for the GA subset overall (for both GA groups).

3. What proportion of each group (CPAP/SURF) overall and for each strata (24-25 /26-27) was entirely normal (i.e. cognitive score 85+, GMFCS normal (DMS code 1); no functional hearing impairment (& no hearing aid/no cochlear implant), vision normal)

MG: I will add this to the next version of the tables.

Thanks!

Yvonne

Yvonne E. Vaucher, M.D., M.P.H.
Division of Neonatal/Perinatal Medicine
Clinical Professor of Pediatrics
UCSD School of Medicine

tele: 619-543-3759
FAX: 619-543-3812

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "wcarlo@peds.uab.edu"
Subject: Re: Safe Use of Oxygen Therapy for Preterm Infants
Date: Saturday, August 27, 2011 1:27:44 PM

Let me know what you need from me.

I also emailed (b)(6) and got the same. Answer - not easy

Rose

From: Wally Carlo, M.D. <WCarlo@peds.uab.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Fri Aug 26 21:45:34 2011
Subject: Re: Safe Use of Oxygen Therapy for Preterm Infants

Ok. We can do it.

I send het a nice note but she just thanked me without giving details.

Wally

-----Original message-----

From: "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>
To: "'wcarlo@peds.uab.edu'" <wcarlo@peds.uab.edu>
Sent: Sat, Aug 27, 2011 01:24:55 GMT+00:00
Subject: Re: Safe Use of Oxygen Therapy for Preterm Infants

I can but this would need to go through nichd clearance. We need about a week.
Let me know if this is possible.

Also, how is (b)(6)

Rose

From: Wally Carlo, M.D.
To: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Fri Aug 26 17:23:21 2011
Subject: FW: Safe Use of Oxygen Therapy for Preterm Infants

Hi Rose:

I have been asked to write this review. Would you like to be a co-author? It is due on Sept 6. I would have a draft to you by the middle of next week.

Wally

Wally Carlo, M.D.

Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
1700 6th Avenue South
176F Suite 9380R
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Cell: 205 (b)(6)

From: Kristen Ziegler [mailto:KZiegler@advanceweb.com]
Sent: Monday, July 11, 2011 3:35 PM
To: Wally Carlo, M.D.
Subject: RE: Safe Use of Oxygen Therapy for Preterm Infants
Importance: High

Wonderful! Thank you, Wally. Of course your two colleagues can join you in writing this piece. I've included writer's guidelines in the attached author's contract. If you and your colleagues could also please fill out the attached disclosure statement, that would be great. Please let me know if you have any questions or concerns. I look forward to working with you!

Best,
Kristen

Kristen Ziegler

Associate Editor / Web Editor

ADVANCE for Respiratory Care & Sleep Medicine

Phone: (800) 355-5627 x1803

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Friday, July 08, 2011 10:24 AM
To: Kristen Ziegler
Subject: [Junk released by User action] RE: Safe Use of Oxygen Therapy for Preterm Infants

Hi Kristen:

Sure, I can do it. Can I do it with two other colleagues?

Wally

From: Kristen Ziegler [mailto:KZiegler@advanceweb.com]

Sent: Thu 7/7/2011 3:49 PM
To: Wally Carlo, M.D.
Subject: Safe Use of Oxygen Therapy for Preterm Infants
Wally Carlo, MD
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
Birmingham, AL

Dear Dr. Carlo,

I am looking for an expert to write an article for ADVANCE for Respiratory Care & Sleep Medicine who will give a brief discussion of safe and optimal oxygen therapy in preterm infants.

Your colleague, Pablo J. Sánchez, MD, of the University of Texas Southwestern Medical Center recommended you for this project. I saw that you have extensively researched the use of oxygen in preterm infants as part of the Eunice Kennedy Shriver National Institute of Child Health and Human Development Global Network for Women's and Children's Health Research and I'm hoping that you'd be willing to share your expertise with our readers.

In general, the article should discuss existing controversies about targeting lower oxygen saturation levels in premature infants. Please briefly explain the questions surrounding its effect on retinopathy of prematurity, bronchopulmonary dysplasia, death, etc. Provide supporting evidence from recent literature when possible. Please also describe ongoing research into the effects on neurodevelopmental impairment and survival without ventilation. Also, any best practice tips for current practice would be valuable to our readers.

ADVANCE is a monthly trade publication with a readership of more than 20,000 medical directors, pulmonologists and respiratory department managers. The article would be featured in our September issue and should be approximately 1,200 words in length (four to five typed, double-spaced pages) due by August 12, 2011. Our articles present important information in an informal, reader-friendly style. I would be happy to send you a copy of the publication and writers guidelines.

If you are unable to pursue this project, I would appreciate it if you could recommend any peers who might be interested in writing the article.

Thanks so much for your help; I look forward to hearing from you.

Best,
Kristen

Kristen Ziegler

Associate Editor / Web Editor

ADVANCE for Respiratory Care & Sleep Medicine

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Visit: Website | Facebook<http://www.facebook.com/AdvanceRespCare?v=wall&ref=ts> | Twitter<http://twitter.com/ADVANCERespCare> | LinkedIn<http://www.linkedin.com/groups/ADVANCE-Respiratory-Care-Sleep-Medicine-3879940?home=&gid=3879940&trk=anet_ug_hm>

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Wally Carlo, M.D."
Subject: RE: SUPPORT FU PAPERS??
Date: Thursday, August 25, 2011 8:48:00 AM

If there is a need to assist with the writing, I can help.

Thanks
Rose

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From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Thursday, August 25, 2011 8:47 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT FU PAPERS??

I agree. I have sent Myriam reminders.

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
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From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, August 25, 2011 7:44 AM
To: 'Yvonne Vaucher'; Myriam Peralta, M.D.
Cc: nfiner@ucsd.edu; Wally Carlo, M.D.; Gantz, Marie; 'Wallace, Dennis'; 'Das, Abhik'
Subject: SUPPORT FU PAPERS??

Hi,

How are we doing on the manuscript drafts of the SUPPORT FU papers? Please let us know as we

would like to get these moving.

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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From: Higgins, Rosemary (NIH/NICHD) [E]
To: Blaisdell, Carol (NIH/NHLBI) [E]; Gail, Dorothy (NIH/NHLBI) [E]
Subject: another SUPPORT manuscript
Date: Wednesday, August 24, 2011 10:46:00 AM
Attachments: Rich, Antenatal Consent for SUPPORT and GDB, 2011-06-08 swa.docx

Here is a manuscript that is in review in the NRN. If you look at Table 3, you can see the enrolled versus non-enrolled infants and their outcomes.

Thanks for your support

Rose

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Antenatal Consent for SUPPORT – Is the enrolled population representative of all eligible ELBW Infants?

Wade Rich, BSHS RRT[1]; Marie G. Gantz, PhD[2]; Neil N. Finer, MD[1]; Nancy S. Newman, RN[3]; Angelita M. Hensman, RN BSN[4]; Ellen C. Hale, RN BS CCRC[5]; Kathy J. Auten, MSHS[6]; Kurt Schibler, MD[7]; Roger G. Faix, MD[8]; Abbot R. Laptook, MD[4]; Bradley A. Yoder, MD[8]; Abhik Das, PhD[9]; Seetha Shankaran, MD[10]; and the SUPPORT and Generic Database Subcommittees of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network

Short title: Antenatal Consent in a Large Multicenter Trial

Correspondence and reprint requests to:

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Keywords: Clinical Research/Trials, Informed Consent, Antenatal Steroids, Neonatal

The authors have no financial disclosures or conflicts of interest.

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[5] Emory University School of Medicine, Department of Pediatrics, and Children's Healthcare of Atlanta, Atlanta, GA
[6] Department of Pediatrics, Duke University, Durham, NC
[7] Department of Pediatrics, Cincinnati Children's Hospital Medical Center and University of Cincinnati, Cincinnati, OH
[8] Department of Pediatrics, Division of Neonatology, University of Utah School of Medicine, Salt Lake City, UT
[9] Statistics and Epidemiology Unit, RTI International, Rockville, MD
[10] Department of Pediatrics, Wayne State University, Detroit, MI

Acknowledgements

The National Institutes of Health, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), and the National Heart, Lung, and Blood Institute (NHLBI) provided grant support for the Neonatal Research Network's SUPPORT Trial.

Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Drs. Abhik Das (DCC Principal Investigator) and Marie Gantz (DCC Statistician) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study. The following investigators, in addition to those listed as authors, participated in this study:

NRN Steering Committee Chairs: Alan H. Jobe, MD PhD, University of Cincinnati (2003-2006); Michael S. Caplan, MD, University of Chicago, Pritzker School of Medicine (2006-2011).

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Emory University, Children's Healthcare of Atlanta, Grady Memorial Hospital, and Emory Crawford Long Hospital (U10 HD27851, UL1 RR25008, M01 RR39) - Barbara J. Stoll, MD; Susie Buchter, MD; Anthony Piazza, MD; David P. Carlton, MD.

Eunice Kennedy Shriver National Institute of Child Health and Human Development - Rosemary D. Higgins, MD; Stephanie Wilson Archer, MA.

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National Heart, Lung, and Blood Institute - Mary Anne Berberich, PhD; Carol J. Blaisdell, MD; Dorothy B. Gail, PhD; James P. Kiley, PhD.

RTI International (U10 HD36790) - W. Kenneth Poole, PhD; Margaret Cunningham, BS; Betty K. Hastings; Amanda R. Irene, BS; Jeanette O'Donnell Auman, BS; Carolyn Petrie Huitema, MS; James W. Pickett II, BS; Dennis Wallace, PhD; Kristin M. Zaterka-Baxter, RN BSN.

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University of New Mexico Health Sciences Center (U10 HD53089, M01 RR997) - Kristi L. Watterberg, MD; Robin K. Ohls, MD; Julie Rohr, MSN RNC CNS; Conra Backstrom Lacy, RN.

University of Rochester Medical Center, Golisano Children's Hospital (U10 HD40521, M01 RR44) - Nirupama Laroia, MD; Dale L. Phelps, MD; Linda J. Reubens, RN CCRC; Erica Burnell, RN.

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Wake Forest University, Baptist Medical Center, Brenner Children's Hospital, and Forsyth Medical Center (U10 HD40498, M01 RR7122) - T. Michael O'Shea, MD MPH; Nancy J. Peters, RN CCRP.

Wayne State University, Hutzel Women's Hospital, and Children's Hospital of Michigan (U10 HD21385) - Beena G. Sood, MD MS; Rebecca Bara, RN BSN; Elizabeth Billian, RN MBA; Mary Johnson, RN BSN.

Yale University, Yale-New Haven Children's Hospital, and Bridgeport Hospital (U10 HD27871, UL1 RR24139, M01 RR125, M01 RR6022) - Vineet Bhandari, MD DM; Richard A. Ehrenkranz, MD; Harris C. Jacobs, MD; Pat Cervone, RN; Patricia Gettner, RN; Monica Konstantino, RN BSN; JoAnn Poulsen, RN; Janet Taft, RN BSN.

Abstract

Background

The initial results of the SUPPORT antenatal consent study demonstrated that mothers of enrolled infants enrolled into the SUPPORT trial requiring antenatal parental consent were more educated, more likely to receive prenatal medical care, and were more likely to have received antenatal steroids (ANS), partial or full course compared to mothers of eligible but not enrolled infants.

Objective

The objective of this analysis was to compare the outcomes of death, severe intraventricular hemorrhage or periventricular leukomalacia (IVH/PVL) and death/severe IVH/PVL for infants enrolled in SUPPORT compared with eligible non-enrolled infants born at Neonatal Research Network centers during the period of SUPPORT trial recruitment (March 2005 through February 2009).

Methods:

Perinatal characteristics and neonatal outcomes were compared for enrolled and non-enrolled infants in bivariate analyses using t tests and chi-square tests. Logistic regression models were created to test the effect of enrollment in SUPPORT on outcomes, controlling for baseline perinatal characteristics.

Results

1316 infants were enrolled in SUPPORT, and 3053 infants were eligible but not enrolled during the same period. In bivariate analyses, SUPPORT infants were significantly older, heavier, and more likely to be of Non-Hispanic white origin ($p<.01$). A full course of antenatal steroids was provided to 71.7% of enrollees, and 49.4% of eligible infants not enrolled ($p<.001$). The frequency of 1 and 5 minute APGARs <3 was significantly greater in the non-enrolled group

(p<.001). Delivery room interventions, including intubation, compressions and epinephrine were significantly more frequent in the non-enrolled group (p<.001). The frequency of death in the first 12 hours was significantly higher in the non-enrolled group (4.1% vs. 2.0%, p<.001). In unadjusted analyses, infants enrolled in SUPPORT had significantly lower rates of death before discharge, severe IVH/PVL and death/severe IVH/PVL when compared to infants eligible but not enrolled (p<.001). In logistic regression models, enrollment in SUPPORT was not a significant predictor of the outcomes after controlling for GA, birth weight, sex, race, center, and ANS.

Conclusions

The results demonstrate important outcome differences among enrolled and non-enrolled infants in a neonatal trial employing antenatal consent. In future trials requiring antenatal consent, there may be a need to balance such important factors as receipt of ANS and prenatal care in selecting the approached families. Pursuit of a waiver of parental consent for minimal-risk trials of interventions in the delivery room or shortly after birth should be considered to promote generalizability of results.

Introduction

The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants (SUPPORT) was a randomized, 2X2 factorial designed multi-center trial conducted by the *Eunice Kennedy Shriver* NICHD Neonatal Research Network (NRN) (Clinical Trials Gov. Number, NCT 00233324). [1,2] The trial prospectively compared Continuous Positive Airway Pressure and a protocol driven limited ventilatory strategy begun in the delivery room and continuing in the Neonatal Intensive Care Unit with the early (< 1 hour) intratracheal administration of surfactant followed by conventional mechanical ventilation. Infants were also randomized to a prospective comparison of a lower oxygen saturation target range (85% to 89%) with a higher, more conventional target range (91% to 95%) until the infant was no longer requiring ventilatory support or oxygen, using purpose altered oximeters. Eligible infants were those born at NRN centers at 24 0/7 to 27 6/7 weeks gestational age (GA), without known major congenital malformations, and with full resuscitation intended. Antenatal consent was required for enrollment. Early screening and enrollment in SUPPORT suggested that antenatal screening and consent were labor intensive and that the number of patients enrolled seemed to be much lower than the number screened.

A prospective cohort study of the antenatal consenting practices of SUPPORT research personnel was conducted during the last half of the trial and the results published.[3] As part of the ongoing NRN Generic Database (GDB) observational study, data were collected routinely for inborn infants at NRN centers, including most of those who met the GA eligibility criteria for SUPPORT. These data were used to identify eligible, non-enrolled infants. In this previous analysis comparisons were made between enrolled vs non-enrolled eligible infants as well as between infants whose mothers were approached vs. not approached. Comparing all GDB infants who were eligible for SUPPORT but whose mothers were not approached to those whose

mothers were approached and consented revealed that mothers in the latter group were significantly more likely to be older, to have a high school degree, private medical insurance, and at least one prenatal care (PNC) visit. Infants of these mothers were more likely to be non-Hispanic white. Failure to be treated with antenatal steroids (ANS) was over 4 times more prevalent among infants who were eligible but not enrolled in SUPPORT compared to those enrolled.

In view of these results, we felt that it was essential to determine if the outcomes of infants enrolled in SUPPORT differed in substantial ways from infants enrolled in the GDB during the same period who were SUPPORT eligible but were not enrolled.

We postulated that the infants enrolled in SUPPORT would have lower mortality, a decreased incidence of death or IVH or PVL compared with infants of the same gestational ages who were entered into the NRN GDB during the period of SUPPORT recruitment (March 2005 through February 2009) but not enrolled in the trial.

Methods

This analysis compared infants enrolled in SUPPORT to those infants born at NRN centers who were eligible but not enrolled. Perinatal characteristics, delivery room interventions, and neonatal outcomes were compared for enrolled and non-enrolled infants in bivariate analyses using t-tests and chi-square tests.

Logistic regression models were created to test the effect of enrollment in SUPPORT on outcomes, controlling for perinatal characteristics.

Results

Infants in the non-enrolled group were significantly more likely to have an APGAR score of less than 3 at both 1 and 5 minutes, and delivery room interventions, including intubation, compressions and epinephrine were significantly more frequent in the non-enrolled group.

(Table 2) In unadjusted analysis of outcomes, infants enrolled in SUPPORT had significantly lower rates of death before discharge, severe intraventricular hemorrhage or periventricular leukomalacia (IVH/PVL), and death/severe IVH/PVL when compared to infants eligible but not enrolled. (Table 3)

In order to test the hypothesis that enrollment in SUPPORT itself played a role in the outcome differences seen, we tested the effect of enrollment on outcomes in logistic regression models which were corrected for birth weight, GA, sex, race, center, and ANS (any and full course). In these adjusted models, enrollment in SUPPORT was not a significant predictor of the outcomes.

Discussion

When providing the enrollment tables for their trials, authors generally start with an enumeration of eligible subjects, and then describe how many refused, had missing data, etc. This group of eligible subjects is better described as "identified eligible subjects," in other words, those whom the investigator identified as eligible at the time they would normally be approached for consent. What are missing from this group are those subjects who were missed by the investigators due to time of day, rapidity of admission, duration of stay, etc. Due to the nature of the GDB database of the Neonatal Research Network, which identifies and tracks all infants fitting broad gestational age criteria, we were able to look not just at the enrolled subjects, but also those who were not enrolled or in some cases were not even identified as eligible by the research team. This allowed us to make a unique comparison of all infants who were born in NRN centers who met the SUPPORT study criteria, both those who were enrolled and those who were not.

Our findings suggest that using antenatal consent to carry out a trial such as SUPPORT under the constraints of pre-intervention informed consent creates a situation where population bias is a

significant issue. Title 45 of the Code of Federal Regulations allows institutional review boards to waive some or all elements of consent.[4] Our previous observations, combined with the further analysis of this trial, suggest that allowing for the deferral of consent until after birth for trials comparing routinely used interventions can help to insure that we include the sickest and most at-risk populations, and thus contribute to a more generalizable study population

What remains unclear is how to deal with trials of greater than minimal risk that require antenatal consent. Current standards for waiver of consent would be the same as those used for 'emergency' trials, such as the use of a blood substitute in a pre-hospital environment. These requirements include high risk balanced with a life-threatening situation, a direct benefit, public disclosure, and the existence of an independent data safety board. Most near-birth trials would not meet the standard of a life-threatening situation, and neonatal trials with pre-specified direct benefit are also extremely uncommon.

We suggest that a middle ground, which includes most of the requirements of the Final Rule regarding waiver of consent, but eliminates the need for a life-threatening situation or a direct benefit, may be a reasonable compromise under certain circumstances to seek a waiver and a postnatal written consent to utilize the infant's information. This stipulation allows parents to decide if they want their infant's information included in the study if they disagree with their infant's participation. Such a stipulation should be considered when submitting such protocols to the Human Subjects Committee.

Conclusion

The results of this analysis demonstrate important outcome differences between enrolled and non-enrolled infants in the eligible population of a trial employing antenatal consent. In future trials requiring antenatal consent, there may be a need to balance such important factors as receipt of ANS and prenatal care in selecting the approached families. Pursuit of a waiver of

parental consent for minimal-risk trials of interventions in the delivery room or shortly after birth should be considered to promote generalizability of results.

Table 1.

Variable	Enrolled (N=1316)	Non-Enrolled (N=3053)	P-value
GA (weeks) (mean ± standard deviation)	26.2 +/- 1.1	26.0 +/- 1.2	<0.001
Birth weight (grams) (mean ± standard deviation)	830.1 +/- 193.2	812.5 +/- 191.8	0.006
Male	54.1%	52.6%	0.373
White, non-Hispanic	39.6%	36.1%	0.030
Prenatal Antibiotics	78.1%	65.4%	<0.001
Antenatal steroids (any)	96.2%	84.4%	<0.001
Antenatal steroids (full course)	71.7%	49.4	<0.001

Table 2.

Variable	Enrolled (N=1316)	Non-Enrolled (N=3053)	P-value
Apgar < 3 at 1 minute	24.4%	31.9%	<0.001
Apgar < 3 at 5 minutes	4.4%	8.4%	<0.001
PPV in the DR	65.7%		

CPAP in the DR	81.1%		
Intubated in DR	63.6%	75.8%	<0.001
Surfactant in DR or NICU	82.5%	86.5%	<0.001
Chest compressions in DR	5.9%	9.7%	<0.001
Epinephrine in DR	3.1%	6.0%	<0.001

Table 3.

Outcome	SUPPORT Enrolled (N=1316)	Non-Enrolled (N=3053)	p-value	Adjusted p-value
Death	18.0%	24.1%	<0.001	0.164
Intraventricular Hemorrhage (IVH) grade 3-4	13.0	17.6	<0.001	0.343
Periventricular Leukomalacia (PVL)	3.8%	5.1%	0.068	0.417
IVH 3-4 or PVL	15.1%	19.8%	<0.001	0.336
Death or IVH 3-4 or PVL	27.4%	35.6%	<0.001	0.103

Legends

Table 1 - **Demographic information for randomized versus non enrolled infants**

Table 2 - **Delivery room status and interventions**

Table 3 – **Neonatal outcomes. Adjusted values corrected for birth weight, GA, sex, race, center, and ANS.**

[1] SUPPORT Study Group of the *Eunice Kennedy Schriver* NICHD Neonatal Research Network, Finer, N. N. ; Carlo, W. A.; Walsh, M. C.; Rich, W.; Gantz, M. G.; Laptook, A. Ret al. Early CPAP versus Surfactant in Extremely Preterm Infants. N Engl J Meds. 2010; 362(21):1970-1979.

[2] SUPPORT Study Group of the *Eunice Kennedy Shriver* NICHD Neonatal Research Network, Carlo WA, Finer NN, Walsh MC, Rich W, Gantz MG, Laptook AR, et al. Target ranges of oxygen saturation in extremely preterm infants. N Engl J Med. 2010; 362(21):1959-69.

[3] Rich W, Auten K, Gantz M, Hale E, Hensman A and for the National Institute of Child Health and Human Development Neonatal Research Network. Antenatal Consent in the SUPPORT Trial: Challenges, Costs, and Representative Enrollment. Pediatrics 2010;126;e215-e221

[4] US Department of Health and Human Services. General requirements for informed consent, 45 CFR §46.116d

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Zaterka-Baxter, Kristin"
Subject: RE: Secondary SUPPORT Study
Date: Tuesday, August 23, 2011 3:28:00 PM

Ok
I'll get SC sign off on the call

Rose

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From: Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]
Sent: Tuesday, August 23, 2011 3:28 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Secondary SUPPORT Study

FYI Dennis and Abhik are fine with posting it to the public site too.

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, August 23, 2011 1:41 PM
To: Zaterka-Baxter, Kristin
Subject: Re: Secondary SUPPORT Study

I will ask the sc on today's call

From: Zaterka-Baxter, Kristin <kzaterka@rti.org>
To: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tue Aug 23 13:38:57 2011
Subject: RE: Secondary SUPPORT Study

Hi,
Since Matt's paper is now published, do you have any hesitation or concern about posting the estimator tool on the public site?
Thanks,
Kris

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, August 23, 2011 1:25 PM
To: 'Bradley.yoder@hsc.utah.edu'
Cc: Zaterka-Baxter, Kristin
Subject: Re: Secondary SUPPORT Study

Brad
You can submit a secondary to SUPPORT- it goes to the subcommittee first.
The BPD calculator was on the private website and should be available soon to the public.
I included Kris on the email as she handles the website.

Let me know if you need a protocol outline.
Thanks
Rose

From: Bradley Yoder <Bradley.Yoder@hsc.utah.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tue Aug 23 12:54:45 2011
Subject: Secondary SUPPORT Study

Hi Rose, hope you are well & surviving the DC summer.
I am contacting you to see if it is an option for me to request a secondary study related to the SUPPORT trial.
Although we are not now in the NRN, as a still function as a member of the sub-committee for SUPPORT I wondered if that meant I could submit a secondary study request.

Also, do you know if (and when if "yes") the NRN will be putting the BPD predictor algorithm on the website for public use?
As a different study I am interested in trying to apply this algorithm to the large NIPPV study group (2011 babies < 1000 gms) that we just completed as an external study group for further validation of the algorithm....obviously with NRN blessing and full involvement of the core group responsible for its development.

Thanks for your time and response to my questions.

Best regards,

Brad

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Bradley Yoder"
Cc: "kzaterka@rti.org"
Subject: RE: Secondary SUPPORT Study
Date: Tuesday, August 23, 2011 3:27:00 PM
Attachments: Protocol outline.doc

Here you go

Rose

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From: Bradley Yoder [mailto:Bradley.Yoder@hsc.utah.edu]
Sent: Tuesday, August 23, 2011 1:34 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: 'kzaterka@rti.org'
Subject: RE: Secondary SUPPORT Study

Yes, an outline would be very helpful.
Thank you for your quick reply!

Brad Yoder
Division of Neonatology
University of Utah SOM

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, August 23, 2011 11:25 AM
To: Bradley Yoder
Cc: 'kzaterka@rti.org'
Subject: Re: Secondary SUPPORT Study

Brad
You can submit a secondary to SUPPORT- it goes to the subcommittee first.
The BPD calculator was on the private website and should be available soon to the public.
I included Kris on the email as she handles the website.

Let me know if you need a protocol outline.
Thanks

Rose

From: Bradley Yoder <Bradley.Yoder@hsc.utah.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tue Aug 23 12:54:45 2011
Subject: Secondary SUPPORT Study

Hi Rose, hope you are well & surviving the DC summer.
I am contacting you to see if it is an option for me to request a secondary study related to the SUPPORT trial.
Although we are not now in the NRN, as a still function as a member of the sub-committee for SUPPORT I wondered if that meant I could submit a secondary study request.

Also, do you know if (and when if "yes") the NRN will be putting the BPD predictor algorithm on the website for public use?
As a different study I am interested in trying to apply this algorithm to the large NIPPV study group (1011 babies < 1000 gms) that we just completed as an external study group for further validation of the algorithm....obviously with NRN blessing and full involvement of the core group responsible for its development.

Thanks for your time and response to my questions.

Best regards,

Brad

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Protocol outline

A. Abstract

B. Statement of the Problem

C. Hypothesis

D. Specific Aims

E. Rationale/justification

F. Background / Previous Studies

G. Method/ Procedures

1. Description of study design (masked, randomized etc.)_
2. Definition of study population (with inclusion/exclusion criteria)
3. Description of study intervention
4. Precise definition of primary/secondary outcomes
5. Sample size estimate with some statistical support (including estimate of compliance and consent rates) based upon primary outcome.
6. Available population/compatibility with other ongoing protocols
7. Estimate of projected recruitment time

H. Risks/benefits, with estimate of frequency/severity of risks.

I. Budget estimate

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Gantz, Marie"; "Wally Carlo, M.D."; "Myriam Peralta, M.D."; "yvaucher@ucsd.edu"; "Finer, Neil"; "Das, Abhik"
Cc: "Zaterka-Baxter, Kristin"; "Auman, Jeanette O."
Subject: RE: Updated SUPPORT results
Date: Monday, August 22, 2011 8:47:00 AM

We did adjudicate these – most were missing the Bayley scores, so not able to assign a primary outcome as the children were not deaf, blind or had CP>

Rose

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From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Friday, August 19, 2011 2:16 PM
To: Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; Myriam Peralta, M.D.; yvaucher@ucsd.edu; Finer, Neil; Das, Abhik
Cc: Zaterka-Baxter, Kristin; Auman, Jeanette O.
Subject: RE: Updated SUPPORT results

Wally,

In response to your question about adjudication, we were only able to adjudicate one or two cases. We could do sensitivity analysis using the "worse case" scenario or another assumption regarding the outcomes of those lost to FU.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
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919-541-6255

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Friday, July 29, 2011 5:03 PM
To: Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; Myriam Peralta, M.D.; yvaucher@ucsd.edu; Finer, Neil; Das, Abhik
Cc: Zaterka-Baxter, Kristin; Auman, Jeanette O.
Subject: RE: Updated SUPPORT results

Thanks, Marie.

All:

Is there something we can do to get the FU rates higher?

Where are we with the adjudication analysis? Worst case scenario analysis?

Have a great weekend.

Wally

Wally Carlo, M.D.
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From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Friday, July 29, 2011 3:54 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Myriam Peralta, M.D.; yvaucher@ucsd.edu; Wally Carlo, M.D.; Finer, Neil; Das, Abhik
Cc: Zaterka-Baxter, Kristin; Auman, Jeanette O.
Subject: Updated SUPPORT results

Hi all,

Attached are updated FU results from SUPPORT. Please note the following.

1) Centers responded to the hearing queries, but in three cases the edit that the center said they made did not appear in the data. Jenny manually edited the data to match the email response from the center and prompted them to change the data on their end.
2) There were two cases where an SF09a was deleted (correctly) by a center at Jenny's request (because both SF and NF forms had been entered) but there was no NF09a entered, which resulted in a missing NDI outcome. Jenny requested that the center enter the NF09a (which they did) but for purposes of this report I used archived SF09a data for those two children.
3) I have added z scores to Table 3. They are based on the WHO growth curves. A few values (fewer than 10) were flagged as being extreme (unlikely), and I have run the numbers with and without those flagged values. It makes no difference in the results.
4) I have included comparisons of infants lost to FU vs. those with a FU visits (excludes deaths prior to FU) in Table 6.

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Despite the issues noted above, I think we can consider these data to be final if the group agrees (and unless we want to pursue the survival to 18-22 months issue). I will be out of the office on vacation next week (and Abhik will also be out) but I will be back on August 15. Please circulate these results to the subcommittee as appropriate – I am only sending them directly to this small group.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Vaucher, Yvonne
To: Gantz, Marie; Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; Myriam Peralta, M.D.; Finer, Neil; Das, Abhik
Cc: Zaterka-Baxter, Kristin; Auman, Jeanette O.
Subject: RE: Updated SUPPORT results
Date: Friday, August 19, 2011 6:43:19 PM

If we don't have essential information we can't adjudicate them (.e.g all other results are normal but we do not have the cognitive score).

Yvonne

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Friday, August 19, 2011 11:43 AM
To: Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; Myriam Peralta, M.D.; Vaucher, Yvonne; Finer, Neil; Das, Abhik
Cc: Zaterka-Baxter, Kristin; Auman, Jeanette O.
Subject: RE: Updated SUPPORT results

Wally,

The limiting factor in the adjudication was the lack of Bayley III cognitive score. For infants who were not otherwise impaired, the group could not adjudicate an outcome if that piece of information was missing.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Friday, August 19, 2011 2:25 PM
To: Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; Myriam Peralta, M.D.; yvaucher@ucsd.edu; Finer, Neil; Das, Abhik
Cc: Zaterka-Baxter, Kristin; Auman, Jeanette O.
Subject: RE: Updated SUPPORT results

Marie:

I think it may be very useful to both develop an algorithm so we could adjudicate more and use worst case scenarios ultimately.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham

Director, Division of Neonatology
Director, Newborn Nurseries
1700 6th Avenue South
176F Suite 9380R
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Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 (b)(6)

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Friday, August 19, 2011 1:16 PM
To: Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; Myriam Peralta, M.D.; yvaucher@ucsd.edu; Finer, Neil; Das, Abhik
Cc: Zaterka-Baxter, Kristin; Auman, Jeanette O.
Subject: RE: Updated SUPPORT results

Wally,

In response to your question about adjudication, we were only able to adjudicate one or two cases. We could do sensitivity analysis using the "worse case" scenario or another assumption regarding the outcomes of those lost to FU.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-354-6255

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Friday, July 29, 2011 5:03 PM
To: Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; Myriam Peralta, M.D.; yvaucher@ucsd.edu; Finer, Neil; Das, Abhik
Cc: Zaterka-Baxter, Kristin; Auman, Jeanette O.
Subject: RE: Updated SUPPORT results

Thanks, Marie.

All:

Is there something we can do to get the FU rates higher?

Where are we with the adjudication analysis? Worst case scenario analysis?

Have a great weekend.

Wally

Wally Carlo, M.D.

Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
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Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 (b)(6)

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Friday, July 29, 2011 3:54 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Myriam Peralta, M.D.; yvaucher@ucsd.edu; Wally Carlo, M.D.; Finer, Neil; Das, Abhik
Cc: Zaterka-Baxter, Kristin; Auman, Jeanette O.
Subject: Updated SUPPORT results

Hi all,

Attached are updated FU results from SUPPORT. Please note the following.

1) Centers responded to the hearing queries, but in three cases the edit that the center said they made did not appear in the data. Jenny manually edited the data to match the email response from the center and prompted them to change the data on their end.
2) There were two cases where an SF09a was deleted (correctly) by a center at Jenny's request (because both SF and NF forms had been entered) but there was no NF09a entered, which resulted in a missing NDI outcome. Jenny requested that the center enter the NF09a (which they did) but for purposes of this report I used archived SF09a data for those two children.
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From: Vaucher, Yvonne
To: Gantz, Marie; Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; Myriam Peralta, M.D.; Finer, Neil; Das, Abhik
Cc: Zaterka-Baxter, Kristin; Auman, Jeanette O.; Wallace, Dennis
Subject: RE: Updated SUPPORT results
Date: Wednesday, August 17, 2011 11:45:08 AM

yes

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Wednesday, August 17, 2011 7:46 AM
To: Gantz, Marie; Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; Myriam Peralta, M.D.; Vaucher, Yvonne; Finer, Neil; Das, Abhik
Cc: Zaterka-Baxter, Kristin; Auman, Jeanette O.; Wallace, Dennis
Subject: RE: Updated SUPPORT results

Also, any comment on the 17 cases where the center seemed to be in contact with the family when the child was 17+ months but "child alive" was not noted on the NF12? Do you want us to ask the centers to confirm that the child was known to be alive at that time?

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Gantz, Marie
Sent: Wednesday, August 17, 2011 10:44 AM
To: 'Wally Carlo, M.D.'; Higgins, Rosemary (NIH/NICHD) [E]; Myriam Peralta, M.D.; yvaucher@ucsd.edu; Finer, Neil; Das, Abhik
Cc: Zaterka-Baxter, Kristin; Auman, Jeanette O.; Wallace, Dennis
Subject: RE: Updated SUPPORT results

Thanks, Wally. I will look to see if we have the Utah data already and add it in if we do.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Wednesday, August 17, 2011 10:17 AM
To: Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; Myriam Peralta, M.D.; yvaucher@ucsd.edu; Finer, Neil; Das, Abhik
Cc: Zaterka-Baxter, Kristin; Auman, Jeanette O.; Wallace, Dennis
Subject: RE: Updated SUPPORT results

I would include the Utah baby. We should continue to make efforts to get our FU as high as possible.

Can the drafts of the two papers be circulated?

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
1700 6th Avenue South
176F Suite 9380R
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
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From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Wednesday, August 17, 2011 9:03 AM
To: Gantz, Marie; Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; Myriam Peralta, M.D.; yvaucher@ucsd.edu; Finer, Neil; Das, Abhik
Cc: Zaterka-Baxter, Kristin; Auman, Jeanette O.; Wallace, Dennis
Subject: RE: Updated SUPPORT results

Hi all,

Where are we with these papers? Have drafts been circulated? I did not receive an answer to my question from last week about final data lock (please see below).

I still owe Yvonne details of the resolution of the hearing queries.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Gantz, Marie
Sent: Tuesday, August 09, 2011 1:29 PM
To: 'Wally Carlo, M.D.'; Higgins, Rosemary (NIH/NICHD) [E]; Myriam Peralta, M.D.; yvaucher@ucsd.edu; Finer, Neil; Das, Abhik
Cc: Zaterka-Baxter, Kristin; Auman, Jeanette O.; Wallace, Dennis
Subject: RE: Updated SUPPORT results

Hi all,

Just wanted to touch base now that I am back from vacation. Yvonne has asked to see the results of the hearing queries, and I will send out that information this week (the results sent on 7/29 already

reflect the results of the queries). Was there any conversation last week about whether to contact the centers to confirm whether the 17 infants referred to in bullet #5 of my email below were alive at 17+ months? Also, we received word last week that a LTFU patient at Utah was just seen for FU – do we want to include those data and rerun the results? We need to decide at what point to consider the data locked.

Have any drafts of the papers been circulated?

Marie

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mgantz@rti.org
828-254-6255

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Friday, July 29, 2011 5:03 PM
To: Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; Myriam Peralta, M.D.; yvaucher@ucsd.edu; Finer, Neil; Das, Abhik
Cc: Zaterka-Baxter, Kristin; Auman, Jeanette O.
Subject: RE: Updated SUPPORT results

Thanks, Marie.

All:

Is there something we can do to get the FU rates higher?

Where are we with the adjudication analysis? Worst case scenario analysis?

Have a great weekend.

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From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Friday, July 29, 2011 3:54 PM

To: Higgins, Rosemary (NIH/NICHD) [E]; Myriam Peralta, M.D.; yvaucher@ucsd.edu; Wally Carlo, M.D.; Finer, Neil; Das, Abhik
Cc: Zaterka-Baxter, Kristin; Auman, Jeanette O.
Subject: Updated SUPPORT results

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1) Centers responded to the hearing queries, but in three cases the edit that the center said they made did not appear in the data. Jenny manually edited the data to match the email response from the center and prompted them to change the data on their end.
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Marie

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Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Walsh, Michele
To: Wrage, Lisa Ann; Higgins, Rosemary (NIH/NICHD) [E]; Martin, Richard; Julie Di Fiore
Cc: Wallace, Dennis; Gantz, Marie
Subject: RE: Interesting look at IH in Low/High groups by GA
Date: Tuesday, August 16, 2011 10:46:34 AM

That's an interesting point Lisa and one that we have been aware of since the inception of this analysis. I feel that a decision to change the analytic approach is one the primary investigator/s Needs to be involved in- a complete switch in the statistical model at this point is rather Drastic..... I would not be comfortable doing so. Dennis: await your input. This is time sensitive.

Michele Walsh, MD
Chief, Division of Neonatology
216.844.3759

It's not what you look at that matters, it's what you see. Thoreau

From: Wrage, Lisa Ann [mailto:wrage@rti.org]
Sent: Tuesday, August 16, 2011 10:42 AM
To: Walsh, Michele; Higgins, Rosemary (NIH/NICHD) [E]; Martin, Richard; Julie Di Fiore
Cc: Das, Abhik; Wallace, Dennis; Gantz, Marie
Subject: RE: Interesting look at IH in Low/High groups by GA

Hi Michele,
I did not realize until recently that deaths, discharges, days off oximeter, etc. are considered 'missing' data in a longitudinal model (yes, even though they really are not relevant) and essentially problematic for GEE models as well as other types of longitudinal models and also are generally handled with sophisticated techniques. I am hoping to simply switch to thinking of this data as cross-sectional data rather than longitudinal, which allows the population to be dynamic, and is basically more of a conditional analysis (i.e. alive, in hospital, on oximeter)-- It is really more a switch in perspective because it is a minor technical change to the analysis. It makes sense to me, however I am getting input from the senior statisticians because I am not comfortable making that decision on my own and I much prefer to deal with this now than when a reviewer asks about it! I understand that you want to get this through however it is a complicated study and I'd rather be careful about methods.
Thanks.
Lisa

From: Walsh, Michele [mailto:Michele.Walsh@UHhospitals.org]
Sent: Tuesday, August 16, 2011 10:26 AM
To: Wrage, Lisa Ann; Higgins, Rosemary (NIH/NICHD) [E]; Martin, Richard; Julie Di Fiore
Cc: Das, Abhik; Wallace, Dennis; Gantz, Marie
Subject: RE: Interesting look at IH in Low/High groups by GA

Hi Lisa: Can you be more specific about what needs to be resolved on your end?
It would seem that updating the graphs from the abstracts should be a fairly Simple task. The issue of drop out as kids improve (eg stopped getting sat data) is a limitation of the study Design, and will need to be acknowledged as such. I am not convinced this is Something that can be dealt with in analysis. My vote would be to move forward and

Get this paper out as there is much interest in the neonatology community.

Michele Walsh, MD
Chief, Division of Neonatology
216.844.3759

It's not what you look at that matters, it's what you see. Thoreau

---

From: Wrage, Lisa Ann [mailto:wrage@rti.org]
Sent: Monday, August 15, 2011 4:56 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Walsh, Michele; Martin, Richard; Julie Di Fiore
Cc: Das, Abhik; Wallace, Dennis; Gantz, Marie
Subject: RE: Interesting look at IH in Low/High groups by GA

Hi,
We are discussing this on our end so I will let you know when there is resolution.
Lisa

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, August 15, 2011 8:35 AM
To: 'Walsh, Michele'; Martin, Richard; Julie Di Fiore; Wrage, Lisa Ann
Cc: Das, Abhik; Wallace, Dennis; Gantz, Marie
Subject: RE: Interesting look at IH in Low/High groups by GA

HI Michele and all –
Abhik is away (b)(6) I've included Marie and Dennis so you can get an answer/closure on this one

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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For overnight delivery use Rockville, MD 20852
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301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Walsh, Michele [mailto:Michele.Walsh@UHhospitals.org]
Sent: Monday, August 15, 2011 8:31 AM
To: Martin, Richard; Julie Di Fiore; Wrage, Lisa Ann
Cc: Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Interesting look at IH in Low/High groups by GA

Lisa and Abhik: Can we get this analysis finished in the next 10 days
so we can submit? This manuscript needs to get finished before we deal with new abstracts.
It would not be fair to start new work before this analysis is finished-
especially since PAS submissions are months away.

From: Martin, Richard
Sent: Sat 8/13/2011 9:11 AM
To: Julie Di Fiore; Wrage, Lisa Ann
Cc: Richard Martin; Walsh, Michele; Das, Abhik
Subject: RE: Interesting look at IH in Low/High groups by GA

sounds like it needs Michele to bring this paper to closure.

Richard J. Martin, M.D.
Drusinsky-Fanaroff Chair in Neonatology
Rainbow Babies & Children's Hospital
Professor of Pediatrics
Case Western Reserve University
11100 Euclid Avenue
Cleveland, OH 44106-6010
Phone: (216) 844-3387
Fax: (216) 844-3380
email to: rxm6@case.edu

From: Julie Di Fiore [mailto:jmd3@case.edu]
Sent: Friday, August 12, 2011 7:01 PM
To: Wrage, Lisa Ann
Cc: Richard Martin; Walsh, Michele; Das, Abhik
Subject: Re: Interesting look at IH in Low/High groups by GA

I understood that we were going to be wrapping this up soon. Since we are waiting for the stats to finish this paper up what kind of time line are we on?

On 8/12/2011 5:52 PM, Wrage, Lisa Ann wrote:
Julie,
I don't think that we should do a stratified analysis with so little data. What exactly was the research question of interest with regard to PMA?
The issue of missing data is a more general one, and not specifically tied to PMA. The issue has come up recently (at a class on longitudinal data analysis I took in June, and on a SUPPORT secondary analysis). What is considered 'missing' data and how to handle it for longitudinal data analysis models is an advanced subject that we honestly don't have lot of experience with it so it is currently under review. We also have not had Abhik much this month (and not at all now through the end of August) due to (b)(6) Plus we are also currently in the PAS crunch - I have several abstracts to work on and will be very focused on them (primarily in August and September). What all of this means is that any follow-up work to look at the missing data issue for this analysis will not be immediately forthcoming (but trust me it is on my mind!). Sorry if that was not clear before.

Let me know if you have questions.

Lisa

From: Juliann Di Fiore [mailto:jmd3@case.edu]
Sent: Friday, August 12, 2011 2:23 PM
To: Richard Martin; Michele Walsh; Wrage, Lisa Ann
Subject: Interesting look at IH in Low/High groups by GA

RE IH in the Low/High Target Groups: Lisa and I have had some preliminary discussions trying to address the issue of postmenstrual age. This is problematic statistically since there will be so many drop outs at the early PMAs. So, instead I plotted the # of IH events in separate plots stratifying the infants into 4 GA groups with some interesting results.

Keeping in mind that combining the GA groups together the main finding of our study is a higher # of IH events in the Low group at <6 and >66 days of life. In the combined group we went out to 80+ days since there were more infants. Unfortunately, splitting the infants into 4 groups resulted in so many missing cells at the later ages I had to cut the graphs shorter if there were too few cells.

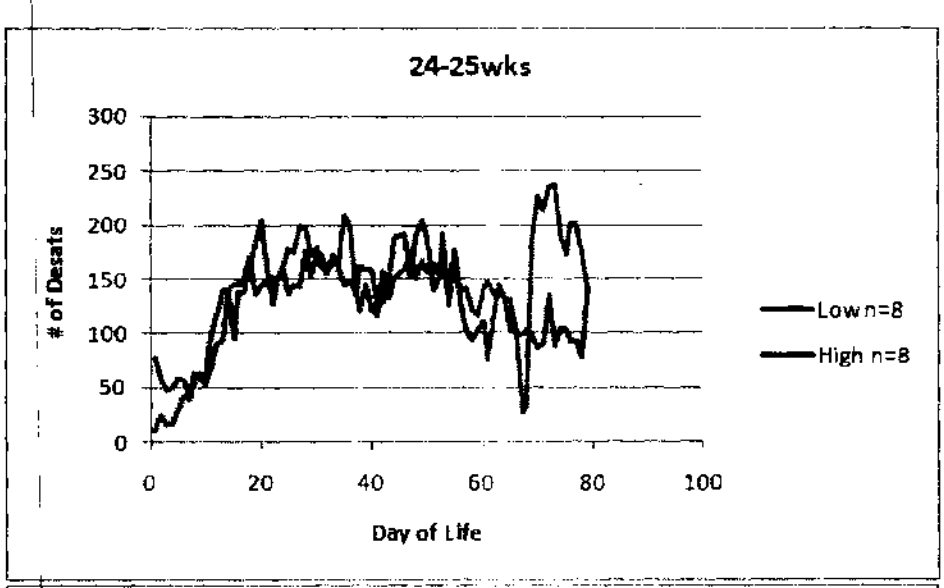
Points of Interest (by visual inspection. No statistics done):

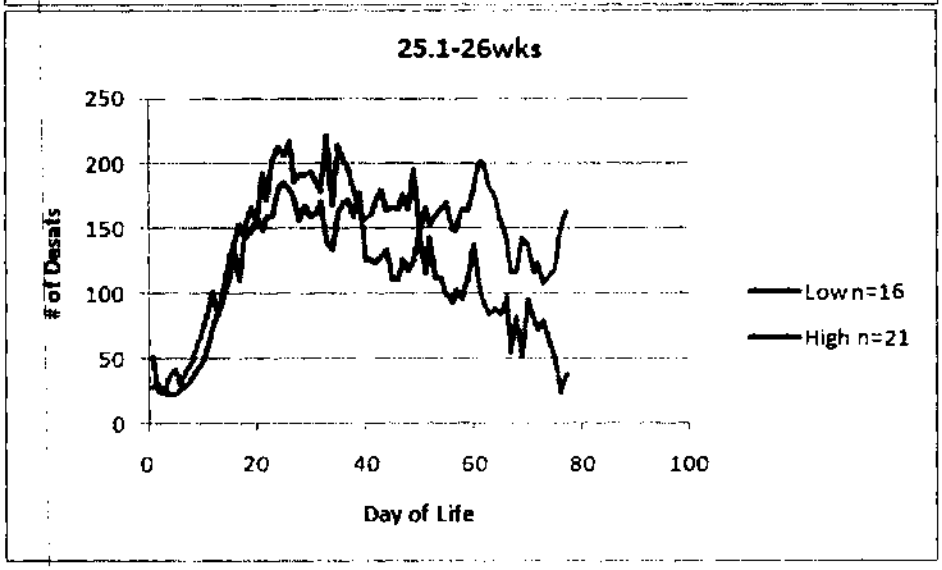
1. For the PAS, we found that GA is a significant covariate (higher # events with lower GA) in the combined cohort. However, as seen in these graphs, the overall pattern of IH, starting low and increasing with time, seems to be independent of GA in this age range.
2. The main finding of Higher events in the low group at <6 days of life seems to be focused on the infants of 24-25wks gestation.
3. The differences between groups after 1 weeks seemed to be focused on the 25-26 and 26-27 wk infants.
4. There are actually less IH events in the low target group in the oldest cohort of 27-28wks. I have checked this data 3 times to make sure I didn't get the groups backwards.

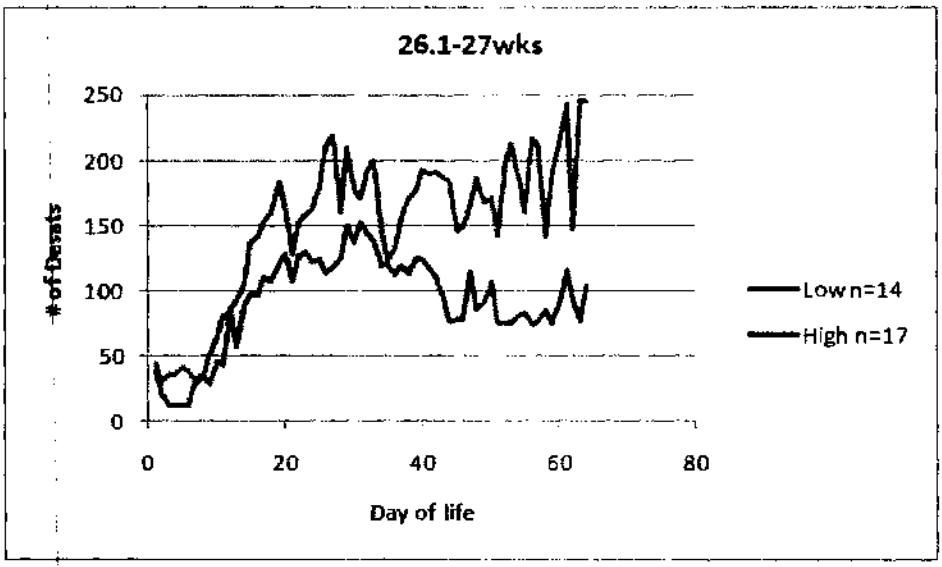
Now these are mean graphs with no error bars and small sample sizes (n's stated in the legends).
Lisa- do you think it would be possible to do stats on these graphs or are the numbers too small and too many missing cells? (I will send you the spread sheet in a following email so you can see the distribution)

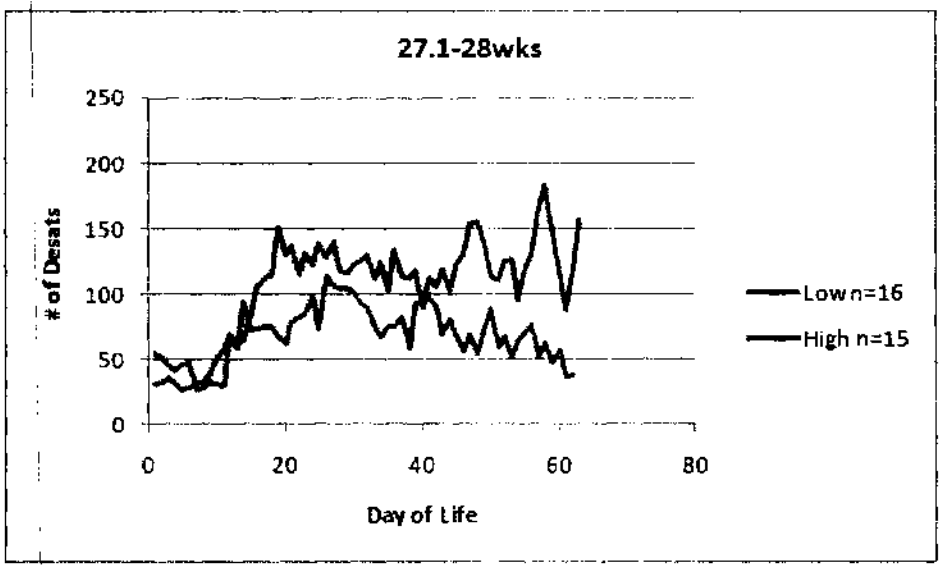
Thoughts?

Julie









--
Juliann Di Fiore
Research Engineer
Case Western Reserve University
Rainbow Babies & Children's Hospital
Division of Neonatology, room 3100
11100 Euclid Ave
Cleveland, OH 44106
(216) 844-1478

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From: Walsh, Michele
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Interesting look at IH in Low/High groups by GA
Date: Monday, August 15, 2011 11:01:09 AM

My understanding is that we just need the graphs updated from
The abstract, not a re-analysis. I think Lisa may be over thinking it....
It's a limitation of the design, not something we can fix in the analysis.

Michele Walsh, MD
Chief, Division of Neonatology
216.844.3759

It's not what you look at that matters, it's what you see. Thoreau

---

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, August 15, 2011 8:35 AM
To: Walsh, Michele; Martin, Richard; Julie Di Fiore; Wrage, Lisa Ann
Cc: Das, Abhik; Wallace, Dennis; 'Gantz, Marie'
Subject: RE: Interesting look at IH in Low/High groups by GA

HI Michele and all –
Abhik is away (b)(6) I've included Marie and Dennis so you can get an answer/closure on this one

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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higginsr@mail.nih.gov

From: Walsh, Michele [mailto:Michele.Walsh@UHhospitals.org]
Sent: Monday, August 15, 2011 8:31 AM
To: Martin, Richard; Julie Di Fiore; Wrage, Lisa Ann
Cc: Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Interesting look at IH in Low/High groups by GA

Lisa and Abhik: Can we get this analysis finished in the next 10 days
so we can submit? This manuscript needs to get finished before we deal with new abstracts.
It would not be fair to start new work before this analysis is finished-

especially since PAS submissions are months away.

From: Martin, Richard
Sent: Sat 8/13/2011 9:11 AM
To: Julie Di Fiore; Wrage, Lisa Ann
Cc: Richard Martin; Walsh, Michele; Das, Abhik
Subject: RE: Interesting look at IH in Low/High groups by GA

sounds like it needs Michele to bring this paper to closure.

Richard J. Martin, M.D.
Drusinsky-Fanaroff Chair in Neonatology
Rainbow Babies & Children's Hospital
Professor of Pediatrics
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email to: rxm6@case.edu

From: Julie Di Fiore [mailto:jmd3@case.edu]
Sent: Friday, August 12, 2011 7:01 PM
To: Wrage, Lisa Ann
Cc: Richard Martin; Walsh, Michele; Das, Abhik
Subject: Re: Interesting look at IH in Low/High groups by GA

I understood that we were going to be wrapping this up soon. Since we are waiting for the stats to finish this paper up what kind of time line are we on?

On 8/12/2011 5:52 PM, Wrage, Lisa Ann wrote:
Julie,
I don't think that we should do a stratified analysis with so little data. What exactly was the research question of interest with regard to PMA?
The issue of missing data is a more general one, and not specifically tied to PMA. The issue has come up recently (at a class on longitudinal data analysis I took in June, and on a SUPPORT secondary analysis). What is considered 'missing' data and how to handle it for longitudinal data analysis models is an advanced subject that we honestly don't have lot of experience with it so it is currently under review. We also have not had Abhik much this month (and not at all now through the end of August) due to (b)(6) Plus we are also currently in the PAS crunch - I have several abstracts to work on and will be very focused on them (primarily in August and September). What all of this means is that any follow-up work to look at the missing data issue for this analysis will not be immediately forthcoming (but trust me it is on my mind!). Sorry if that was not clear before.
Let me know if you have questions.
Lisa

From: Juliann Di Fiore [mailto:jmd3@case.edu]

Sent: Friday, August 12, 2011 2:23 PM
To: Richard Martin; Michele Walsh; Wrage, Lisa Ann
Subject: Interesting look at IH in Low/High groups by GA

RE IH in the Low/High Target Groups: Lisa and I have had some preliminary discussions trying to address the issue of postmenstrual age. This is problematic statistically since there will be so many drop outs at the early PMAs. So, instead I plotted the # of IH events in separate plots stratifying the infants into 4 GA groups with some interesting results.

Keeping in mind that combining the GA groups together the main finding of our study is a higher # of IH events in the Low group at <6 and >66 days of life. In the combined group we went out to 80+ days since there were more infants. Unfortunately, splitting the infants into 4 groups resulted in so many missing cells at the later ages I had to cut the graphs shorter if there were too few cells.

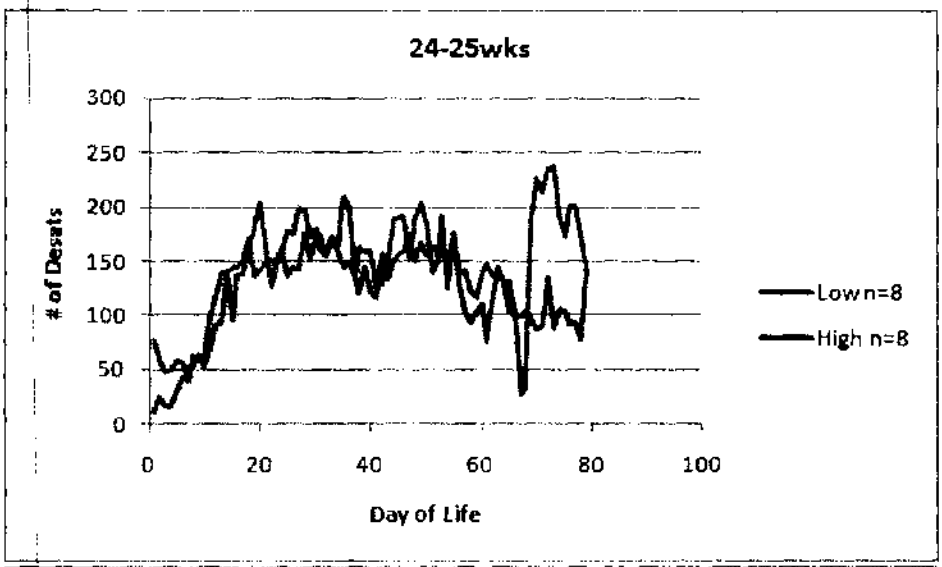
Points of Interest (by visual inspection. No statistics done):

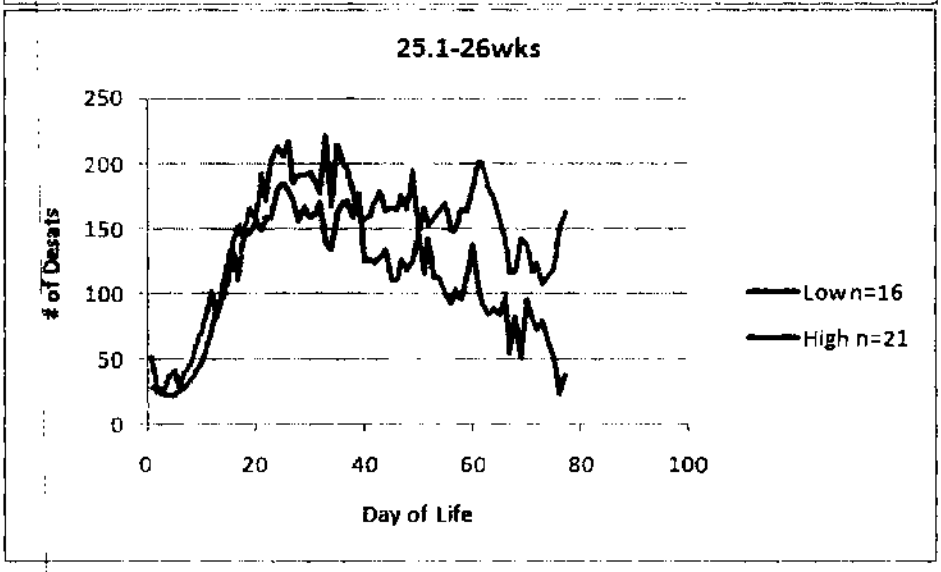
1. For the PAS, we found that GA is a significant covariate (higher # events with lower GA) in the combined cohort. However, as seen in these graphs, the overall pattern of IH, starting low and increasing with time, seems to be independent of GA in this age range.
2. The main finding of Higher events in the low group at <6 days of life seems to be focused on the infants of 24-25wks gestation.
3. The differences between groups after 1 weeks seemed to be focused on the 25-26 and 26-27 wk infants.
4. There are actually less IH events in the low target group in the oldest cohort of 27-28wks. I have checked this data 3 times to make sure I didn't get the groups backwards.

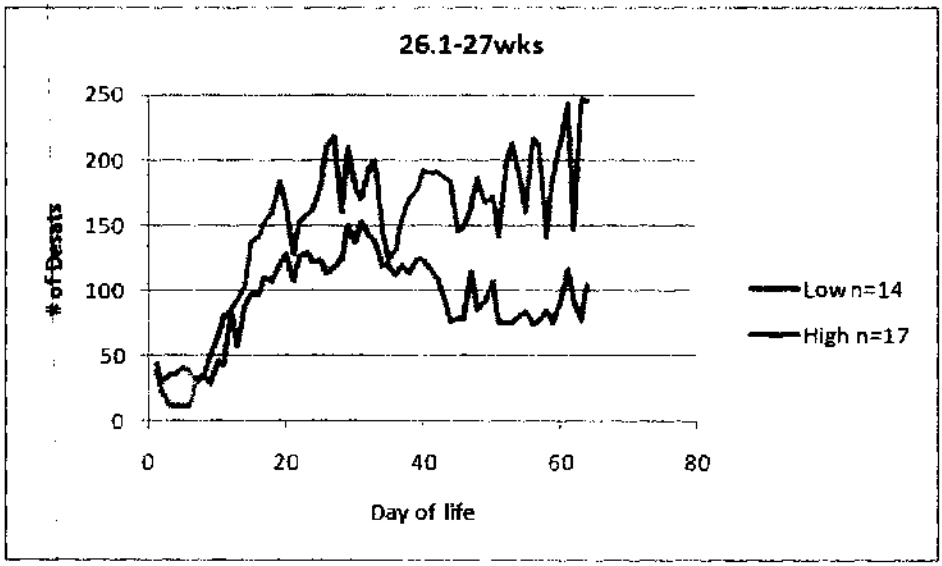
Now these are mean graphs with no error bars and small sample sizes (n's stated in the legends).
Lisa- do you think it would be possible to do stats on these graphs or are the numbers too small and too many missing cells? (I will send you the spread sheet in a following email so you can see the distribution)

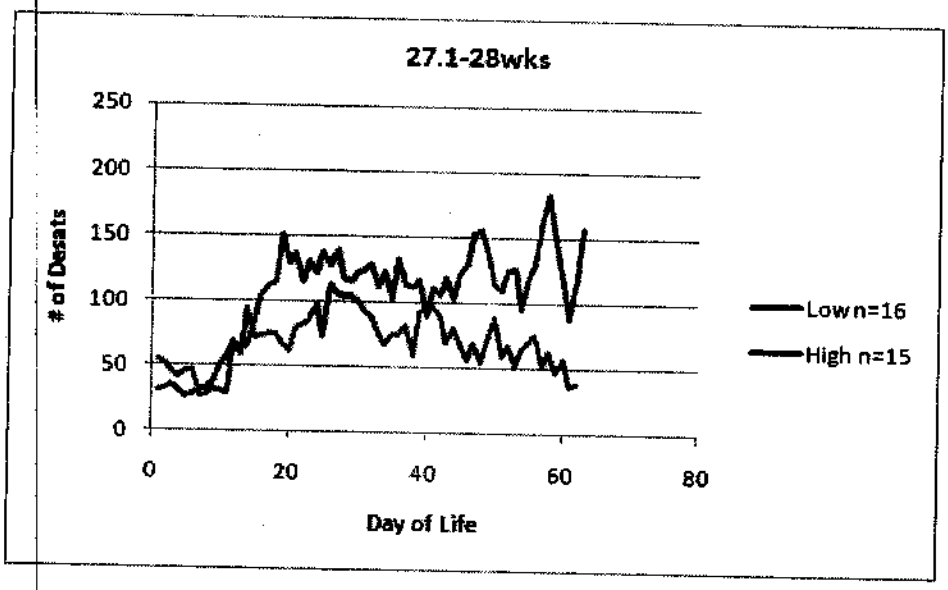
Thoughts?

Julie









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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Myriam Peralta-Carcelen (MPeralta@peds.uab.edu)"; "Yvonne Vaucher"
Cc: "Finer, Neil"; "Wally Carlo, M.D."
Subject: SUPPORT FU manuscripts
Date: Wednesday, August 10, 2011 11:20:00 AM

Hi,

I am wondering how we are doing on the SUPPORT FU papers. Can you send me the latest drafts??

Thanks

Rose

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From: Phelps, Dale
To: Gantz, Marie; Wrage, Lisa Ann; Kennedy, Kathleen A; Higgins, Rosemary (NIH/NICHD) [E]
Cc: Das, Abhik
Subject: RE: ROP Natural History analysis update
Date: Wednesday, August 10, 2011 2:38:32 AM

Hi Marie,
You are correct that it is better to reference time of diagnosis. Unfortunately, we would all love to know when the onset was, but we usually can not know this.
Dale Phelps

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Friday, June 03, 2011 1:26 PM
To: Wrage, Lisa Ann; Kennedy, Kathleen A; Higgins, Rosemary (NIH/NICHD) [E]; Phelps, Dale
Cc: Das, Abhik
Subject: RE: ROP Natural History analysis update

I just had a chance to look at this. Would it be more accurate to reference time of "diagnosis" rather than "onset" of ROP, since we know the date of the exam during which ROP was diagnosed, but onset probably occurred some amount of time earlier?

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

From: Wrage, Lisa Ann
Sent: Thursday, May 26, 2011 10:41 AM
To: 'Kennedy, Kathleen A'; Higgins, Rosemary (NIH/NICHD) [E]; Phelps, Dale
Cc: Das, Abhik; Gantz, Marie
Subject: ROP Natural History analysis update

Hello,
I attach an update to the ROP Natural History analysis (I have updated the flowchart and added the first few tables & a draft of the first figure). I look forward to any comments you have.
I will continue on to the next items in June.
Thanks.
Lisa

Lisa Wrage, MPH
Research Statistician
Statistics & Epidemiology
RTI International
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919-220-2653

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "wcarlo@peds.uab.edu"
Subject: Re: SUPPORT
Date: Tuesday, August 09, 2011 5:31:07 PM

No problem

From: Wally Carlo, M.D. <WCarlo@peds.uab.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tue Aug 09 17:25:08 2011
Subject: RE: SUPPORT

Sorry she bothered you with this. She did not tell me she would do it. I met with her this AM and have plans for the UAB meeting tomorrow.

SORYY!

Wally

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From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, August 09, 2011 3:40 PM
To: Shirley Cosby
Cc: Wally Carlo, M.D.
Subject: RE: SUPPORT

I would suggest you get clarification from OHRP.

Thanks

Rose

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From: Shirley Cosby [mailto:SCosby@peds.uab.edu]
Sent: Tuesday, August 09, 2011 3:43 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: SUPPORT

Hi Rose, I have a meeting tomorrow morning with our IRB regarding the OHRP letter that we received. I am hoping that you can help clarify something on the letter for me. On page 2 Number 2b in the letter, they are requesting "the IRB-approved informed consent documents from each enrollment site." We are trying to figure out if that just means the enrollment sites within our own site or if it is all participating sites. Everything else in this list relates to us specifically but I thought I would check on this one request as we don't have access to approved consent forms other than our own.

Thanks,

Shirley

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205-934-3100 (fax)

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Gabrio, Jenna"
Subject: SUPPORT Subcommittee Call 07 11 2011
Date: Monday, August 08, 2011 11:57:00 AM
Attachments: SUPPORT Subcommittee Call 07 11 2011.doc

Do I owe you any more??
Thanks
Rose

SUPPORT Subcommittee Call
July 11, 2011

Participants: Yvonne Vaucher, Wade Rich, Abhik Das, Roger Faix, Marie Gantz, Myriam Peralta, Michele Walsh
NICHD: Rose Higgins,
Data Coordinating Center: Jenna Gabrio, Kris Zaterka-Baxter

- *These results are to remain confidential.*
- CPAP Outcomes
  - There were trends in significance for ICH ~~and~~ [redacted] ~~seen~~ in the main study.
  - Follow Up cohort includes all infants who had some follow up. They at least had the physical exam, but not all had the Bayley. This reflected the original cohort.
  - Outcome—no difference in death or NDI. There is a trend of more death in the surfactant group and this is significant in the lower GA strata. [redacted]
  - There were more hearing impaired children in the CPAP group.
    - Marie Gantz adjusted for this and noted that hearing impaired is adjusted for everything.
    - This is based on the one question from the NF05.
  - Question: Was this center dependent? Or were they distributed across the network?
    - This is adjusted for center. There were 6 centers that did not have any hearing impaired infants.
    - It was noted that results are the same adjusted and not adjusted for center.
  - CPAP group had more NEC, which is associated with worse outcomes.
    - Higher strata had less infants with NEC, more with IVH/PVL
    - Need to ask if they had more survivors with NEC. Are the CPAP deaths associated with having NEC in the hospital?
  - Question: Do we have data about hearing screenings at discharge? Could this be acquired after discharge?
    - We ask what hearing screen was used and the results before status.
    - In the trial publication we did not look at hearing vs. hospital discharge. This may be worth going back and looking to see if there was a hearing screen.
  - Dr. Das said that we should probably just compare Bayley 3 cognitive scores as a continuous variable across groups.
  - Dr. Higgins would also like to do a cut point of less than 85. This is already in the tables.
  - Dr. Higgins said that mortality in lower GA persists [redacted] at 18-22 months, which is significant.
  - ~~Question: Is there a way to see if hearing impaired had a higher rate of NEC, IVH/PVL, or lower rate of [redacted]?~~
    - Marie Gantz indicated that we will look at this.
    - We have a model that looks at these things, but they are [redacted] or baseline differences. If it is not related to another morbidity in the hospital then we need to come up with an alternative.

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- Oximetry
  - We have no data on [redacted] approximately 56 infants. If we knew they were alive at 17 months or some were known to be alive after the NF12 are accounted for, but the ones

we don't know anything about weren't counted. This is why we need to look at the composite with death.

- ~~For the saturation on death nothing else is showing up. Some suspect that we won't see anything else in terms of saturation [redacted].~~
- Seems like the conclusions will be very similar to the first study. Hearing loss could still be due to a Type 1 error. This is the same with the saturation.
- ~~There is no mitigating factor for [redacted]~~
- It was noted that ROP benefits in low sat. infants do not translate into less blind infants.
  - Marie Gantz indicated that this included questions 4 and 5 off of the form. This was used for NDI. The 'other' and the glasses are included in table 3.
- There is likely not going to be evidence of the changes in periphery at this point.
- Dr. Faix said that either the intervention was effective or the nature of the disease was not as fundamentally different as we thought based on criteria. Absence of difference with visual impairment is very important to know.
- First round low saturation was associated with more death, but now we don't see this as much at 18-22 months. It seems that we may still be able to make the argument to avoid low saturations.
- Question: Is anyone surpised by the low CP rates?

[redacted]

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- Other Notes:
  - Marie Gantz will send out Table 4 today. Table 2 has all of the components of NDI.
  - Combination of Death or any of the outcomes are not in any of these tables yet.
  - Did not include one infant because did not have Bayley. Only 15 infants did not have an NDI, which is impressive.
  - Would be nice to know if the 51 missing were alive or dead. Deaths are reported on the state basis so we could ask sites to check vital records again. However this is challenging since it is possible that the subject's name has changed.
  - In the CPAP arm it is reassuring that the spread in the low for the smaller infants has narrowed.
  - Question: What do you make of ROP among the surfactant arm in the follow up cohort?
    - It is lower in the smaller infants and higher in the larger infants.
    - However, ROP is not the endpoint; it is death or visual impairment at 18 months.
    - Question: For outcome we are looking at the most adverse outcome→are there differences in the less adverse outcomes?
      - There are only 2 extra subjects who were blind in only one eye.
  - Subcommittee will meet at the upcoming Steering Committee Meeting on Thursday 7/14. We will figure out the phone lines and send out the call in information ASAP.

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Gabrio, Jenna"
Subject: SUPPORT Growth Call 07 11 2011
Date: Monday, August 01, 2011 4:55:00 PM
Attachments: SUPPORT Growth Call 07 11 2011.doc

SUPPORT Growth Call
July 11, 2011

Participants: Kurt Schibler, Roger Faix, Nancy Newman, Yvonne Vaucher, Lisa Wrage, Charlie Bauer, Michele Walsh, Abhik Das, Shahnaz Duara, Christina Navarrete, Wade Rich
NICHD: Rose Higgins
Data Coordinating Center: Jenna Gabrio, Kris Zaterka-Baxter

- Secondary study proposed a few months after starting the SUPPORT trial. Around 300 patients have been enrolled. Proposed to look if there was a difference in growth among infants randomized to different arms. The hypothesis was that the lower arm would have better group growth and better growth trajectory. Were allowed to gather extra information, one form, that would be weekly, which will look into the nutritional intake of these infants.
- Also wanted to combine the two groups and compare them to the independent of saturation group and see if they were within the target range of 84-96. Additionally, they wanted to see if those with Physiologic BPD would have better growth. This is why all of the analysis has been delayed. Some of the information would only be obtained at 18-22 month follow up.
- Dr. Das said that resources at the DCC are extremely tight so you need to focus on one or two outcomes. If you to get this done in reasonable amount of time should only focus on the two primary hypotheses.
- Question: How will the deaths be treated in statistical analyses?
    - Wanted to include the deaths and growth failure at 18-22 month follow up and discharge.
    - If infant died at 30 weeks but infant falls off these data points will still be used in the overall analysis. It is not clear in the protocol how they will be treated.
    - It was noted that competing outcomes do not work for continuous outcomes. Informative censoring would occur. Dr. Das suggested that the trajectory analyses would have to look into a method that deals with the infants who die [redacted], which are not simple and may take time to figure out. Would take all subsequent points and do some kind of imputation and explore that to see if there are big differences or not.
- For now we should look at the tables and only keep those that look at the comparison between the two intervention groups. A lot of these analyses are already done from the main trial.
- It was noted that looking at Z-scores will take more time because will have to look at death more closely.
- Question: What would be the first table you would want to create with the data?
    - Composite with death would be easier. We can report what is here and add composite with death.
- Growth trajectory graph—need to figure out how we handle deaths. Just by knowing the deaths we will probably end up with a biased analysis.
- Categorical data can be death and less than 10 percentile. We should we do them each together and separately.
- Question: How do you treat kids that were alive at discharge but then died?
    - Other way to do this is to do trajectory of growth percentile for the less than 10 percentile. But if we don't know where they started focusing infants less than 10 percentile then this might not show the full results.
    - Z-Scores are an issue until we figure out how to handle the death.

  - Death was part of original hypotheses for SUPPORT and it only becomes an issue if you have a continuous outcome. We haven't had one yet in SUPPORT.
- Based on highlighting it was decided that it was not a representative population. Thus we decided to just use the Kramer Growth curve for the inpatient and the new CDC curve for the outpatient.
  - On the Kramer curve it looked like it was related to the most recent birth cohort. Dr. Faix said this makes sense, but we need to make sure that the readership is aware of what the reference is.
  - We should use the Growth curve from 2003.
- Richard Ehrenkranz was interested in working on this. We will invite him to the working group.
- It was difficult to extrapolate from the figures, but the table with the raw data was most helpful.
- We do not know off-hand what the difference would be. Someone estimated that the most difference would be in the first year. We will look this up and send a final decision to Dr. Higgins and Dr. Ehrenkranz. We will do this by email, then once that decision is made Lisa Wrage will do a first attempt at the analyses.
- Question: Is there a reason protein was not included in the calorie calculations on the document accompanying the protocol?
  - Initially we thought that if we exclude it a lot of the sites that use calculation for calories—protein is for growth and not for energy. Others felt that protein adds to growth.
- Question: What proportion of the population is receiving breast milk?
  - Guessing that it is around 20%. Hopefully it will be equal among the groups.
  - Likely not more than 25-30% if it hasn't changed. However, others indicated that this has changed.
  - There are more educated mothers in this population than the typical GDB. Would not be surprised if it pans out differently from this.
- We will figure out the growth curves that will be used by email. We will also involve Brenda Poindexter on this Growth Subcommittee.

From: Finer, Neil
To: Wally Carlo, M.D.
Cc: Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]; Wallace, Dennis
Subject: Re: OHRP
Date: Friday, July 29, 2011 4:09:15 PM

Thanks Wally
I will keep our IRB in the loop
Neil

On Jul 29, 2011, at 7:06 AM, "Wally Carlo, M.D." <WCarlo@peds.uab.edu> wrote:

> Neil:
>
> Sure, I will. My university people say they will be the ones responding
> but will use our input.
>
> Wally
>
> Wally Carlo, M.D.
> Edwin M. Dixon Professor of Pediatrics
> University of Alabama at Birmingham
> Director, Division of Neonatology
> Director, Newborn Nurseries
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> Cell: 205 (b)(6)
>
>
> -----Original Message-----
> From: Finer, Neil [mailto:nfiner@ucsd.edu]
> Sent: Friday, July 29, 2011 11:09 AM
> To: Wally Carlo, M.D.
> Cc: Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]; Wallace, Dennis
> Subject: Re: OHRP
>
> Hi Wally
> Will you send me the final response to OHRP?
> Thanks
> Neil
>
> On Jul 29, 2011, at 1:57 AM, "Wally Carlo, M.D." <WCarlo@peds.uab.edu>
> wrote:
>
>>

From: Finer, Neil
To: Wally Carlo, M.D.
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Wallace, Dennis; Wally Carlo, M.D.; Rich, Wade
Subject: Re: OHRP
Date: Wednesday, July 27, 2011 11:03:51 PM

Hi Wally
I would add that a previous study. Tin et al suggested improved outcomes using very low spo2 limits as low as 70%, far lower than used in the SUPPORT trial
Our trial postulated a decrease in the combined outcome of death /ROP
There was no antecedent information that using either a range of 85%~89% compared with 91%~95% was associated with any increase in death
Indeed a previous recent US experience suggested a lower ROP rate using even lower limits 83% without increase in morbidity or death. [Chow et al Pediatrics]
the SUPPORT study was reigned to test which range was superior while staying w Irgun the usual limits in the US at the time the trial began
Parents were told that we did not know which range was better and that we needed to find out
There had been a trend for all units to lower their SpO2 ranges without any data to support this change
Wally I believe that our consent and explanation were as they should be
I have referred the information to the head of our IRB
Even if we believed that this trial was minimal risk we did not ask for a waiver
We obtained consent in an appropriate fashion
I did most of our consents and I know that we we're careful and detailed and that our consenting families were well informed
Can you speculate why this has occurred?
We will deal with this from an overall study perspective!
Keep me in the loop
Neil
Sent from my iPad

On Jul 27, 2011, at 12:08 PM, "Wally Carlo, M.D." <WCarlo@peds.uab.edu> wrote:

> I am enclosing a draft of the two major points made in the allegation.
>
> I would appreciate any suggestions.
>
> Wally
>
> Wally Carlo, M.D.
> Edwin M. Dixon Professor of Pediatrics
> University of Alabama at Birmingham
> Director, Division of Neonatology
> Director, Newborn Nurseries
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>
>
> -----Original Message-----
> From: Finer, Neil [mailto:nfiner@ucsd.edu]
> Sent: Wednesday, July 27, 2011 11:59 AM
> To: Wally Carlo, M.D.

> Cc: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Wallace, Dennis; Monica Collins
> Subject: Re: OHRP
>
> Wally
> Do you hive more detail regarding this issue.
> I am traveling but getting email
> Thanks
> Neil
>
> Sent from my iPad
>
> On Jul 27, 2011, at 5:06 AM, "Wally Carlo, M.D." <WCarlo@peds.uab.edu<mailto:WCarlo@peds.uab.edu>> wrote:
>
> Hi Rose:
>
> The wording on the statement regarding the consent form on the OHRP allegation comes from the sample consent form in the MOO and not from the UAB consent so we believe this is not a local request. Monica and I have prepared a draft response. When we complete a better draft, we will share it with you, Neil, Abhik, and Dennis as this seems to be more of a whole NRN issue.
>
> Wally
>
> Wally Carlo, M.D.
> Edwin M. Dixon Professor of Pediatrics
> University of Alabama at Birmingham
> Director, Division of Neonatology
> Director, Newborn Nurseries
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> Phone: 205 934 4680
> FAX: 205 934 3100
> Cell: 205 (b)(6)
>
> <Letter to Dr Borror 7-26-11.doc>

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "wcarlo@peds.uab.edu"
Subject: Re: SUPPORT OHRP request
Date: Tuesday, July 26, 2011 3:24:13 PM

Yes

From: Wally Carlo, M.D. <WCarlo@peds.uab.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tue Jul 26 14:56:12 2011
Subject: SUPPORT OHRP request

Hi Rose:

I assume everyone is going to get this. Can we discuss it today on the call?

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
1700 6th Avenue South
176F Suite 9380R
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 (b)(6)

From: Marcus Humphrey
Sent: Tuesday, July 26, 2011 1:47 PM
To: Wally Carlo, M.D.
Subject:

Marcus J. Humphrey
UAB Division of Neonatology
1700 6th Avenue South - 176F Suite 9380W
Birmingham, AL 35249-7333
Phone 205 934-4680
Cell 256 (b)(6)
Fax 205 934-3100
mhumphrey@peds.uab.edu

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Spong, Catherine (NIH/NICHD) [E]
Subject: Fw: SUPPORT OHRP request
Date: Tuesday, July 26, 2011 3:21:18 PM
Attachments: 20110726134644.pdf

This was just discussed on our monthly SC call
Rose

From: Wally Carlo, M.D. <WCarlo@peds.uab.edu>
To: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Tue Jul 26 14:56:12 2011
Subject: SUPPORT OHRP request

Hi Rose:

I assume everyone is going to get this. Can we discuss it today on the call?

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
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Phone: 205 934 4680
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From: Marcus Humphrey
Sent: Tuesday, July 26, 2011 1:47 PM
To: Wally Carlo, M.D.
Subject:

Marcus J. Humphrey
UAB Division of Neonatology
1700 6th Avenue South - 176F Suite 9380W
Birmingham, AL 35249-7333
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Fax 205 934-3100
mhumphrey@peds.uab.edu

DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of the Assistant Secretary for Health

Office for Human Research Protections
The Tower Building
1101 Wootton Parkway, Suite 200
Rockville, Maryland 20852
Telephone: 240-453-8132
FAX: 240-453-6909
E-mail: Kristina.Borror@hhs.gov

July 18, 2011

Richard B. Marchase, PhD
VP for Research & Economic Development
University of Alabama at Birmingham (UAB)
AB 720E
701 20th Street South
Birmingham, AL 35294-0107

E. Ward Sax, M.B.A.
V.P., Treasurer and Chief Risk Officer
Research Triangle Institute (RTI)
3040 Cornwallis Road, P.O. Box 12194
Research Triangle Park, NC 27709-2194

RE: Human Research Protections Under Federalwide Assurance FWA-5960 and -FWA-3331

Research Project: The SUrfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants: The SUPPORT Trial
Principal Investigator: Dr. Waldemar Carlo
HHS Protocol Number: 2U10HD034216

Dear Dr. Marchase:

We have received allegations of noncompliance with Department of Health and Human Services (HHS) regulations for the protection of human research subjects (45 CFR Part 46) involving the above-referenced research.

The complainant alleges and we are concerned regarding the following:

Failure of the informed consent documents for this study to include or adequately address the following basic elements required by HHS regulations at 45 CFR 46.116(a):

(a) Section 46.116(a)(2): A description of any reasonably foreseeable risks and discomforts. In specific, we are concerned that the informed consent document states "Because all of the treatments proposed in this study are standard of care, there is no predictable increase in risk for your baby." However, this study involved randomizing subjects to either higher or lower ranges of oxygen saturation. This was clearly a departure from allowing a clinician to decide what oxygen saturation level they considered to be best for each particular infant. Moreover, the researchers were well aware of the possibility of substantially different outcomes, resulting from the assignment to a treatment arm, at least based on mortality, and chance of blindness and other types of morbidity.

(b) Section 46.116(a)(1)(ii): an explanation of the purposes of the research. In specific, we are concerned that the informed consent document states as the purpose related to oxygen saturation "To compare low range (85-89%) oxygen saturation levels with high range (91-95%) levels to determine if a lower range results in decreased ROP (Retinopathy of Prematurity, an eye disease that may result in impairment of vision or even blindness, which may be caused by excessive levels of oxygen" whereas the protocol stated "if relative to infants managed with a higher SpO2 range that the use of a lower SpO2 range (85% to 89%) will result in an increase in survival without the occurrence of threshold ROP and/or the need for surgical intervention." There is no mention in the informed consent document related to the purpose the endpoints of survival differences.

Consistent with its obligations under HHS regulations at 45 CFR 46.115(b) and under Public Law 99-158, I am requesting that your institutions investigate this matter and forward to us a written report of its investigation (see OHRP Compliance Oversight Procedures dated October 14, 2009 at http://www.hhs.gov/ohrp/compliance/evaluation/index.html).
Please include the following with the report:

(1) A detailed response to each allegation referenced above.

(2) A copy of the complete IRB file for the research, including the following:

(a) The IRB-approved research protocol and any applicable grant applications.
(b) The IRB-approved informed consent documents from each enrollment site.
(c) The relevant IRB minutes, including initial review, continuing review, review of changes to the research or to the informed consent document, and review of any adverse or unanticipated events.
(d) All correspondence between the IRB and the investigators.
(e) All continuing review reports.

(f) A list of subjects (code numbers only) and dates of enrollment.
(g) A chronological summary of the dates of the IRB's actions.
(h) A copy of any publications or presentations which were derived from this research project.
(i) Any other pertinent information.

(3) Clarification of the extent to which the research was supported in any way, even partially or indirectly, by HHS or any other federal agency.

(4) If your investigation reveals noncompliance, a description of any corrective actions that have been or will be taken by your institution to prevent such noncompliance from recurring.

Please forward your report so that we receive it no later than August 29, 2011.

We appreciate the continued commitment of your institutions to the protection of human research subjects. Please do not hesitate to contact me should you have any questions.

Sincerely,

Kristina C. Borror, Ph.D.
Director, Division of Compliance Oversight

cc:
Ms. Sheila D. Moore, Director, Office of the IRB, UAB
Dr. Ferdinand Urthaler, Chair, UAB IRBs
Dr. Waldemar Carlo, UAB
Dr. Juesta M. Caddell, Director, Office of Research Protection, RTI
Mr. David Borasky, Chair IRB#1, RTI
Ms. Angela Greene, Chair IRB#2, RTI
Dr. Juesta M. Caddell, Chair IRB#3, RTI

Dr. Margaret Hamburg, Commissioner, Food and Drug Administration (FDA)
Dr. Joanne Less, FDA
Dr. Sherry Mills, National Institutes of Health (NIH)
Mr. Joseph Ellis, NIH
Dr. Alan E. Guttmacher, Director, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD)
Dr. Yvonne Maddox, Deputy Director NICHD

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Maddox, Yvonne (NIH/NICHD) [E]; Hayunga, Eugene G. (NIH/NICHD) [E]
Cc: Spong, Catherine (NIH/NICHD) [E]
Subject: RE: Request Re: SUPPORT STUDY
Date: Friday, July 22, 2011 3:29:00 PM
Attachments: FW Inquiry re SUPPORT trial.msg
Importance: High

The coordinating center at RTI forwarded the attachment to me.

Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
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Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Maddox, Yvonne (NIH/NICHD) [E]
Sent: Friday, July 22, 2011 10:02 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: Request Re: SUPPORT STUDY

I will make a follow up call. Tks

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Maddox, Yvonne (NIH/NICHD) [E]; Hayunga, Eugene G. (NIH/NICHD) [E]
Cc: Spong, Catherine (NIH/NICHD) [E]
Sent: Fri Jul 22 09:55:48 2011
Subject: RE: Request Re: SUPPORT STUDY

HI
I have not heard any follow up at this point from OHRP. As we discussed, you had wanted me to let you know after our call with OHRP if we had further communication.
Let me know if you would like me to do anything further.

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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CDBPM, NIH

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Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
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higginsr@mail.nih.gov

From: Maddox, Yvonne (NIH/NICHD) [E]
Sent: Monday, June 20, 2011 12:54 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Hayunga, Eugene G. (NIH/NICHD) [E]
Cc: Spong, Catherine (NIH/NICHD) [E]
Subject: RE: Request Re: SUPPORT STUDY

Rose, I need to be on the call, think, but if not Gene can represent us, perhaps.

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Monday, June 20, 2011 12:38 PM
To: Hayunga, Eugene G. (NIH/NICHD) [E]; Maddox, Yvonne (NIH/NICHD) [E]
Cc: Spong, Catherine (NIH/NICHD) [E]
Subject: FW: Request Re: SUPPORT STUDY

Gene and Yvonne
This is in reference to the request from OHRP and the NICHD Neonatal Research Network's SUPPORT Trial.

Do you want to be on the call?
Let me know and I can send them a response.

Thanks
Rose

Rosemary D. Higgins, MD
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higginsr@mail.nih.gov

From: Borror, Kristina C (HHS/OASH)
Sent: Monday, June 20, 2011 11:41 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Request Re: SUPPORT STUDY

Thanks a lot, Rosemary. We were wondering if we could set up a conference call with you and any other appropriate experts at NICHD regarding this study. What is your availability Friday, July 1 or the week of July 5?

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Wednesday, June 01, 2011 11:32 AM
To: Borror, Kristina C (HHS/OASH)
Cc: Maddox, Yvonne (NIH/NICHD) [E]
Subject: RE: Request Re: SUPPORT STUDY

Hi Dr. Borror,
I have obtained the protocol and the portion of the Manual of Operations with a model consent form (MOP B1-3) from our data coordinating center at Research Triangle Institute International. The model consent form served as a template for sites. Each individual site was responsible for their own consent forms which would include boilerplate language required by the consent as well as modification to meet their local IRB standards.
Let me know if there are further questions.

Regards
Rose

Rosemary D. Higgins, MD
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301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Maddox, Yvonne (NIH/NICHD) [E]
Sent: Wednesday, June 01, 2011 11:05 AM
To: Maddox, Yvonne (NIH/NICHD) [E]; Borror, Kristina C (HHS/OASH)
Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Request Re: SUPPORT STUDY

Dear Dr. Borror.
Thank you for your return call this morning. As promised, Dr. Higgins will be forwarding you the protocol and at least a sample of a consent form used at one of the 20 sites involved in this study. Feel free to contact Rose if you have any additional questions. Thanks

---

From: Maddox, Yvonne (NIH/NICHD) [E]
Sent: Wednesday, June 01, 2011 9:58 AM
To: Borror, Kristina C (HHS/OASH)

Cc: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Request Re: SUPPORT STUDY

Dear Kristina,

I am the Research Integrity officer at NICHD and would appreciate a phone call regarding your request regarding allegations related to the above study. thanks

Yvonne T. Maddox, Ph.D.
Deputy Director
Eunice Kennedy Shriver National Institute of
Child Health and Human Development
National Institutes of Health
31 Center Drive, Room 2A03, MSC 2425
Bethesda, MD 20892
Phone: 301-496-1848
Fax: 301-402-1104
E-mail: maddoxy@mail.nih.gov

Blansfield, Earl (NIH/NICHD) [E]

From: Zaterka-Baxter, Kristin <kzaterka@rti.org>
Sent: Friday, July 22, 2011 3:13 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: Inquiry re: SUPPORT trial

Importance: High

I am calling you about this now:

From: Borasky, David
Sent: Friday, July 22, 2011 3:08 PM
To: Zaterka-Baxter, Kristin; Das, Abhik
Subject: RE: Inquiry re: SUPPORT trial

Here are the substantive paragraphs (making an executive decision to send these since they're from a letter subject to FOIA)

a. Section 46.116(a)(2): A description of any reasonably foreseeable risks and discomforts. In specific, we are concerned that the informed consent document stats "Because all of the treatments proposed in the study are standard of care, there is no predictable increase in risk for your baby." However, this study involved randomizing subjects to either higher or lower ranges of oxygen saturation. This was clearly a departure from allowing a clinician to decide what oxygen saturation level the considered to be best for each particular infant. Moreover, the researchers were well aware of the possibility of substantially different outcomes, resulting from the assignment to a treatment arm, at least based on mortality, and chance of blindness and other types of morbidity.

b. Section 46.116(a)(1)(ii): an explanation of the purpose of the research. In specific, we are concerned that the informed consent document states as the purpose related to oxygen saturation "To compare low range (85-89%) oxygen saturation levels with high range (91-95%) levels to determine if a lower range results in decreased ROP (Retinopathy of Prematurity, an eye disease that may result in impairment of vision or even blindness, which may be caused by excessive levels of oxygen" whereas the protocol stated "if relative to infants managed with a higher SpO2 range that the use of a lower SpO2 range (85 to 89%) will result in an increase in survival without the occurrence of threshold ROP and/or the need for surgical intervention." There is no mention in the informed consent document related to the purpose the endpoints of survival differences.

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Gantz, Marie"
Cc: "Das, Abbot"
Subject: FW: URGENT SUPPORT QUERIES
Date: Friday, July 22, 2011 9:22:00 AM

Many of these have changed. Let us know when the analysis can be rerun. I suspect that the results may change!
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Simonini, Joan [mailto:JSimonini@WIHRI.org]
Sent: Friday, July 22, 2011 9:13 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Laptook, Abbot; Vohr, Betty; Hensman, Angelita; Bishop, Carmena D
Subject: RE: URGENT SUPPORT QUERIES

Four (4) corrections were made and they are as follows:

(b)(6)

Joan

From: Hensman, Angelita
Sent: Monday, July 18, 2011 9:49 AM
To: Bishop, Carmena D
Cc: Simonini, Joan; Vohr, Betty
Subject: FW: URGENT SUPPORT QUERIES

Hi Nina,

Please pull the charts below for Dr. Vohr to review and make changes if needed and send to Joan ASAP for entering.

Thanks!

Angelita

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, July 18, 2011 9:22 AM
To: Laptook, Abbot; Vohr, Betty; Hensman, Angelita; Ventura, Suzy
Cc: 'Gantz, Marie'; Auman, Jeanette O.
Subject: URGENT SUPPORT QUERIES

Hi
Attached are hearing queries for infants from the SUPPORT trial – please verify that the information for each patient listed is correct. Please get back to us by Friday July 22.

Thanks for all the effort!!
Rose

CENTER NETWORK ECENTER EQLNUM infant QUERY

(b)(6)

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Vaucher, Yvonne
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Hot Topics: :brochure info YVaucher
Date: Thursday, July 21, 2011 3:19:49 PM

I did: Clinical Professor of Pediatrics-retired

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]
Sent: Thursday, July 21, 2011 12:10 PM
To: Vaucher, Yvonne
Cc: Finer, Neil
Subject: RE: Hot Topics: :brochure info YVaucher

I suggest giving your academic rank
Rose

Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network
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higginsr@mail.nih.gov

-----Original Message-----
From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]
Sent: Thursday, July 21, 2011 3:05 PM
To: Bidus, Karen
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil
Subject: RE: Hot Topics: :brochure info YVaucher

All,

Is this OK? I wasn't sure whether to include the "Follow Up PI for SUPPORT..." line or no which Wade says is my offipial designation for SUPPORT.

Yvonne

Yvonne E. Vaucher, M.D., M.P.H.
Follow Up PI, NICHD Neonatal Research Network SUPPORT trial
Clinical Professor of Pediatrics-retired
University of California, San Diego
San Diego, California

From: Bidus, Karen [kbidus@NEMOURS.ORG]

Sent: Thursday, July 21, 2011 11:25 AM
To: Vaucher, Yvonne
Subject: RE: Hot TOpics

December 6 - you will get a formal speaker letter with all of the details shortly-

I need your name as you would like it to appear in the brochure - title of the talk is set - Dr. Peralta's info below as an example.

Myriam Peralta Carcelen MD MPH
Director UAB Newborn Follow Up Clinic
Professor of Pediatrics
University of Alabama at Birmingham
Birmingham Alabama

Thanks!

Karen Bidus
Director, Office of CME
Alfred I. duPont Hospital for Children
302-651-6752

-----Original Message-----
From: Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]
Sent: Thursday, July 21, 2011 2:19 PM
To: Bidus, Karen
Subject: RE: Hot TOpics

Karen,

What oither information besides name, title do you need.
Tuesday is December 6, not the 4th as indicated below. Which is correct-date or time?
Either one is OK for me.

Yvonne Vaucher

From: Bidus, Karen [kbidus@NEMOURS.ORG]
Sent: Thursday, July 21, 2011 7:40 AM
To: Higgins, Rosemary (NIH/NICHD) [E]; Jerold Lucey; Greenspan, Jay
Cc: mperalta@peds.uab.edu; Vaucher, Yvonne; Stong, Karen
Subject: RE: Hot TOpics

After speaking with Dr. Lucey and Dr. Higgins , we have made the follow adjustment to the schedule for the Hot Topics conference on Tuesday, December 4 -

the 3 p.m. talk will be titled NICHD Support Trial Follow-up Outcomes
Speaker 1 will speak from 3-3:20 on Oximetry Speaker 2 will speak from 3:20 -3:40 on CPAP . .. .
We will have a 20 minute Q and A with a 4 p.m. adjourn . . . .

Dr. Peralta and Dr. Vaucher - I will need the following from you today, please, as the brochure is set to go to press.

Your info for the brochure.

Your full name and credentials
your academic/hospital/ research appointments (no more than 4 lines, please!)

if you have any questions, please contact me today - I need to get the brochure printed so we can get the word out about registration ASAP.

Thanks very much.

Karen Bidus
Director, Office of CME
Alfred I. duPont Hospital for Children
302-651-6752

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Thursday, July 21, 2011 10:25 AM
To: Bidus, Karen
Subject: FW: Hot TOpics
Importance: High

NICHD SUPPORT Trial Follow Up Outcomes

The speakers would be Myriam Peralta (UAB) and Yvonne Vaucher (UCSD).

Yvonne's contact information is
yvaucher@ucsd.edu<mailto:yvaucher@ucsd.edu>

Rosemary D. Higgins, MD
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301-496-3790 (FAX)
higginsr@mail.nih.gov<mailto:higginsr@mail.nih.gov>

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Monday, July 18, 2011 3:02 PM
To: 'jerold.lucey@yahoo.com'
Subject: Hot TOpics
Importance: High

Jerry -
The NRN Steering committee would like both arms of the SUPPORT Trial FU (Oximetry and the CPAP vs surfactant) presented at this year's Hot Topics- is this possible? Yvonne Vaucher from UCSD is the PI for the CPAP/surf FU arm of the trial.

Let me know and then Myriam Peralta can send in her response to the Nemours folks.

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network Pregnancy and Perinatology Branch CDBPM, NIH 6100 Executive Blvd., Room 4B03 MSC 7510 Bethesda, MD 20892 For overnight delivery use Rockville, MD 20852
301-435-7909
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301-496-3790 (FAX)
higginsr@mail.nih.gov<mailto:higginsr@mail.nih.gov>

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Furey, Anne M"; "Frantz, Ivan"; "McGowan, Elisabeth C"
Cc: "Auman, Jeanette O."; "Gantz, Marie"
Subject: RE: URGENT SUPPORT QUERIES
Date: Thursday, July 21, 2011 3:12:00 PM

THANKS
ROSE

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Furey, Anne M [mailto:afurey@tuftsmedicalcenter.org]
Sent: Thursday, July 21, 2011 3:00 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Frantz, Ivan; McGowan, Elisabeth C
Cc: Auman, Jeanette O.; Gantz, Marie
Subject: RE: URGENT SUPPORT QUERIES

Liz McGowan reviewed these.

(b)(6) is accurate as already recorded: hearing impairment = 2, hearing aid requirement = 0
(b)(6) was changed to hearing impairment = 1

I updated the system, put in FS comments as applicable and transmitted.

Anne

Anne Furey, MPH
Division of Newborn Medicine
Floating Hospital for Children at Tufts Medical Center
800 Washington Street, Box 44
Boston, MA 02111
Phone: 617-636-7134
Fax: 617-636-1456
Pager: 617-(b)(6)
afurey@tuftsmedicalcenter.org

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Mon 7/18/2011 9:27 AM
To: Frantz, Ivan; Furey, Anne M; McGowan, Elisabeth C
Cc: Auman, Jeanette O.; 'Gantz, Marie'
Subject: URGENT SUPPORT QUERIES

Hi
Attached are hearing queries for infants from the SUPPORT trial – please verify that the information for each patient listed is correct. Please get back to us by Friday July 22.

Thanks for all the effort!!
Rose

CENTER	NETWORK	FCENTER	FOLNUM	infant	QUERY
(b)(6)					

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Wally Carlo, M.D."
Subject: RE: Hot Topics brochure/ NICHD Support Trial/LAST CALL
Date: Thursday, July 21, 2011 11:19:00 AM

JAMA is fine

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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Bethesda, MD 20892
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301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]
Sent: Thursday, July 21, 2011 10:35 AM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Hot Topics brochure/ NICHD Support Trial/LAST CALL

GREAT!

I am back, by the way.

I am working on revising the ANS paper. I was going to try JAMA first if ok with you.

Wally

Wally Carlo, M.D.
Edwin M. Dixon Professor of Pediatrics
University of Alabama at Birmingham
Director, Division of Neonatology
Director, Newborn Nurseries
1700 6th Avenue South
176F Suite 9380R
Birmingham, AL 35233-7335
Phone: 205 934 4680
FAX: 205 934 3100
Cell: 205 (b)(6)

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]

Sent: Thursday, July 21, 2011 9:30 AM
To: Myriam Peralta, M.D.; 'yvaucher@ucsd.edu'
Cc: Wally Carlo, M.D.; 'Finer, Neil'; 'Das, Abhik'; Gantz, Marie
Subject: RE: Hot Topics brochure/ NICHD Support Trial/LAST CALL

Hi all
I just spoke to Karen Bidus who had been in touch with Dr. Lucey – both arms of the SUPPORT can be presented at Hot Topics as requested by the steering committee. They will be on Tuesday December 6 from 3-4 PM ET.

Myriam and Yvonne – Karen will email Yvonne this am with the official invitation. Please let Karen know ASAP your information as well as availability for presentation. If either of you are not available, then perhaps Wally or Neil can do the presentation.

Thanks for all the hard work!!
Rose

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higginsr@mail.nih.gov

From: Myriam Peralta, M.D. [mailto:MPeralta@peds.uab.edu]
Sent: Monday, July 18, 2011 2:32 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: Hot Topics brochure/ NICHD Support Trial/LAST CALL
Importance: High

I have not heard from you regarding the final decision on presenting on hot topics or not, just let me know thanks

---

From: Bidus, Karen [mailto:kbidus@NEMOURS.ORG]
Sent: Monday, July 18, 2011 9:05 AM
To: Bidus, Karen ; Myriam Peralta, M.D.
Cc: Stong, Karen
Subject: Hot Topics brochure/ NICHD Support Trial/LAST CALL
Importance: High

Dr. Peralta -

As you can see from the attached brochure, we are ready to go to press with the Hot Topics brochure,

with the exception of your information - can you please get back to me no later than end of day Wednesday, July 20 with your name and credentials as you would like them listed in the brochure, as well as the name of your talk if you would like something different - Your talk is scheduled at 3 p.m. on Tuesday- the closing talk of the symposium.

If you are not able to get back to me by the end of the day Wednesday, we will need to print the brochure as is . . .

Thanks very much.

Karen Bidus
Director, Office of CME
Alfred I. duPont Hospital for Children
302-651-6752

From: Bidus, Karen
Sent: Tuesday, July 05, 2011 2:52 PM
To: 'mperalta@peds.uab.edu'
Cc: Stong, Karen
Subject: FW: NICHD Support Trial
Importance: High

Dr. Peralta -

I've just received word that you will be presenting at *Hot Topics* - I will follow up with official speaker paperwork shortly, but unfortunately we are up against a printing deadline for the brochure. Can you please provide me with your name and credentials as you would like them to appear in the brochure - and the title of your talk - we currently have NICHD Support Trial 02 Follow-Up.

Thanks very much - please don't hesitate to contact me with any questions.

Karen Bidus
Director, Office of CME
Alfred I. duPont Hospital for Children
302-651-6752

recipient(s) is not a waiver of any applicable privilege. If you received this confidential communication in error, please notify the sender immediately by reply e-mail message and permanently delete the original message from your system.

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, July 05, 2011 2:16 PM
To: 'Gail M. Murphy'; 'jerold.lucey@yahoo.com'
Cc: Bidus, Karen
Subject: RE: NICHD Support Trial

HI
Dr. Myriam Peralta from the University of Alabama will be the first author for the SUPPORT oximetry follow up outcome paper.

Here contact information is:
Myriam Peralta-Carcelen, M.D.
mperalta@peds.uab.edu
General Pediatrics
CPPI 410
1600 7th Ave. So.
Birmingham AL 35233
(205)934-4531

She should be the network investigator to present the results. Dr. Hintz is the PI for the neuroimaging and outcome secondary study for the SUPPORT trial.

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network Pregnancy and Perinatology Branch CDBPM, NIH 6100 Executive Blvd., Room 4B03 MSC 7510 Bethesda, MD 20892 For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Gratton, Teresa (grattotd)
To: Higgins, Rosemary (NIH/NICHD) [E]; CHM-Schibler, Kurt (kurt.schibler); CHM-Yolton, Kimberly (kimberly.yolton); Grisby, Cathy (grisbyca)
Cc: 'Gantz, Marie'; Auman, Jeanette O.
Subject: RE: URGENT SUPPORT HEARING QUERIES
Date: Thursday, July 21, 2011 11:09:00 AM

Hi Rose,

A correction was made for this infant. F/U is (b) and the new data was entered (b)(6)

Thanks.
Tari

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, July 18, 2011 9:20 AM
To: CHM-Schibler, Kurt (kurt.schibler); CHM-Yolton, Kimberly (kimberly.yolton); Grisby, Cathy (grisbyca); Gratton, Teresa (grattotd)
Cc: 'Gantz, Marie'; Auman, Jeanette O.
Subject: URGENT SUPPORT HEARING QUERIES

Hi
Attached are hearing queries for infants from the SUPPORT trial – please verify that the information for each patient listed is correct. Please get back to us by Friday July 22.

Thanks for all the effort!!
Rose

CENTER NETWORK ECENTER EOLNUM infant QUERY
(b)(6)

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Vivien Phillips"; "Wally Carlo, M.D."; "Myriam Peralta, M.D."; "Shirley Cosby"; "Monica Collins"
Cc: "Gantz, Marie"; "Auman, Jeanette O."; "Das, Abhik"
Subject: RE: URGENT SUPPORT QUERIES
Date: Wednesday, July 20, 2011 3:18:00 PM

Jenny or Marie
Can these be fixed in the data set by hand??

Thanks
Rose

Rosemary D. Higgins, MD
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301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Vivien Phillips [mailto:VPhillips@peds.uab.edu]
Sent: Wednesday, July 20, 2011 3:18 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.; Myriam Peralta, M.D.; Shirley Cosby; Monica Collins
Cc: Gantz, Marie; Auman, Jeanette O.
Subject: RE: URGENT SUPPORT QUERIES

After reviewing the study/medical charts, the information is incorrect. Both cases should have been coded as "1" - No apparent functional impairment, these infants had mild hearing loss at the 18 month visit. I won't be able to correct the data entry in the network computer because we had computer problems and ended up sending the hard drive to RTI yesterday.
Vivien

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Mon 7/18/2011 8:23 AM
To: Wally Carlo, M.D.; Myriam Peralta, M.D.; Shirley Cosby; Vivien Phillips; Monica Collins
Cc: 'Gantz, Marie'; Auman, Jeanette O.
Subject: URGENT SUPPORT QUERIES

Hi
Attached are hearing queries for infants from the SUPPORT trial – please verify that the information for each patient listed is correct. Please get back to us by Friday July 22.

Thanks for all the effort!!
Rose

CENTER	NETWORK	FCENTER	FOLNUM	infant	QUERY
(b)(6)					

Rosemary D. Higgins, MD
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301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Poindexter, Brenda B"
Subject: RE: 7.11 growth secondary discussionHiggins, Rosemary (NIH/NICHD) [E]
Date: Wednesday, July 20, 2011 2:55:00 PM

Enjoy!!

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
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For overnight delivery use Rockville, MD 20852
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301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Poindexter, Brenda B [mailto:bpoindex@iupui.edu]
Sent: Wednesday, July 20, 2011 2:55 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: Re: 7.11 growth secondary discussionHiggins, Rosemary (NIH/NICHD) [E]

(b)(6)

(b)(6) .. Tiring but fun, and always special to have just one of them.

Sent from my iPad

On Jul 20, 2011, at 2:47 PM, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> wrote:

> Hope you are someplace fun!!!
>
> Rosemary D. Higgins, MD
> Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
> Pregnancy and Perinatology Branch
> CDBPM, NIH
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> For overnight delivery use Rockville, MD 20852
> 301-435-7909
> 301-496-5575
> 301-496-3790 (FAX)
> higginsr@mail.nih.gov

From: Poindexter, Brenda B [mailto:bpoindex@iupui.edu]
Sent: Wednesday, July 20, 2011 2:47 PM
To: Vaucher, Yvonne
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; kurt.schibler@cchmc.org; alaptook@WIHRI.org; Myriam Peralta, M.D.; mcw3@cwru.edu; Roger Faix; Bradley Yoder; nancy newman; Rich, Wade; Das, Abhik; Wallace, Dennis; Archer, Stephanie (NIH/NICHD) [E]; sduara@miami.edu; Navarrete, Cristina; Richard Ehrenkranz; Wally Carlo, M.D.
Subject: Re: 7.11 growth secondary discussionHiggins, Rosemary (NIH/NICHD) [E]

Shahnaz and all,
Thanks for including me in this important secondary. I'm (b)(6) this week, but will send comments early next week when I get back.
Thanks, Brenda

Sent from my iPad

On Jul 20, 2011, at 2:34 PM, "Vaucher, Yvonne" <yvaucher@ucsd.edu> wrote:

> Protein calories should be included though the whole caloric intake calculation is problematic considering the non-uniform feeding (full or partial formula, MBM, DBM, supplements). We often find that growth improves with supplementing MBM with extra protein (1 gm/kg) when caloric intake is already adequate. MBM also varies calorically from 16 to 25 kcal/oz and is often supplemented. Although types of feeding and caloric intake at any given point in time may not reflect the intake for the preceding interval, it is a cross-sectional comparison of caloric and nutrient intake at that time.
>
> Concerning which groups (CPAP/Surfactant; Low/Higher sat) to analyze: Feeding onset/advancement, and hence growth (esp. early growth), may be influenced by type of respiratory support initially provided. In addition there was more NEC in the CPAP group so it may be worth looking at the growth of the CPAP/Surf group as well as the low/higher sat group.
>
> Yvonne
>
> ---
>
> **From:** Richard Ehrenkranz [mailto:richard.ehrenkranz@yale.edu]
> **Sent:** Tuesday, July 19, 2011 9:03 AM
> **To:** Wally Carlo, M.D.
> **Cc:** Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; kurt.schibler@cchmc.org; alaptook@WIHRI.org; Vaucher, Yvonne; Myriam Peralta, M.D.; mcw3@cwru.edu; Roger Faix; Bradley Yoder; nancy newman; Rich, Wade; Das, Abhik; Wallace, Dennis; bpoindex@iupui.edu; Archer, Stephanie (NIH/NICHD) [E]; sduara@miami.edu; Navarrete, Cristina
> **Subject:** Re: 7.11 growth secondary discussion
>
> Hi:
> 1. I share Wally's concern's expressed in point #1 below. However, we will probably also want to perform the analysis for survivors (whole cohort, AGA, SGA) to 36 wks PMA.

2. With respect to the choice of growth curves:

a. Consider Olsen (Pediatrics 2010; 125:e214-224) for the in-hospital growth. In contrast to Fenton's paper, Olsen's paper is based upon a Pediatrix administrative dataset and presents weight, length, and HC data (percentiles and mean ± SD) by gender on the same patients. Plus the infants were born in 33 US states from 1998-2006). I have attached a pdf of the paper.

b. The WHO 2006 curves are recommended over the CDC 2000 curves. However, it might decrease the number (%) of infants who are < 10th%tile at 18-22 mos corrected age.

3. What was meant by the statement to "include analysis by birth weight strata as in major trial"? In SUPPORT, data were reported by GA strata.

4. I agree with the need to perform analyses by AGA and SGA.

5. Page 8: How will growth velocity be calculated? I suggest the exponential method described by Patel (Pediatrics 2005; 116:1466-1473); a pdf of the paper is attached.

6. Page 8: With respect to calorie calculations: I prefer option #2- including protein calories.

Thanks for including me on this secondary study.
Richard

On 7/19/2011 3:27 AM, Wally Carlo, M.D. wrote:
I missed the call as I was (b)(6). Sorry. Here are some comments but first, congratulations to Cristina and others for putting all of this together.

1) I agree that death should be considered in the analysis. An issue is whether it should be part of the primary hypothesis which would require dichotomizing the growth outcomes (e.g. death or <10%ile weight). In view of the large difference in mortality in the saturation trial, this analytical approach may be the best.

2) I think we need to prespecify the primary outcome better using a single measure rather than as "growth", using multiple measures (weight, length, HC).

3) Table 1 could have percent of infants with weight less than 10th percentile at birth as well as raw values for length and HC. Currently, percentile is used for HC and length versus raw data for BW. If SGA refers to 10th percentile, it may be best to be consistent with the rest of the table and use percentile.

4) Table 2 (clinical outcomes) should more closely follow the table from the original paper particularly including death as the first or second outcome measure. RDS may not be a good outcomes measure. It is difficult to rule out the diagnosis when prophylactic

surfactant is given.

5) We need to be very careful with multiple comparisons. For example, just the Primary Outcomes table has 48 comparisons. In addition to specifying a single primary outcomes, we should prespecify a correction for multiple analyses.
Wally

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Mon 7/18/2011 3:56 PM
To: 'Finer, Neil'; 'kurt.schibler@cchmc.org'; 'alaptook@WIHRI.org'; Wally Carlo, M.D.; 'yvaucher@ucsd.edu'; Myriam Peralta, M.D.; 'mcw3@cwru.edu'; 'Roger Faix'; 'Bradley Yoder'; 'nancy newman'; 'Rich, Wade'; Das, Abhik; Wallace, Dennis; bpoindex@iupui.edu; Richard A. Ehrenkranz
Cc: Archer, Stephanie (NIH/NICHD) [E]; 'sduara@miami.edu'; 'Navarrete, Cristina'
Subject: FW: 7.11 growth secondary discussion

Hi
Here is the information for the growth secondary study to SUPPORT. Please send your comments by email by July 29,

Thanks
Rose

Rosemary D. Higgins, MD
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301-496-3790 (FAX)
higginsr@mail.nih.gov

-----Original Message-----
From: Navarrete, Cristina [mailto:CNavarrete@med.miami.edu]
Sent: Thursday, July 14, 2011 3:50 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Duara, Shahnaz
Subject: 7.11 growth secondary discussion

Hello Dr. Higgins,
Attached is the revised document that reflects the discussion on 7/11, plus the reference growth chart articles. Please forward it to the subcommittee members, including Drs. Ehrenkranz and Poindexter, for concensus. Also, please let us know if there are any objections, so that we can ammend it if needed.
Thank you,
Cristina

--
Richard A. Ehrenkranz, MD
Department of Pediatrics
Yale University School of Medicine
333 Cedar Street
PO Box 208064
New Haven, CT 06520-8064
tele: 203-688-2320
fax: 203-688-5426

From: Walsh, Michele
To: Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; kurt.schibler@cchmc.org; alaptook@WIHRI.org; Wally Carlo, M.D.; yvaucher@ucsd.edu; Myriam Peralta, M.D.; mcw3@cwru.edu; Roger Faix; Bradley Yoder; nancy newman; Rich, Wade; Das, Abhik; Wallace, Dennis; bpoindex@iupui.edu; Richard A. Ehrenkranz
Cc: Archer, Stephanie (NIH/NICHD) [E]; sduara@miami.edu; Navarrete, Cristina
Subject: RE: 7.11 growth secondary discussion
Date: Wednesday, July 20, 2011 12:30:00 PM

I feel that the analyses should focus only on
The cohort randomized to the different saturation arms.
An overall statement about total nutritional intake on
The days assayed should satisfy reviewers that intake is not
Different between groups. A figure (rather than tables) showing growth in low Versus high over time may have the highest impact.
Other analyses such as the "as treated" - would have to come back as proposals that compete for the limited funding pool with other projects
(or obtain outside funding).
Analyses of growth will have to take into death, (given higher death in the low sat arm), and the right censoring this entails in the evaluation- this needs some thought.

Michele Walsh
216|844.3759

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Monday, July 18, 2011 4:56 PM
To: Finer, Neil'; 'kurt.schibler@cchmc.org'; 'alaptook@WIHRI.org'; 'Wally Carlo, M.D.'; 'yvaucher@ucsd.edu'; 'Myriam Peralta, M.D.'; 'mcw3@cwru.edu'; 'Roger Faix'; 'Bradley Yoder'; 'nancy newman'; 'Rich, Wade'; Das, Abhik; Wallace, Dennis; bpoindex@iupui.edu; Richard A. Ehrenkranz
Cc: Archer, Stephanie (NIH/NICHD) [E]; 'sduara@miami.edu'; 'Navarrete, Cristina'
Subject: FW: 7.11 growth secondary discussion

Hi
Here is the information for the growth secondary study to SUPPORT. Please send your comments by email by July 29,

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network
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301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

-----Original Message-----
From: Navarrete, Cristina [mailto:CNavarrete@med.miami.edu]

Sent: Thursday, July 14, 2011 3:50 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Cc: Duara, Shahnaz
Subject: 7.11 growth secondary discussion

Hello Dr. Higgins,
Attached is the revised document that reflects the discussion on 7/11, plus the reference growth chart articles. Please forward it to the subcommittee members, including Drs. Ehrenkranz and Poindexter, for concensus. Also, please let us know if there are any objections, so that we can ammend it if needed.
Thank you,
Cristina

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Gantz, Marie"
Subject: RE: SUPPORT hearing data
Date: Tuesday, July 19, 2011 3:23:00 PM

So I sent all of them out already

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
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301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

-----Original Message-----
From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Tuesday, July 19, 2011 3:13 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT hearing data

The queries were for the infants on the printout (there was complete overlap).

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, July 19, 2011 3:08 PM
To: Gantz, Marie
Subject: RE: SUPPORT hearing data

Were some of the queries I sent relevant to the infants listed on the printout you sent?? IN other words, have I already asked the sites??

Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network
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-----Original Message-----
From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Tuesday, July 19, 2011 3:06 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: SUPPORT hearing data

Rose,

Can you tell me what you mean by "overlap?"

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255
-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, July 19, 2011 2:35 PM
To: Gantz, Marie
Subject: RE: SUPPORT hearing data

Marie
I sent queries yesterday - how many overlap?

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network
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For overnight delivery use Rockville, MD 20852
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301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

-----Original Message-----
From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Friday, July 15, 2011 5:09 PM
To: Zaterka-Baxter, Kristin; Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]; MPeralta@PEDS.UAB.EDU; nfiner@ucsd.edu; Wally Carlo, M.D.; Yvonne Vaucher
Subject: SUPPORT hearing data

Attached are hearing data from GDB and FU for SUPPORT children classified as noted below:

1) 14 children coded on NF05 as 1='No hearing impairment' and hearing aid requirement 1='Right only.'
2) 1 child coded on NF05 as 1='No hearing impairment' and hearing aid requirement 3='Both.'
3) 19 children coded on NF05 as 2='Impairment' and hearing aid requirement 0='None.'

Please let Abhik and I know if any of these cases require queries to go out to the center. FYI, I will be attending a steering committee meeting for another network next week, but the queries are ready to be sent out in my absence (if necessary).

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

-----Original Message-----
From: Gantz, Marie
Sent: Thursday, July 14, 2011 11:09 AM
To: Zaterka-Baxter, Kristin; 'Abbot Laptook (alaptook@WIHRI.org)'; 'Bradley Yoder'; Das, Abhik; 'Higgins, Rosemary (NIH/NICHD) [E]'; 'kurt.schibler@cchmc.org'; 'mcw3@cwru.edu'; 'MPeralta@PEDS.UAB.EDU'; 'nancy newman'; 'nfiner@ucsd.edu'; 'Roger.Faix@hsc.utah.edu'; Wallace, Dennis; 'Wally Carlo, M.D.'; 'wrich@ucsd.edu'; 'Yvonne Vaucher'
Subject: RE: SUPPORT FU results

Table 5 with combinations of death and NDI components is attached. Break-outs by GA strata are included.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

-----Original Message-----
From: Gantz, Marie
Sent: Wednesday, July 13, 2011 4:57 PM
To: Zaterka-Baxter, Kristin; 'Abbot Laptook (alaptook@WIHRI.org)'; 'Bradley Yoder'; Das, Abhik; 'Higgins, Rosemary (NIH/NICHD) [E]'; 'kurt.schibler@cchmc.org'; 'mcw3@cwru.edu'; 'MPeralta@PEDS.UAB.EDU'; 'nancy newman'; 'nfiner@ucsd.edu'; 'Roger.Faix@hsc.utah.edu'; Wallace, Dennis; 'Wally Carlo, M.D.'; 'wrich@ucsd.edu'; 'Yvonne Vaucher'
Subject: RE: SUPPORT FU results

Table 3 with other FU outcomes is attached. This version does not include z scores or a break-out by GA strata. Those will be included in the next iteration of the tables.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

-----Original Message-----
From: Gantz, Marie
Sent: Tuesday, July 12, 2011 9:54 AM
To: Zaterka-Baxter, Kristin; 'Abbot Laptook (alaptook@WIHRI.org)'; 'Bradley Yoder'; Das, Abhik; 'Higgins, Rosemary (NIH/NICHD) [E]'; 'kurt.schibler@cchmc.org'; 'mcw3@cwru.edu'; 'MPeralta@PEDS.UAB.EDU'; 'nancy newman'; 'nfiner@ucsd.edu'; 'Roger.Faix@hsc.utah.edu'; Wallace, Dennis; 'Wally Carlo, M.D.'; 'wrich@ucsd.edu'; 'Yvonne Vaucher'
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From: Zaterka-Baxter, Kristin
Sent: Monday, July 11, 2011 1:05 PM
To: 'Abbot Laptook (alaptook@WIHRI.org)'; 'Bradley Yoder'; Das, Abhik; Gantz, Marie; 'Higgins, Rosemary (NIH/NICHD) [E]'; 'kurt.schibler@cchmc.org'; 'mcw3@cwru.edu'; 'MPeralta@PEDS.UAB.EDU'; 'nancy newman'; 'nfiner@ucsd.edu'; 'Roger.Faix@hsc.utah.edu'; Wallace, Dennis; 'Wally Carlo, M.D.'; 'wrich@ucsd.edu'; 'Yvonne Vaucher'
Subject: FW: SUPPORT FU results

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From: Gantz, Marie
Sent: Monday, July 11, 2011 1:03 PM
To: Zaterka-Baxter, Kristin
Subject: FW: SUPPORT FU results

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Research Statistician
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-----Original Message-----
From: Gantz, Marie
Sent: Monday, July 11, 2011 12:42 PM
To: 'Vaucher, Yvonne'; 'Myriam Peralta, M.D.'; 'Finer, Neil'; Das, Abhik; 'Higgins, Rosemary (NIH/NICHD) [E]'; 'Wally Carlo, M.D.'
Cc: 'Archer, Stephanie (NIH/NICHD) [E]'
Subject: RE: SUPPORT FU results

Attached are new versions of the tables that went out on Friday with the addition of (1) unadjusted p values in table 1 (significance requested by Rose) and (2) all tables broken out by GA groups.

These tables have not gone to the entire subcommittee. Should they be sent out for the meeting today at 1:00?

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-----Original Message-----
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Sent: Friday, July 08, 2011 7:23 PM
To: 'Vaucher, Yvonne'; Myriam Peralta, M.D.; Finer, Neil; Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.
Cc: Archer, Stephanie (NIH/NICHD) [E]
Subject: SUPPORT FU results

PRELIMINARY DATA for Tables 1 and 2 are attached. I will try to get you the other two tables before our meeting on Monday. Please note the following:

1) Rose sent out a few queries today (14), a small number of which could impact the Bayley/NDI outcome. We will have final data next week and I will rerun the tables.

2) I did not include the infant with the Bayley II and MDI<70 in the outcome of NDI/death. The reason is that I looked at the MDI and PDI data for the other handful of infants who had both Bayley exams, and there were a couple that we would have classified as NDI if we were judging by the Bayley II, but they were not NDI per the Bayley III. Those scores were not much different from the one we observed in the adjudicated case, so I felt it was more appropriate to leave that infant out of the NDI outcome, at least for now.

3) In Table 2, the outcomes are adjusted for the design effects (GA, familial clustering, center) except blindness (both eyes and unilateral) which is not adjusted for center because the number of children with blindness was so small.

Looking forward to discussing these tables with you on Monday.

Marie

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From: Vaucher, Yvonne
To: Gantz, Marie; Zaterka-Baxter, Kristin; Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]; MPeralta@PEDS.UAB.EDU; Finer, Neil; Wally Carlo, M.D.
Subject: RE: SUPPORT hearing data
Date: Tuesday, July 19, 2011 1:58:44 PM

It would be important to inquire about the outcome of those children who had hearing impairment but had "consults pending" as outcomes for a few children could change the level of significance for hearing impairment CPAP vs. Surfactant. It would therefore be helpful to know if any of these children required amplification and if so did they still have hearing impairment?

Yvonne

-----Original Message-----
From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Friday, July 15, 2011 2:09 PM
To: Zaterka-Baxter, Kristin; Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]; MPeralta@PEDS.UAB.EDU; Finer, Neil; Wally Carlo, M.D.; Vaucher, Yvonne
Subject: SUPPORT hearing data

Attached are hearing data from GDB and FU for SUPPORT children classified as noted below:

1) 14 children coded on NF05 as 1='No hearing impairment' and hearing aid requirement 1='Right only.'
2) 1 child coded on NF05 as 1='No hearing impairment' and hearing aid requirement 3='Both.'
3) 19 children coded on NF05 as 2='Impairment' and hearing aid requirement 0='None.'

Please let Abhik and I know if any of these cases require queries to go out to the center. FYI, I will be attending a steering committee meeting for another network next week, but the queries are ready to be sent out in my absence (if necessary).

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
828-254-6255

-----Original Message-----
From: Gantz, Marie
Sent: Thursday, July 14, 2011 11:09 AM
To: Zaterka-Baxter, Kristin; 'Abbot Laptook (alaptook@WIHRI.org)'; 'Bradley Yoder'; Das, Abhik; 'Higgins, Rosemary (NIH/NICHD) [E]'; 'kurt.schibler@cchmc.org'; 'mcw3@cwru.edu'; 'MPeralta@PEDS.UAB.EDU'; 'nancy newman'; 'nfiner@ucsd.edu'; 'Roger.Faix@hsc.utah.edu'; Wallace, Dennis; 'Wally Carlo, M.D.'; 'wrich@ucsd.edu'; 'Yvonne Vaucher'
Subject: RE: SUPPORT FU results

Table 5 with combinations of death and NDI components is attached. Break-outs by GA strata are included.

Marie

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Subject: FW: SUPPORT FU results

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Subject: FW: SUPPORT FU results

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828-254-6255

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Myriam Peralta, M.D."
Subject: RE: Hot Topics brochure/ NICHD Support Trial/LAST CALL
Date: Monday, July 18, 2011 4:53:00 PM

I am still waiting to hear from Jerry Lucey about both presentations.

Rose

Rosemary D. Higgins, MD
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network
Pregnancy and Perinatology Branch
CDBPM, NIH
6100 Executive Blvd., Room 4B03
MSC 7510
Bethesda, MD 20892
For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Myriam Peralta, M.D. [mailto:MPeralta@peds.uab.edu]
Sent: Monday, July 18, 2011 2:32 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: FW: Hot Topics brochure/ NICHD Support Trial/LAST CALL
Importance: High

I have not heard from you regarding the final decision on presenting on hot topics or not, just let me know thanks

---

From: Bidus, Karen [mailto:kbidus@NEMOURS.ORG]
Sent: Monday, July 18, 2011 9:05 AM
To: Bidus, Karen ; Myriam Peralta, M.D.
Cc: Stong, Karen
Subject: Hot Topics brochure/ NICHD Support Trial/LAST CALL
Importance: High

Dr. Peralta -

As you can see from the attached brochure, we are ready to go to press with the Hot Topics brochure, with the exception of your information - can you please get back to me no later than end of day Wednesday, July 20 with your name and credentials as you would like them listed in the brochure, as well as the name of your talk if you would like something different - Your talk is scheduled at 3 p.m. on Tuesday- the closing talk of the symposium.

If you are not able to get back to me by the end of the day Wednesday, we will need to print the brochure as is . . .

Thanks very much.

Karen Bidus
Director, Office of CME
Alfred I. duPont Hospital for Children
302-651-6752

Nemours has received Accreditation with Commendation from the ACCME.

Please consider the environment before printing this e-mail.

From: Bidus, Karen
Sent: Tuesday, July 05, 2011 2:52 PM
To: 'mperalta@peds.uab.edu'
Cc: Stong, Karen
Subject: FW: NICHD Support Trial
Importance: High

Dr. Peralta -

I've just received word that you will be presenting at *Hot Topics* - I will follow up with official speaker paperwork shortly, but unfortunately we are up against a printing deadline for the brochure. Can you please provide me with your name and credentials as you would like them to appear in the brochure - and the title of your talk - we currently have NICHD Support Trial 02 Follow-Up.

Thanks very much - please don't hesitate to contact me with any questions.

Karen Bidus
Director, Office of CME
Alfred I. duPont Hospital for Children
302-651-6752
Nemours has received Accreditation with Commendation from the ACCME.
Please consider the environment before printing this e-mail.
NOTICE...This electronic transmission is intended only for the person(s) named. It may contain information that is (i) proprietary to the sender, and/or (ii) privileged, confidential and/or otherwise exempt from disclosure under applicable State and Federal law, including, but not limited to, privacy standards imposed pursuant to the federal Health Insurance Portability and Accountability Act of 1996 (HIPAA). Receipt by anyone other than the named recipient(s) is not a waiver of any applicable privilege. If you received this confidential communication in error, please notify the sender immediately by reply e-mail message and permanently delete the original message from your system.

-----Original Message-----
From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Tuesday, July 05, 2011 2:16 PM
To: 'Gail M. Murphy'; 'jerold.lucey@yahoo.com'
Cc: Bidus, Karen
Subject: RE: NICHD Support Trial

HI

Dr. Myriam Peralta from the University of Alabama will be the first author for the SUPPORT oximetry follow up outcome paper.

Here contact information is:
Myriam Peralta-Carcelen, M.D.
mperalta@peds.uab.edu
General Pediatrics
CPPI 410
1600 7th Ave. So.
Birmingham AL 35233
(205)934-4531

She should be the network investigator to present the results. Dr. Hintz is the PI for the neuroimaging and outcome secondary study for the SUPPORT trial.

Thanks
Rose

Rosemary D. Higgins, MD
Program Scientist for the Eunice Kennedy Shriver NICHD Neonatal Research Network Pregnancy and Perinatology Branch CDBPM, NIH 6100 Executive Blvd., Room 4B03 MSC 7510 Bethesda, MD 20892 For overnight delivery use Rockville, MD 20852
301-435-7909
301-496-5575
301-496-3790 (FAX)
higginsr@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Blaisdell, Carol (NIH/NHLBI) [E]
Subject: RE: Rich, Antenatal Consent for SUPPORT and GDB, 2011-06-08 swa
Date: Monday, July 18, 2011 2:55:00 PM

We have a proposal that has been approved to look at CPAP use before, during and after the SUPPORT Trial as well as the usual other items of mortality and outcome, so this is in the works!! We need about 1 more year of data collection.

Thanks
Rose

Rosemary D. Higgins, MD
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From: Blaisdell, Carol (NIH/NHLBI) [E]
Sent: Monday, July 18, 2011 2:35 PM
To: Higgins, Rosemary (NIH/NICHD) [E]
Subject: RE: Rich, Antenatal Consent for SUPPORT and GDB, 2011-06-08 swa

Thanks Rose,
This is an important issue and raises the question of how the SUPPPORT strategies in the DR might be generalized to a higher risk premature group of infants—what is your sense from the SUPPORT trial PIs? Are there changes in practice that some plan to implement or are they suggesting more evidence is needed?
It will be interesting to see at those sites where practice changes are implemented based on the interpretation of findings from SUPPORT how outcomes are effected in "all-comers".

Carol

Carol J. Blaisdell M.D.
Medical Officer
Lung Development and Pediatrics
Lung Biology and Diseases Branch
Division of Lung Diseases
NHLBI, NIH
301-435-0222

From: Higgins, Rosemary (NIH/NICHD) [E]
Sent: Monday, July 18, 2011 1:53 PM
To: Blaisdell, Carol (NIH/NHLBI) [E]
Subject: Rich, Antenatal Consent for SUPPORT and GDB, 2011-06-08 swa

Carol
Here is a penultimate copy of a paper from the SUPPORT Trial (comparing to our generic database).
Let me know if you have any suggestions – it has gone through NICHD clearance.
Thanks for all your help and support.
Rose

From: Higgins, Rosemary (NIH/NICHD) [E]
To: Blaisdell, Carol (NIH/NHLBI) [E]
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Attachments: Rich, Antenatal Consent for SUPPORT and GDB, 2011-06-08 swa.docx

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Antenatal Consent for SUPPORT – Is the enrolled population representative of all eligible ELBW Infants?

Wade Rich, BSHS RRT[1]; Marie G. Gantz, PhD[2]; Neil N. Finer, MD[1]; Nancy S. Newman, RN[3]; Angelita M. Hensman, RN BSN[4]; Ellen C. Hale, RN BS CCRC[5]; Kathy J. Auten, MSHS[6]; Kurt Schibler, MD[7]; Roger G. Faix, MD[8]; Abbot R. Laptook, MD[4]; Bradley A. Yoder, MD[8]; Abhik Das, PhD[9]; Seetha Shankaran, MD[10]; and the SUPPORT and Generic Database Subcommittees of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network

Short title: Antenatal Consent in a Large Multicenter Trial

Correspondence and reprint requests to:

Wade Rich
402 Dickinson St
MPF Building Suite 1-140
San Diego Ca 92103-8774
email - wrich@ucsd.edu
Phone 619 543 3759
Fax 619 543 3812

Keywords: Clinical Research/Trials, Informed Consent, Antenatal Steroids, Neonatal

The authors have no financial disclosures or conflicts of interest.

[1] University of California at San Diego, San Diego, CA
[2] Statistics and Epidemiology Unit, RTI International, Research Triangle Park, NC
[3] Department of Pediatrics, Rainbow Babies & Children's Hospital, Case Western Reserve University, Cleveland, OH
[4] Department of Pediatrics, Women & Infants Hospital, Brown University, Providence, RI
[5] Emory University School of Medicine, Department of Pediatrics, and Children's Healthcare of Atlanta, Atlanta, GA
[6] Department of Pediatrics, Duke University, Durham, NC
[7] Department of Pediatrics, Cincinnati Children's Hospital Medical Center and University of Cincinnati, Cincinnati, OH
[8] Department of Pediatrics, Division of Neonatology, University of Utah School of Medicine, Salt Lake City, UT
[9] Statistics and Epidemiology Unit, RTI International, Rockville, MD
[10] Department of Pediatrics, Wayne State University, Detroit, MI

Acknowledgements

The National Institutes of Health, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), and the National Heart, Lung, and Blood Institute (NHLBI) provided grant support for the Neonatal Research Network's SUPPORT Trial.

Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Drs. Abhik Das (DCC Principal Investigator) and Marie Gantz (DCC Statistician) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study. The following investigators, in addition to those listed as authors, participated in this study:

NRN Steering Committee Chairs: Alan H. Jobe, MD PhD, University of Cincinnati (2003-2006); Michael S. Caplan, MD, University of Chicago, Pritzker School of Medicine (2006-2011).

Alpert Medical School of Brown University and Women & Infants Hospital of Rhode Island (U10 HD27904) - William Oh, MD; Dan Gingras, RRT; Susan Barnett, RRT; Sarah Lillie, RRT; Kim Francis, RN; Dawn Andrews, RN; Kristen Angela, RN.

Case Western Reserve University, Rainbow Babies & Children's Hospital (U10 HD21364, M01 RR80) - Michele C. Walsh, MD MS; Avroy A. Fanaroff, MD; Bonnie S. Siner, RN.

Cincinnati Children's Hospital Medical Center, University Hospital, and Good Samaritan Hospital (U10 HD27853, M01 RR8084) - Vivek Narendran, MD MRCP; Kate Bridges, MD; Barbara Alexander, RN; Cathy Grisby, BSN CCRC; Marcia Worley Mersmann, RN CCRC; Holly L. Mincey, RN BSN; Jody Hessling, RN.

Duke University School of Medicine, University Hospital, Alamance Regional Medical Center, and Durham Regional Hospital (U10 HD40492, M01 RR30) - C. Michael Cotten, MD MHS; Ronald N. Goldberg, MD; Kimberly A. Fisher, PhD, FNP-BC, IBCLC; Katherine A. Foy, RN; Gloria Siaw, BSN CRA.

Emory University, Children's Healthcare of Atlanta, Grady Memorial Hospital, and Emory Crawford Long Hospital (U10 HD27851, UL1 RR25008, M01 RR39) - Barbara J. Stoll, MD; Susie Buchter, MD; Anthony Piazza, MD; David P. Carlton, MD.

Eunice Kennedy Shriver National Institute of Child Health and Human Development - Rosemary D. Higgins, MD; Stephanie Wilson Archer, MA.

Indiana University, University Hospital, Methodist Hospital, Riley Hospital for Children, and Wishard Health Services (U10 HD27856, M01 RR750) - Brenda B. Poindexter, MD MS; James A. Lemons, MD; Faithe Hamer, BS; Dianne E. Herron, RN; Lucy C. Miller, RN BSN CCRC; Leslie D. Wilson, BSN CCRC.

National Heart, Lung, and Blood Institute - Mary Anne Berberich, PhD; Carol J. Blaisdell, MD; Dorothy B. Gail, PhD; James P. Kiley, PhD.

RTI International (U10 HD36790) - W. Kenneth Poole, PhD; Margaret Cunningham, BS; Betty K. Hastings; Amanda R. Irene, BS; Jeanette O'Donnell Auman, BS; Carolyn Petrie Huitema, MS; James W. Pickett II, BS; Dennis Wallace, PhD; Kristin M. Zaterka-Baxter, RN BSN.

Stanford University, Lucile Packard Children's Hospital (U10 HD27880, UL1 RR25744, M01 RR70) - Krisa P. Van Meurs, MD; David K. Stevenson, MD; M. Bethany Ball, BS CCRC, Melinda S. Proud, RCP.

Tufts Medical Center, Floating Hospital for Children (U10 HD53119, M01 RR54) - Ivan D. Frantz III, MD; John M. Fiascone, MD; Anne Furey, MPH; Brenda L. MacKinnon, RNC; Ellen Nylen, RN BSN.

University of Alabama at Birmingham Health System and Children's Hospital of Alabama (U10 HD34216, M01 RR32) - Waldemar A. Carlo, MD; Namasivayam Ambalavanan, MD; Monica V. Collins, RN BSN MaEd; Shirley S. Cosby, RN BSN. Vivien A. Phillips, RN BSN.

University of California - San Diego Medical Center and Sharp Mary Birch Hospital for Women (U10 HD40461) - Maynard R. Rasmussen, MD; Paul R. Wozniak, MD; Kathy Arnell, RNC; Renee Bridge, RN; Clarence Demetrio, RN.

University of Iowa Children's Hospital (U10 HD53109, UL1 RR24979, M01 RR59) - Edward F. Bell, MD; John A. Widness, MD; Jonathan M. Klein, MD; Karen J. Johnson, RN BSN.

University of Miami Holtz Children's Hospital (U10 HD21397, M01 RR16587) - Shahnaz Duara, MD; Ruth Everett-Thomas, RN MSN.

University of New Mexico Health Sciences Center (U10 HD53089, M01 RR997) - Kristi L. Watterberg, MD; Robin K. Ohls, MD; Julie Rohr, MSN RNC CNS; Conra Backstrom Lacy, RN.

University of Rochester Medical Center, Golisano Children's Hospital (U10 HD40521, M01 RR44) - Nirupama Laroia, MD; Dale L. Phelps, MD; Linda J. Reubens, RN CCRC; Erica Burnell, RN.

University of Texas Southwestern Medical Center at Dallas, Parkland Health & Hospital System, and Children's Medical Center Dallas (U10 HD40689, M01 RR633) - Pablo J. Sánchez, MD; Charles R. Rosenfeld, MD; Walid A. Salhab, MD; James Allen, RRT; Alicia Guzman; Gaynelle Hensley, RN; Melissa H. Lepps, RN; Melissa Martin, RN; Nancy A. Miller, RN; Araceli Solis, RRT; Diana M Vasil, RNC-NIC; Kerry Wilder, RN.

University of Texas Health Science Center at Houston Medical School and Children's Memorial Hermann Hospital (U10 HD21373) - Kathleen A. Kennedy, MD MPH; Jon E. Tyson, MD MPH; Brenda H. Morris, MD; Beverly Foley Harris, RN BSN; Anna E. Lis, RN BSN; Sarah Martin, RN BSN; Georgia E. McDavid, RN; Patti L. Tate, RCP; Sharon L. Wright, MT (ASCP).

University of Utah Medical Center, Intermountain Medical Center, LDS Hospital, and Primary Children's Medical Center (U10 HD53124, M01 RR64) - Jill Burnett, RN; Jennifer J. Jensen, RN BSN; Karen A. Osborne, RN BSN CCRC; Cynthia Spencer, RNC; Kimberlee Weaver-Lewis, RN BSN.

Wake Forest University, Baptist Medical Center, Brenner Children's Hospital, and Forsyth Medical Center (U10 HD40498, M01 RR7122) - T. Michael O'Shea, MD MPH; Nancy J. Peters, RN CCRP.

Wayne State University, Hutzel Women's Hospital, and Children's Hospital of Michigan (U10 HD21385) - Beena G. Sood, MD MS; Rebecca Bara, RN BSN; Elizabeth Billian, RN MBA; Mary Johnson, RN BSN.

Yale University, Yale-New Haven Children's Hospital, and Bridgeport Hospital (U10 HD27871, UL1 RR24139, M01 RR125, M01 RR6022) - Vineet Bhandari, MD DM; Richard A. Ehrenkranz, MD; Harris C. Jacobs, MD; Pat Cervone, RN; Patricia Gettner, RN; Monica Konstantino, RN BSN; JoAnn Poulsen, RN; Janet Taft, RN BSN.

Abstract

Background

The initial results of the SUPPORT antenatal consent study demonstrated that mothers of enrolled infants enrolled into the SUPPORT trial requiring antenatal parental consent were more educated, more likely to receive prenatal medical care, and were more likely to have received antenatal steroids (ANS), partial or full course compared to mothers of eligible but not enrolled infants.

Objective

The objective of this analysis was to compare the outcomes of death, severe intraventricular hemorrhage or periventricular leukomalacia (IVH/PVL) and death/severe IVH/PVL for infants enrolled in SUPPORT compared with eligible non-enrolled infants born at Neonatal Research Network centers during the period of SUPPORT trial recruitment (March 2005 through February 2009).

Methods:

Perinatal characteristics and neonatal outcomes were compared for enrolled and non-enrolled infants in bivariate analyses using t tests and chi-square tests. Logistic regression models were created to test the effect of enrollment in SUPPORT on outcomes, controlling for baseline perinatal characteristics.

Results

1316 infants were enrolled in SUPPORT, and 3053 infants were eligible but not enrolled during the same period. In bivariate analyses, SUPPORT infants were significantly older, heavier, and more likely to be of Non-Hispanic white origin ($p<.01$). A full course of antenatal steroids was provided to 71.7% of enrollees, and 49.4% of eligible infants not enrolled ($p<.001$). The frequency of 1 and 5 minute APGARs <3 was significantly greater in the non-enrolled group

($p<.001$). Delivery room interventions, including intubation, compressions and epinephrine were significantly more frequent in the non-enrolled group ($p<.001$). The frequency of death in the first 12 hours was significantly higher in the non-enrolled group (4.1% vs. 2.0%, $p<.001$). In unadjusted analyses, infants enrolled in SUPPORT had significantly lower rates of death before discharge, severe IVH/PVL and death/severe IVH/PVL when compared to infants eligible but not enrolled ($p<.001$). In logistic regression models, enrollment in SUPPORT was not a significant predictor of the outcomes after controlling for GA, birth weight, sex, race, center, and ANS.

Conclusions

The results demonstrate important outcome differences among enrolled and non-enrolled infants in a neonatal trial employing antenatal consent. In future trials requiring antenatal consent, there may be a need to balance such important factors as receipt of ANS and prenatal care in selecting the approached families. Pursuit of a waiver of parental consent for minimal-risk trials of interventions in the delivery room or shortly after birth should be considered to promote generalizability of results.

Introduction

The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants (SUPPORT) was a randomized, 2X2 factorial designed multi-center trial conducted by the *Eunice Kennedy Shriver* NICHD Neonatal Research Network (NRN) (Clinical Trials Gov. Number, NCT 00233324). [1,2] The trial prospectively compared Continuous Positive Airway Pressure and a protocol driven limited ventilatory strategy begun in the delivery room and continuing in the Neonatal Intensive Care Unit with the early (< 1 hour) intratracheal administration of surfactant followed by conventional mechanical ventilation. Infants were also randomized to a prospective comparison of a lower oxygen saturation target range (85% to 89%) with a higher, more conventional target range (91% to 95%) until the infant was no longer requiring ventilatory support or oxygen, using purpose altered oximeters. Eligible infants were those born at NRN centers at 24 0/7 to 27 6/7 weeks gestational age (GA), without known major congenital malformations, and with full resuscitation intended. Antenatal consent was required for enrollment. Early screening and enrollment in SUPPORT suggested that antenatal screening and consent were labor intensive and that the number of patients enrolled seemed to be much lower than the number screened.

A prospective cohort study of the antenatal consenting practices of SUPPORT research personnel was conducted during the last half of the trial and the results published.[3] As part of the ongoing NRN Generic Database (GDB) observational study, data were collected routinely for inborn infants at NRN centers, including most of those who met the GA eligibility criteria for SUPPORT. These data were used to identify eligible, non-enrolled infants. In this previous analysis comparisons were made between enrolled vs non-enrolled eligible infants as well as between infants whose mothers were approached vs. not approached. Comparing all GDB infants who were eligible for SUPPORT but whose mothers were not approached to those whose

mothers were approached and consented revealed that mothers in the latter group were significantly more likely to be older, to have a high school degree, private medical insurance, and at least one prenatal care (PNC) visit. Infants of these mothers were more likely to be non-Hispanic white. Failure to be treated with antenatal steroids (ANS) was over 4 times more prevalent among infants who were eligible but not enrolled in SUPPORT compared to those enrolled.

In view of these results, we felt that it was essential to determine if the outcomes of infants enrolled in SUPPORT differed in substantial ways from infants enrolled in the GDB during the same period who were SUPPORT eligible but were not enrolled.

We postulated that the infants enrolled in SUPPORT would have lower mortality, a decreased incidence of death or IVH or PVL compared with infants of the same gestational ages who were entered into the NRN GDB during the period of SUPPORT recruitment (March 2005 through February 2009) but not enrolled in the trial.

Methods

This analysis compared infants enrolled in SUPPORT to those infants born at NRN centers who were eligible but not enrolled. Perinatal characteristics, delivery room interventions, and neonatal outcomes were compared for enrolled and non-enrolled infants in bivariate analyses using t-tests and chi-square tests.

Logistic regression models were created to test the effect of enrollment in SUPPORT on outcomes, controlling for perinatal characteristics.

Results

Infants in the non-enrolled group were significantly more likely to have an APGAR score of less than 3 at both 1 and 5 minutes, and delivery room interventions, including intubation, compressions and epinephrine were significantly more frequent in the non-enrolled group.

(Table 2) In unadjusted analysis of outcomes, infants enrolled in SUPPORT had significantly lower rates of death before discharge, severe intraventricular hemorrhage or periventricular leukomalacia (IVH/PVL), and death/severe IVH/PVL when compared to infants eligible but not enrolled. (Table 3)

In order to test the hypothesis that enrollment in SUPPORT itself played a role in the outcome differences seen, we tested the effect of enrollment on outcomes in logistic regression models which were corrected for birth weight, GA, sex, race, center, and ANS (any and full course). In these adjusted models, enrollment in SUPPORT was not a significant predictor of the outcomes.

Discussion

When providing the enrollment tables for their trials, authors generally start with an enumeration of eligible subjects, and then describe how many refused, had missing data, etc. This group of eligible subjects is better described as "identified eligible subjects," in other words, those whom the investigator identified as eligible at the time they would normally be approached for consent. What are missing from this group are those subjects who were missed by the investigators due to time of day, rapidity of admission, duration of stay, etc. Due to the nature of the GDB database of the Neonatal Research Network, which identifies and tracks all infants fitting broad gestational age criteria, we were able to look not just at the enrolled subjects, but also those who were not enrolled or in some cases were not even identified as eligible by the research team. This allowed us to make a unique comparison of all infants who were born in NRN centers who met the SUPPORT study criteria, both those who were enrolled and those who were not.

Our findings suggest that using antenatal consent to carry out a trial such as SUPPORT under the constraints of pre-intervention informed consent creates a situation where population bias is a

significant issue. Title 45 of the Code of Federal Regulations allows institutional review boards to waive some or all elements of consent.[4] Our previous observations, combined with the further analysis of this trial, suggest that allowing for the deferral of consent until after birth for trials comparing routinely used interventions can help to insure that we include the sickest and most at-risk populations, and thus contribute to a more generalizable study population

What remains unclear is how to deal with trials of greater than minimal risk that require antenatal consent. Current standards for waiver of consent would be the same as those used for 'emergency' trials, such as the use of a blood substitute in a pre-hospital environment. These requirements include high risk balanced with a life-threatening situation, a direct benefit, public disclosure, and the existence of an independent data safety board. Most near-birth trials would not meet the standard of a life-threatening situation, and neonatal trials with pre-specified direct benefit are also extremely uncommon.

We suggest that a middle ground, which includes most of the requirements of the Final Rule regarding waiver of consent, but eliminates the need for a life-threatening situation or a direct benefit, may be a reasonable compromise under certain circumstances to seek a waiver and a postnatal written consent to utilize the infant's information. This stipulation allows parents to decide if they want their infant's information included in the study if they disagree with their infant's participation. Such a stipulation should be considered when submitting such protocols to the Human Subjects Committee.

Conclusion

The results of this analysis demonstrate important outcome differences between enrolled and non-enrolled infants in the eligible population of a trial employing antenatal consent. In future trials requiring antenatal consent, there may be a need to balance such important factors as receipt of ANS and prenatal care in selecting the approached families. Pursuit of a waiver of

parental consent for minimal-risk trials of interventions in the delivery room or shortly after birth should be considered to promote generalizability of results.

Table 1.

Variable	Enrolled (N=1316)	Non-Enrolled (N=3053)	P-value
GA (weeks) (mean ± standard deviation)	26.2 +/- 1.1	26.0 +/- 1.2	<0.001
Birth weight (grams) (mean ± standard deviation)	830.1 +/- 193.2	812.5 +/- 191.8	0.006
Male	54.1%	52.6%	0.373
White, non-Hispanic	39.6%	36.1%	0.030
Prenatal Antibiotics	78.1%	65.4%	<0.001
Antenatal steroids (any)	96.2%	84.4%	<0.001
Antenatal steroids (full course)	71.7%	49.4	<0.001

Table 2.

Variable	Enrolled (N=1316)	Non-Enrolled (N=3053)	P-value
Apgar < 3 at 1 minute	24.4%	31.9%	<0.001
Apgar < 3 at 5 minutes	4.4%	8.4%	<0.001
PPV in the DR	65.7%		

CPAP in the DR	81.1%		
Intubated in DR	63.6%	75.8%	<0.001
Surfactant in DR or NICU	82.5%	86.5%	<0.001
Chest compressions in DR	5.9%	9.7%	<0.001
Epinephrine in DR	3.1%	6.0%	<0.001

Table 3.

Outcome	SUPPORT Enrolled (N=1316)	Non-Enrolled (N=3053)	p-value	Adjusted p-value
Death	18.0%	24.1%	<0.001	0.164
Intraventricular Hemorrhage (IVH) grade 3-4	13.0	17.6	<0.001	0.343
Periventricular Leukomalacia (PVL)	3.8%	5.1%	0.068	0.417
IVH 3-4 or PVL	15.1%	19.8%	<0.001	0.336
Death or IVH 3-4 or PVL	27.4%	35.6%	<0.001	0.103

Legends

Table 1 - **Demographic information for randomized versus non enrolled infants**

Table 2 - **Delivery room status and interventions**

Table 3 – **Neonatal outcomes. Adjusted values corrected for birth weight, GA, sex, race, center, and ANS.**

[1] SUPPORT Study Group of the *Eunice Kennedy Schriver* NICHD Neonatal Research Network, Finer, N. N. ; Carlo, W. A.; Walsh, M. C.; Rich, W.; Gantz, M. G.; Laptook, A. Ret al. Early CPAP versus Surfactant in Extremely Preterm Infants. N Engl J Meds. 2010; 362(21):1970-1979.

[2] SUPPORT Study Group of the *Eunice Kennedy Shriver* NICHD Neonatal Research Network, Carlo WA, Finer NN, Walsh MC, Rich W, Gantz MG, Laptook AR, et al. Target ranges of oxygen saturation in extremely preterm infants. N Engl J Med. 2010; 362(21):1959-69.

[3] Rich W, Auten K, Gantz M, Hale E, Hensman A and for the National Institute of Child Health and Human Development Neonatal Research Network. Antenatal Consent in the SUPPORT Trial: Challenges, Costs, and Representative Enrollment. Pediatrics 2010;126;e215-e221

[4] US Department of Health and Human Services. General requirements for informed consent, 45 CFR §46.116d

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Gantz, Marie"
Subject: FW: URGENT SUPPORT QUERIES
Date: Monday, July 18, 2011 1:47:00 PM

Rosemary D. Higgins, MD
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higginsr@mail.nih.gov

From: Rich, Wade [mailto:wrich@ucsd.edu]
Sent: Monday, July 18, 2011 1:00 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Auman, Jeanette O. (joa@rti.org)
Subject: FW: URGENT SUPPORT QUERIES

These were transmitted (I hope !) at 09:53.
Wade

(b)(6)

From: Furey, Anne M
To: Higgins, Rosemary (NIH/NICHD) [E]; Frantz, Ivan; McGowan, Elisabeth C
Cc: Auman, Jeanette O.; Gantz, Marie
Subject: RE: URGENT SUPPORT QUERIES
Date: Monday, July 18, 2011 10:00:53 AM

Rose, we are looking into these quenes.

Anne

Anne Furey, MPH
Division of Newborn Medicine
Floating Hospital for Children at Tufts Medical Center
800 Washington Street, Box 44
Boston, MA 02111
Phone: 617-636-7134
Fax: 617-636-1456
Pager: 617-(b)(6)
afurey@tuftsmedicalcenter.org

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]
Sent: Mon 7/18/2011 9:27 AM
To: Frantz, Ivan; Furey, Anne M; McGowan, Elisabeth C
Cc: Auman, Jeanette O.; 'Gantz, Marie'
Subject: URGENT SUPPORT QUERIES

HI

Attached are hearing queries for infants from the SUPPORT trial – please verify that the information for each patient listed is correct. Please get back to us by Friday July 22.

Thanks for all the effort!!
Rose

CENTER	NETWORK	FCENTER	FOLNUM	infant	QUERY
(b)(6)					

Rosemary D. Higgins, MD
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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Bell, Edward (Pediatrics)"; "Colaizy, Tarah T"; "karen-johnson@uiowa.edu"; "Eastman, Diane"
Cc: "Auman, Jeanette O."; "Gantz, Hana"
Subject: URGETN SUPPORT QUERIES
Date: Monday, July 18, 2011 9:25:00 AM

Hi

Attached are hearing queries for infants from the SUPPORT trial – please verify that the information for each patient listed is correct. Please get back to us by Friday July 22.

Thanks for all the effort!!

Rose

CENTER	NETWORK	ECENTER	FOLNUM	infant	QUERY
(b)(6)					

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higginsr@mail.nih.gov

From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Bich, Vinda"; "Finer, Neil"; "mphillips@ucsd.edu"; "cwrunner@ucsd.edu"
Cc: "Auman, Jeanetta O."; "Glantz, Mirna"
Subject: URGENT SUPPORT QUERIES
Date: Monday, July 18, 2011 9:25:00 AM

Hi
Attached are hearing queries for infants from the SUPPORT trial – please verify that the information for each patient listed is correct. Please get back to us by Friday July 22.

Thanks for all the effort!!
Rose

CENTER NETWORK ECENTER ECLNUM infant QUERY
(b)(6)

Rosemary D. Higgins, MD
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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "goldb008@mc.duke.edu"; "goldb005@mc.duke.edu"; "kimberley.fisher@duke.edu"; "kim.lutz@duke.edu"; "[illegible]@duke.edu"; "Michael Cotten (cotten1@duke.edu)"
Cc: "Ganz, Marie"; "Auman, Jeanette O."
Subject: URGENT SUPPORT QUERIES
Date: Monday, July 18, 2011 9:24:00 AM

Hi
Attached are hearing queries for infants from the SUPPORT trial – please verify that the information for each patient listed is correct. Please get back to us by Friday July 22.

Thanks for all the effort!!
Rose

CENTER	NETWORK	FCENTER	FOLNUM	infant	QUERY
(b)(6)					

Rosemary D. Higgins, MD
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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Wally Carlo, M.D."; "HDurrmeta@peds.uab.edu"; "srosky@peds.uab.edu"; "Vivien Phillips"; "monica collins"
Cc: "Ginter, Marie"; "Auman, Jeanette O."
Subject: URGENT SUPPORT QUERIES
Date: Monday, July 18, 2011 9:23:00 AM

Hi

Attached are hearing queries for infants from the SUPPORT trial – please verify that the information for each patient listed is correct. Please get back to us by Friday July 22.

Thanks for all the effort!!
Rose

CENTER	NETWORK	FCENTER	FOLNUM	infant	QUERY
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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "alantoon@WIHRI.org"; "M.D.Betty Vohr"; "Deanne Wilson"; "M. D. Betty Vohr (E-mail)"; "Hintermeyer, Angela"; "Wrage, Lucy"
Cc: "Geiger, Diane"; "Auman, Jeanette C."
Subject: URGENT SUPPORT QUERIES
Date: Monday, July 18, 2011 9:22:00 AM

Hi
Attached are hearing queries for infants from the SUPPORT trial – please verify that the information for each patient listed is correct. Please get back to us by Friday July 22.

Thanks for all the effort!!
Rose

CENTER	NETWORK	FCENTER	FOLNUM	infant	QUERY
(b)(6)					

Rosemary D. Higgins, MD
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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Brenda Poindexter (bpoindex@iupui.edu)"; "John@iupui.edu"; "Heron, Dianne E"
Cc: "Ayman, Jeanette C."; "Gantz, Marie"
Subject: URGENT SUPPORT QUERIES
Date: Monday, July 18, 2011 9:20:00 AM

Hi

Attached are hearing queries for infants from the SUPPORT trial – please verify that the information for each patient listed is correct. Please get back to us by Friday July 22.

Thanks for all the effort!!

Rose

CENTER	NETWORK	FCENTER	FOLNUM	infant	QUERY
(b)(6)					

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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "kurt.schibler@cchmc.org"; "Kimberly Yolton"; "Gratton, Cathy (gratton)"; "Teresa.Gratton@uc.edu"
Cc: "Glantz, Marie"; "Auman, Jeanette O."
Subject: URGENT SUPPORT HEARING QUERIES
Date: Monday, July 18, 2011 9:19:00 AM

Hi
Attached are hearing queries for infants from the SUPPORT trial – please verify that the information for each patient listed is correct. Please get back to us by Friday July 22.

Thanks for all the effort!!
Rose

CENTER	NETWORK	FCENTER	FOLNUM	infant	QUERY
(b)(6)					

Rosemary O. Higgins, MD
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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Barbara Stoll"; "Ira Adams-Chapman"; "ellen.hale@ped.emory.edu"
Cc: "Auman, Jeanette O."; "Glantz, Marie"
Subject: URGENT SUPPORT HEARING QUERIES
Date: Monday, July 18, 2011 9:18:00 AM

Hi

Attached are hearing queries for infants from the SUPPORT trial – please verify that the information for each patient listed is correct. Please get back to us by Friday July 22.

Thanks for all the effort!!

Rose

CENTER	NETWORK	FCENTER	FOLNUM	Infant	QUERY
(b)(6)					

Rosemary D. Higgins, MD
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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Roy Heyne"; "Pablo Sanchez"; "Janette Torres@utsouthwestern.edu"; "Deana.Vasi@utsouthwestern.edu"; "Jyun.chen@utsouthwestern.edu"
Cc: "Gantz, Marie"; "Auman, Jeanette O."
Subject: URGETN SUPPORT HEARING QUERIES
Date: Monday, July 18, 2011 9:16:00 AM

Hi
Attached are hearing queries for infants from the SUPPORT trial – please verify that the information for each patient listed is correct. Please get back to us by Friday July 22.

Thanks for all the effort!!
Rose

CENTER	NETWORK	FCENTER	FOLNUM	infant	QUERY
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From: Higgins, Rosemary (NIH/NICHD) [E]
To: "Gantz, Marie"; "Das, Abhik"
Cc: "Zaterka-Baxter, Kristin"; "Auman, Jeanette O."
Subject: RE: Possible SUPPORT hearing queries
Date: Monday, July 18, 2011 9:12:00 AM

I think we need to make sure the data are correct – odd that none of the have L hearing loss.

I will send to the sites

Rose

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higginsr@mail.nih.gov

From: Gantz, Marie [mailto:mgantz@rti.org]
Sent: Friday, July 15, 2011 5:11 PM
To: Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik
Cc: Zaterka-Baxter, Kristin; Auman, Jeanette O.
Subject: Possible SUPPORT hearing queries

Attached is a spreadsheet containing hearing data queries that can be sent out if the SUPPORT group deems it necessary.

Marie

Marie Gantz, Ph.D.
Research Statistician
RTI International
mgantz@rti.org
[illegible]