

**From:** [Cunningham, Meg](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Zaterka-Baxter, Kristin](#)  
**Cc:** [Archer, Stephanie \(NIH/NICHD\) \[E\]](#); [Das, Abhik](#)  
**Subject:** RE: SUPPORT and Wade Rich's antenatal consent proposal  
**Date:** Monday, August 23, 2010 5:00:57 PM  
**Attachments:** [Rich, Antenatal Consent for SUPPORT, 2010-07-02 evaluation.docx](#)

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It was not reviewed on the formal SUPPORT call we had. Just looks like GDB reviewed.

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**From:** Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]  
**Sent:** Monday, August 23, 2010 4:52 PM  
**To:** Zaterka-Baxter, Kristin; Cunningham, Meg  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: SUPPORT and Wade Rich's antenatal consent proposal

Perhaps it was not formally reviewed. I know we talk about it on a call awhile back as a planned idea.

Rose

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**From:** Zaterka-Baxter, Kristin [<mailto:kzaterka@rti.org>]  
**Sent:** Monday, August 23, 2010 4:51 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: SUPPORT and Wade Rich's antenatal consent proposal

Looking – Abhik asked the same. I have the original email that asks Robin to set up a call – still looking for more.

Thanks,

KRIs

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**From:** Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]  
**Sent:** Monday, August 23, 2010 4:50 PM  
**To:** Cunningham, Meg; Zaterka-Baxter, Kristin  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** SUPPORT and Wade Rich's antenatal consent proposal

Do you have any record of the SUPPORT subcommittee reviewing this?

I can't seem to find it.

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 20592

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[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)



**PAS Abstract Evaluation**

**Title:** Antenatal Consent for SUPPORT – Is the enrolled population at lesser risk than the excluded population of ELBW Infants?

**Authors:** Wade Rich, Neil Finer (UCSD)

**Datasets:** SUPPORT  
GDB

**Overall evaluation**

X	Accept
	Accept with revisions
	May revise and resubmit (no guaranteed acceptance)
	Reject

**Priority Score = NA**  
(Scores from 1 - 5, with 5 being the highest priority)

**SUPPORT Subcommittee:**

Comments:

**GDB Subcommittee:**

*All GDB Subcommittee members should be listed as coauthors:*

Barbara J. Stoll, MD; Edward F. Bell, MD; Seetha Shankaran, MD; Abbot R. Laptook, MD;  
Michele C. Walsh, MD MS; Abhik Das, PhD; Rosemary D. Higgins, MD; Ellen C. Hale, RN  
BS CCRC; Nancy S. Newman, BA RN

Comments:

- Would help to have flow diagram to see how the population was determined

**ACCEPT**

**From:** Das, Abhik  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Poole, W. Kenneth  
**Subject:** RE: Bilirubin trial and Support: Picking the contrast  
**Date:** Monday, August 23, 2010 4:44:17 PM

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Rose:

I don't think he is talking about the power analyses per se. I think he wants to know more about how the comparator groups were decided upon for Phototherapy and SUPPORT (sat arm).

Thanks

Abhik

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**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Monday, August 23, 2010 4:40 PM  
**To:** Kirpalani, Haresh  
**Cc:** edward-bell@uiowa.edu; john-widness@uiowa.edu; Robin Whyte; Das, Abhik; Poole, W. Kenneth  
**Subject:** RE: Bilirubin trial and Support: Picking the contrast

I defer to Abhik or Ken Poole with respect to the power analyses for the prior studies and have copied them

Rose

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**From:** Kirpalani, Haresh [mailto:KIRPALANIH@email.chop.edu]  
**Sent:** Monday, August 23, 2010 4:37 PM  
**To:** Kirpalani, Haresh; Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** edward-bell@uiowa.edu; john-widness@uiowa.edu; Robin Whyte  
**Subject:** RE: Bilirubin trial and Support: Picking the contrast

Sorry: Speller in the note itself : "contract" should read "contrast".

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**From:** Kirpalani, Haresh  
**Sent:** Monday, August 23, 2010 3:55 PM  
**To:** 'Higgins, Rosemary (NIH/NICHD) [E]'  
**Cc:** 'edward-bell@uiowa.edu'; 'john-widness@uiowa.edu'; 'Robin Whyte'  
**Subject:** Bilirubin trial and Support: Picking the contrast

Dear Rose:

I – like all of us – have been reading thru' the various comments of the sites on TABI, and I am wondering how to best rationalize our responses.

It is not clear to me how these two trial actually picked the numbers to act as a contract. Of course the conceptual issues are exactly the same as in TABI. Do you have any thoughts about that?

In the meantime I with Ed and Jack, & I will get Robin Whyte's input too – are writing a brief response to the comments, which will act as a template for the requisite protocol changes.

Best, Haresh

**From:** Bell, Edward  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Boghossian, Nansi Samir; Hansen, Nellie I.  
**Subject:** RE: Trisomy 13 and 18 comments  
**Date:** Thursday, June 17, 2010 3:00:52 PM  
**Attachments:** Trisomy Proposal 061710.doc

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Thanks, Rose. I know you suggested eliminating "attitude" in favor of "practice" previously, and I thought we had made that change. I've fixed it in the attached draft. In the previous analysis of GDB birth defects for 1998-2005 that Nellie and Barbara did, there were 79 babies with T18 (surprising more than the T21s, which were only 73) and 28 with T13. We propose to include 1994-2009, which is twice as many years, so we should see roughly twice as many babies. I'll copy Nellie in case she has looked more recently at the numbers with T18 and T13. I agree we will have incomplete ascertainment and will have to acknowledge that. I don't know if we can get a handle on the magnitude of under-ascertainment - probably not.

Ed

-----Original Message-----

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
Sent: Thursday, June 17, 2010 12:40 PM  
To: Bell, Edward  
Subject: Trisomy 13 and 18 comments

Ed,

I looked over the draft and have the following comments/suggestions:

We need to know a rough "n" - if i use the rate of 1/5500 births and assume we have 100,000 deliveries peryear in the nrn over 16 years, i get 290 infants. This may be an "over projection" as we have only had 16 sites for 10 of the years. Even half or a third of this number would be more than any other study. We may want to have RTI look in advance of committing to a large analysis.

Specific Aim 6 - i would not use the word "attitude" as we do not collect the thought process of the care providers. I suggest using "practice" instead.

I have a concern that some of these infants may have not been recorded in GDB if the diagnosis was antenatally known and subsequent comfort care was provided only in L+D.

Feel free to forward.

Rose

## **Survival and Morbidity Outcomes of Very Low Birth Weight**

### **Infants with Trisomy 18 and Trisomy 13**

#### **A Proposal for the NICHD Neonatal Research Network**

Nansi S. Boghossian, Nellie I. Hansen, Edward F. Bell, Barbara J. Stoll, Jeffrey C. Murray,

John C. Carey, Ira Adams-Chapman, Seetha Shankaran, Michele C. Walsh,

Abbot R. Laptook, Roger G. Faix, Abhik Das, Rosemary D. Higgins

## **Survival and Morbidity Outcomes of Very Low Birth Weight Infants with Trisomy 18 and Trisomy 13**

### **A. Abstract**

The extensive number of very low birth weight (VLBW) infants accumulated in the Generic Database over the past 2 decades provides the NICHD Neonatal Research Network with unprecedented opportunities for examining rare populations such as VLBW infants with trisomy 18 (T18) and trisomy 13 (T13). The co-occurrence of VLBW and these chromosomal abnormalities presents new ethical dilemmas of whether to withhold resuscitation and other interventions among this group of infants. We propose to examine delivery room interventions, other birth defects, mortality rate (before first hospital discharge), and rates of infection, bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH) or periventricular leukomalacia (PVL), and retinopathy of prematurity (ROP) among VLBW infants with T13 and T18 born between 1994 and 2009.

### **B. Statement of the problem**

Little is known about delivery room interventions, resuscitation efforts, survival, and neonatal morbidities among VLBW infants with T13 and T18. Knowledge of the risks faced by these unfortunate infants will provide additional guidance to parents and caregivers who are faced with decisions about limiting treatment.

### **C. Hypotheses**

1. A shift in intervention and resuscitation efforts among VLBW infants with T13 and T18 has been observed over the years.
2. Examination rates for morbidities such as ROP examinations have improved over the years among VLBW T13 and T18 infants.
3. Survival rates for VLBW T13 and T18 infants have remained consistently low over the years.

### **D. Specific Aims**

1. Examine the mortality rate and age of death in VLBW T13 and T18 infants. Compare these with each other, VLBW T21 infants and VLBW infants without chromosomal abnormality.
2. Examine trends in mortality from 1994 through 2009 among VLBW T13 and T18 infants taking into consideration the change in participating centers in the NICHD.
3. Examine prevalence of T13 and T18 among VLBW infants at birth and stratify by race, ethnicity and NICU level.
4. Examine characteristics of VLBW T13 and T18 infants including maternal age, cesarean delivery, multiple births, birth weight, gestational age, small for gestational age, sex, race/ethnicity and Apgar scores at 1 and 5 minutes.
5. Examine the number of VLBW T13 and T18 infants receiving intensive care in the form of mechanical ventilation. Compare these with each other, VLBW T21 infants and VLBW infants without chromosomal abnormality.
6. Examine if a shift in the practice of care providers exists across the years in providing interventions as c-section deliveries and resuscitation.
7. Examine co-occurring birth defects among VLBW infants with T13 and T18.

8. Among VLBW T13 and T18 survivors, examine the distribution of neonatal morbidities including respiratory distress syndrome, infections, BPD, NEC, IVH or PVL.
9. Identify any surgeries among VLBW T13 and T18 infants.
10. Examine early growth of VLBW T13 and T18 infants by examining weight, length, and head circumference at 36 weeks PMA.

#### **E. Rationale**

Infants with T13 and T18 have been the subject of several ethical dilemmas. Withdrawal of intensive treatment and surgical procedures has been recommended because of the short survival span and the severe physical and mental deficiency among survivors. Recent studies, however, have reported a potential benefit of intensive care management through improved survival. The majority of these studies are based predominantly on full term infants. Management of VLBW T13 and T18 infants with regard to interventions and intensive care management has not been explored. Survival rates and morbidities affecting VLBW T13 and T18 infants represent other gaps in our knowledge. Such data are essential to help clinicians and parents know how long these infants can survive with aggressive support.

#### **F. Background**

Trisomy 18 (T18; Edward syndrome) and trisomy 13 (T13; Patau syndrome) represent the second and third most common chromosomal abnormalities in live born infants, after trisomy 21 (Morris et al, 2008). The combined frequency of both syndromes is estimated to be around 1 in 5500 live births equivalent to approximately 725 annual births in the United States (Carey, 2009 letter). Both abnormalities are characterized by multiple congenital anomalies and an extremely short life span. Median survival time using data from a population based study was 7 days for infants with T13 and 14.5 days for infants with T18. One-year survival has been reported to be 5.6% for T13 and T18 individuals (Rasmussen et al, 2003). Survival to the second decade or longer has been reported for patients with non-mosaic T13 or T18 (Petek et al, 2003). The lives of such patients, however, are marked by severe neurologic and physical handicap (Baty et al, 1994; Baty et al, 1996).

Management of neonates with these chromosomal anomalies has traditionally been limited to comfort care and minor procedures. Several papers have been published suggesting that these infants be considered as patients with a "hopeless outlook" (Bos et al, 1992) and recommending withholding or withdrawal of intensive treatment (reviewed in Kosho, 2006). Interventions such as cesarean delivery are not recommended and surgical procedures as cardiac surgery are also considered unjustified. Historically, there was a general agreement that such conditions are futile and resuscitation was not indicated. Recent American Academy of Pediatrics neonatal resuscitation guidelines, however, excluded T18 from the list of examples of conditions for which withholding resuscitation is considered reasonable but included T13 (American Heart Association, American Academy of Pediatrics, 2005). A shift in attitude toward more aggressive support of infants with T18 has also been reported in a recent paper by McGraw et al. Of the surveyed neonatologists, 44% indicated that they would initiate delivery room resuscitation in a term T18 infant with a congenital heart defect (McGraw et al, 2009).

Heretofore, published studies have addressed survival and interventions among term T18 and T13 infants. The combination of both T18 or T13 and very low birth weight presents greater challenges. The short life span of T18 and T13 infants and the morbidities occurring among VLBW infants in early infancy including retinopathy of prematurity, bronchopulmonary dysplasia, intraventricular hemorrhage, necrotizing enterocolitis, and infection demand a different philosophical framework than is used for term infants with T18 and T13. Interventions and resuscitation efforts in this group of VLBW infants have not been described before. Data on survival, morbidities and risks involved in interventions are essential to

help families and care providers with decisions involving the care of their VLBW infants with T18 or T13. To examine this, an extensive accumulation of T13 and T18 cases is required. The NICHD Neonatal Research Network Generic Database (GDB) provides an excellent opportunity to examine these outcome data among VLBW T18 and T13 infants.

#### **G. Methods**

1. Study design: This will be a descriptive analysis of existing data from the NICHD Neonatal Research Network Generic Database (GDB).
2. Study population: Our study population will consist of T18 and T13 VLBW infants entered into the NRN VLBW registry. We will use data from all birth years for which the diagnosis of T13 and T18 can be determined reliably –1994-2009. For comparison, we will use data for VLBW infants with Trisomy 21 and VLBW infants without chromosomal abnormality.
3. Study intervention: This is not an interventional study.
4. Primary and secondary outcomes: Not applicable.
5. Sample size estimate: Not applicable.
6. Available population: All T18 and T13 infants enrolled in the Generic Database with available information on syndromes and malformations and outcomes will be used for the analysis.
7. Estimated recruitment time: Not applicable.

#### **H. Data Analysis**

The following data from the Generic Database will be used: hospital of birth, date of birth, mode of delivery, sex, ethnicity and race, gestational age, birthweight, 1 and 5 minute Apgar scores, syndromes and major congenital malformations, delivery room resuscitation, days on supplementary oxygen, infection episodes, PDA, BPD, proven NEC, IVH or PVL, ROP including highest stage, lowest zone, presence or absence of plus disease, threshold ROP and intervention therapies, major surgeries, size (weight, length, and head circumference) at 36 weeks PMA, status, and if dead, age at death, and cause of death.

The following will be examined among VLBW T13 and T18 infants and among the comparison groups, VLBW infants with Trisomy 21 and VLBW infants without chromosomal abnormality:

- BPD, NEC, IVH or PVL, ROP and infection rates
- Weight, length, and head circumference at 36 weeks PMA.
- Trends in prevalence of T13 and T18 among VLBW infants from 1994 through 2009.
- Trends in mortality before hospital discharge from 1994 through 2009.

The probability of survival to hospital discharge will be examined using the Kaplan-Meier method. Survival among T13 and T18 infants will be examined overall. Survival will be further studied stratified by birth period, gender, race, and presence of heart defects if the sample sizes allow. Further analyses will address survival among infants receiving surgical intervention versus those without. Univariate analyses using log-rank test will first be conducted to examine possible prognostic factors for survival among T13 and T18 VLBW infants. Subsequently, Cox-proportional hazards models will be used to assess factors associated with longer survival.



## I. Risks and Benefits

No risks or benefits will accrue to individual infants as a result of this analysis.

## J. Budget estimate

The only expense will be the analysis time and effort provided by RTI staff.

## K. References

- American Heart Association & American Academy of Pediatrics. (2006). 2005 American heart association (AHA) guidelines for cardiopulmonary resuscitation (CPR) and emergency cardiovascular care (ECC) of pediatric and neonatal patients: Neonatal resuscitation guidelines. *Pediatrics*, 117(5), e1029-38.
- Baty, B. J., Blackburn, B. L., & Carey, J. C. (1994). Natural history of trisomy 18 and trisomy 13: I. growth, physical assessment, medical histories, survival, and recurrence risk. *American Journal of Medical Genetics*, 49(2), 175-188.
- Baty, B. J., Jorde, L. B., Blackburn, B. L., & Carey, J. C. (1994). Natural history of trisomy 18 and trisomy 13: II. Psychomotor development. *American Journal of Medical Genetics*, 49(2), 189-194.
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- Carey, J. C. (2009). Attitudes of neonatologists toward delivery room management of confirmed trisomy 18: Potential factors influencing a changing dynamic. *Pediatrics*, 123(3), e547-8; author reply e549.
- Kosho, T., Nakamura, T., Kawame, H., Baba, A., Tamura, M., & Fukushima, Y. (2006). Neonatal management of trisomy 18: Clinical details of 24 patients receiving intensive treatment. *American Journal of Medical Genetics. Part A*, 140(9), 937-944.
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- Morris, J. K., & Savva, G. M. (2008). The risk of fetal loss following a prenatal diagnosis of trisomy 13 or trisomy 18. *American Journal of Medical Genetics. Part A*, 146(7), 827-832.
- Petek, E., Pertl, B., Tschernigg, M., Bauer, M., Mayr, J., Wagner, K., et al. (2003). Characterization of a 19-year-old "long-term survivor" with Edwards syndrome. *Genetic Counseling (Geneva, Switzerland)*, 14(2), 239-244.
- Rasmussen, S. A., Wong, L. Y., Yang, Q., May, K. M., & Friedman, J. M. (2003). Population-based analyses of mortality in trisomy 13 and trisomy 18. *Pediatrics*, 111(4 Pt 1), 777-784.

**From:** Zaterka-Baxter, Kristin  
**To:** Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Alexis Davis  
**Subject:** RE: PLEASE READ: Premie aEEG Enrollment COMPLETE  
**Date:** Wednesday, June 16, 2010 12:53:45 PM

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I think historically we've just stopped and those consented (but not yet enrolled) are just told the study met criteria for enrollment/completion (at least for Support that is what we did):

February 27, 2009

**SUPPORT TECHNICAL MEMO # 16;**

**TO: Network Coordinators**

**Network PIs**

**FROM: The Data Coordinating Center**

**SUBJECT: SUPPORT Study Enrollment Complete**

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As of February 27, 2009, enrollment to the Support Trial has been completed. The study accrual goal of 1310 infants has been met per data processed in the DMS. Parents who have been consented and have not delivered may be informed that the study has met accrual goals and enrollment to the study is completed. Infants who are currently enrolled will continue to be followed per protocol and study manual.

All outstanding Support and GDB data forms and edits should be completed and transmitted to the Data Center as soon as possible. A final DSMC meeting to review 100% enrollment will be scheduled when all infants have met study status.

Thanks to everyone for a job well done!

Cc Rosemary Higgins, MD

Thanks,  
Kris

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**From:** Das, Abhik  
**Sent:** Wednesday, June 16, 2010 12:49 PM  
**To:** Zaterka-Baxter, Kristin; 'Higgins, Rosemary (NIH/NICHD) [E]'  
**Subject:** RE: PLEASE READ: Premie aEEG Enrollment COMPLETE

I think we can stop, unless we have policy/precedent that we usually allow consents to be enrolled.

Thanks

Abhik

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**From:** Zaterka-Baxter, Kristin  
**Sent:** Wednesday, June 16, 2010 12:41 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik

**Subject:** PLEASE READ: Premie aEEG Enrollment COMPLETE  
**Importance:** High

Can I send out a notice that enrollment is complete and that all those previously consented (prior to right now) can be enrolled or should we not allow any further enrollment?

Thanks,

Kris

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**From:** Auman, Jeanette O.  
**Sent:** Tuesday, June 15, 2010 10:23 PM  
**To:** 'Alexis Davis'  
**Cc:** Zaterka-Baxter, Kristin; Auman, Jeanette O.  
**Subject:** RE: FW: PaEEG monthly report

Looks like we've got the 100 patients!

*Jenny*

**From:** [Cole, Conrad R](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Barbara Stoll](#); [Conrad Cole](#)  
**Cc:** [Hansen, Nellie I.](#)  
**Subject:** RE: SBS paper-- ready to be reviewed by the subcommittee  
**Date:** Monday, June 14, 2010 9:26:20 AM  
**Attachments:** [BSI in VLBW infants with surgical SBSforreview.doc](#)

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Rose,

Please find attached the version for review by the subcommittee for clearance.

Thanks

Conrad

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**From:** Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]  
**Sent:** Monday, June 14, 2010 9:24 AM  
**To:** Cole, Conrad R; Barbara Stoll; Conrad Cole  
**Subject:** RE: SBS paper-- ready to be reviewed by the subcommittee

Let me know if this version should be sent.

Rose

Rosemary D. Higgins, MD

Program Scientist for the Neonatal Research Network

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**From:** Barbara Stoll [<mailto:Barbara.Stoll@oz.ped.emory.edu>]  
**Sent:** Sunday, June 13, 2010 10:39 PM  
**To:** Conrad Cole; Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** SBS paper-- ready to be reviewed by the subcommittee

Conrad

Great job-- ready to go to the subcommittee for review  
I generally send off without listing authors for now-- so that you can change author placement/order later and won't have hurt feelings-- Conrad Cole for the GDB Subcommittee

A few editorial comments attached

To save words-- you write our 2 or more -- could use >2 symbol

ALSO-- Table with pathogens-- you have about a dozen called "unspecified pathogens" Did we call the sites to actually verify that there was no identification. Were these considered real infections or contaminants? Do we know

Regards

BJS

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  
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**Blood stream infections in very low birth weight infants with surgical short bowel syndrome**

**Short title:** Infections in infants with short bowel syndrome

**Authors**

Conrad R. Cole MD<sup>1</sup>, Nellie I. Hansen MPH<sup>2</sup>, for the GDB subcommittee of the NICHD Neonatal Research Network (NRN)

**Affiliations**

**Corresponding Author:**

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**Financial disclosure:** The Neonatal Research Network's Generic Database and Follow-up Studies (2002-2005) were supported by grants from the National Institutes of Health and the Eunice Kennedy Shriver National Institute of Child Health and Human Development.

**Key words:** Short bowel syndrome, Blood stream infections, Late onset sepsis, Very low birth weight, Nutrition

**Abbreviations:** NICHD – Eunice Kennedy Shriver National Institute of Child Health and Human Development; SBS - Short bowel syndrome; VLBW – Very low birth weight; ELBW – Extremely low birth weight; NEC – Necrotizing enterocolitis; LOS – Late onset sepsis; GA - Gestational age; PDA – Patent ductus arteriosus; IVH – Intraventricular hemorrhage;

## **Abstract**

**Background:** Short bowel syndrome (SBS) is a devastating syndrome most commonly resulting from necrotizing enterocolitis (NEC) in premature infants.

**Objective:** To evaluate the effect of recurrent late-onset blood stream infections (BSI) on duration of parenteral nutrition (PN), time to achieve full feeds and length of hospitalization in infants with SBS.

**Methods:** Data were collected from infants 401-1500 grams at birth who survived >72 hours and received care at NICHD Neonatal Research Network centers. Frequency of culture positive BSI and pathogens were compared for infants with medical NEC, NEC managed surgically without SBS, and surgical SBS. Among SBS infants, number of infections and impact on outcome were evaluated.

**Results:** 942 infants were studied (SBS, n=88; surgical NEC without SBS, n=452; medical NEC, n=402). The proportion of infants with infections after diagnosis was higher for infants with SBS than with surgical NEC ( $p=0.005$ ) or medical NEC ( $p<0.001$ ). Gram positive pathogens were most frequently identified. The proportion with gram negative infections was similar among those with SBS (26%) and surgical NEC (29%), but higher than in infants with medical NEC (19%). For infants with SBS, length of hospitalization ( $p=0.01$ ) and duration on PN ( $p=0.004$ ) increased with number of infections (0, 1,  $\geq 2$  infections; median length of stay: 172, 188, 310; median days on PN: 94, 109, 115), while the proportion who achieved full feeds during the hospitalization decreased (86%, 68%, 44%,  $p=0.01$ ).

**Conclusion:** Recurrent BSIs are common in infants with SBS and associated with duration of PN. Prevention and appropriate management of BSI in infants with SBS could improve outcome and reduce associated long term complications.

## **Introduction**

Bloodstream infections (BSI) are associated with increased morbidity and mortality in infants with short bowel syndrome (SBS) [1]. Very low birth weight (VLBW) infants (defined as birth weight  $\leq 1500$ g) are at increased risk for surgical SBS because of their greater risk of developing necrotizing enterocolitis (NEC) and other predisposing surgical conditions [2, 3]. The incidence of surgical SBS among VLBW infants enrolled in the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Neonatal Research Network (NRN) registry was 0.7% (7/1,000) [2]. Sepsis and complications of NEC were the most commonly reported causes of death among these infants. Among infants born 401-1000 g who completed a comprehensive NRN follow-up visit at 18-22 months corrected age, those with SBS were more likely to have been re-hospitalized, and their number of hospitalizations was also significantly higher compared to infants with medical NEC and surgical NEC without SBS. Recurrent hospitalization has been identified as a significant contributor to the high direct cost associated with the management of children with SBS [4]. Both late onset sepsis (LOS) and NEC are associated with an increased risk of adverse neurodevelopmental outcomes [5]. Furthermore, infants with SBS are more likely to have growth failure which has also been associated with poor neurodevelopmental outcomes. There are limited data on the infecting organisms associated with BSI in infants with SBS and it is not known whether BSI has an impact on the duration of parenteral nutrition (PN), length of hospitalizations and mortality. This study was undertaken to examine culture confirmed BSI and associated pathogens in infants with SBS compared to children with surgical NEC (NEC managed surgically that did not result in SBS) and medical NEC (NEC managed medically without surgery), and to evaluate the impact of infections on duration of PN, time to achieve full feeds, and length of hospitalization among infants with SBS.



## Methods

The NRN, a consortium of academic neonatal centers within the United States, maintains a data registry of VLBW infants [2]. Infants born between January 1, 2002 and June 30, 2005, who were enrolled in the registry and had surgical SBS, surgical NEC without SBS, or medical NEC were the focus of this analysis. Surviving infants with birth weights 401-1000 grams were also eligible for a comprehensive follow-up assessment at 18-22 months corrected age. The institutional review board (IRB) at each center approved participation in the registry and follow-up studies. Informed consent was obtained from parents or legal guardians for follow-up and at 1 center for participation in the registry.

The registry includes maternal and delivery information collected soon after birth and infant data collected from birth until death, hospital discharge, or up to 120 days [6]. Neonatal data collected includes infant birth weight (BW), gestational age (GA), sex, race, duration of parenteral nutrition (PN), whether or not enteral feeds were started, date of first enteral feed, whether full enteral feeds were achieved and date full enteral feeds achieved, as well as in-hospital morbidities including NEC, spontaneous intestinal/gastric perforation, SBS, early-onset sepsis (EOS) and LOS. Infants who are still in the hospital at 120 days are followed for final status (death, discharge, transfer) until one year of age.

Surgical SBS was recorded if an infant had gastrointestinal surgery with significant resection of bowel that resulted in prolonged PN dependence (> 6 weeks) due to malabsorption, severe diarrhea, gastric hypersecretion, secondary bacterial overgrowth, and failure to thrive [2, 7, 8]. NEC was defined as modified Bells stage IIA or greater [9]. Early- and late-onset BSI were defined by a blood culture positive for bacteria or fungi taken in the first 72 hours after birth (EOS) or after 72 hours (LOS) and treatment with antibiotics for  $\geq 5$  days. Infecting pathogen(s) and date for each positive culture treated for  $\geq 5$  days were recorded for both EOS and LOS.

Infants with positive cultures and intent to treat for 5 or more days who died before day 5 of therapy were also considered to have BSI.

Timing of BSI was determined for infants with SBS and/or NEC relative to a diagnosis/onset date. Date of NEC diagnosis or first spontaneous intestinal/gastric perforation (if applicable and date of NEC diagnosis unavailable) was used as the diagnosis date for all infants with medical NEC and surgical NEC without SBS, and for most infants with SBS. The NRN did not record the date of surgery that resulted in SBS. Therefore, for the purpose of determining timing of BSI, the date of NEC diagnosis or first spontaneous intestinal/gastric perforation was used as a surrogate for the SBS surgery/onset date. Four infants who did not have NEC or spontaneous intestinal/gastric perforation, developed SBS as the result of surgery for ileal atresia (2 infants) or volvulus (2 infants). BSI were classified as occurring prior to diagnosis (8 or more days before the diagnosis date), at the time of diagnosis ( $\pm$  7 days around the diagnosis date), or after diagnosis (8 or more days after the diagnosis date). Positive blood cultures taken 0-4 days apart were considered part of the same episode, either one episode with multiple pathogens (if  $>1$  organism was found on a single blood culture, or different organisms were found on repeat cultures) or one episode with a single pathogen (one culture with a single pathogen or repeat cultures 0-4 days with the same pathogen). In cases where a repeat culture positive for coagulase negative staphylococcus (CONS) was taken 0-4 days after a culture positive for a non-CONS organism, CONS was considered to be a contaminant and the infection was considered one episode with the single non-CONS pathogen. Positive blood cultures taken  $\geq$  5 days apart were considered indicative of different episodes.

Information collected at the 18-22 month follow-up assessment included primary caretaker, caretaker's education, household income, child's medical history, weight, length and head circumference. These growth parameters were each classified as below or above the 10<sup>th</sup>

percentile for sex and corrected age using standard Centers for Disease Control and Prevention growth charts [10].

### Statistical analysis

The incidence of BSI and infecting pathogens were compared between infants with SBS, surgical NEC, and medical NEC. Among infants with SBS, clinical, nutritional, and growth outcomes were compared between those with no infections after diagnosis, 1 infection and more than 1 infection. Additionally, these outcomes were compared by pathogen group for infants with SBS who had at least one BSI after the diagnosis. Each infant was classified into one pathogen group only with the groups defined as: CONS—single or multiple episodes involving CONS only; other gram positive—one or more episodes involving non-CONS gram positive organisms or one or more episodes involving both CONS and non-CONS gram positive organisms; gram negative—one or more episodes involving gram negative organisms only; fungal—one or more episodes involving fungal organisms only; combinations—more than one episode involving pathogens of different types (gram positive, gram negative, fungal) or polymicrobial infections involving pathogens of different types (1 blood culture with at least 2 organisms of different types).

Statistical significance for unadjusted comparisons between groups was determined by the Cochran-Mantel-Haenszel raw mean score chi-square test for ordinal outcomes, by Fisher's exact or chi-square tests for categorical variables and Kruskal-Wallis tests for continuous variables. Median length of hospital stay was estimated using Kaplan-Meier curves for time from birth to discharge, with deaths treated as censored observations and significance between groups determined by the log rank test.

## Results

As previously reported, 950 VLBW infants born between January 1, 2002 and June 30, 2005 and enrolled in the NRN registry at one of 16 participating study centers were diagnosed with SBS (n=89), surgical NEC without SBS (n=459), or medical NEC (n=402) [2]. After exclusions for missing data (6 infants with missing diagnosis date and 2 infants with missing LOS information), 942 infants were included in the analysis: SBS, n=88; surgical NEC without SBS, n=452; medical NEC, n=402. For 922 infants (98%) NEC diagnosis date was used to determine timing of BSI. Among the subset of infants with SBS, the NEC date was used as the diagnosis date for 75 infants (85%).

### Number of Infections: Infants with SBS and/or NEC

Among the 942 infants included in the analysis, 135 (14.3%) were diagnosed with NEC within 7 days of birth and were thus excluded from analysis of prior BSI. Among the 807 infants who could be compared, no differences were found in the number of BSIs prior to diagnosis for infants with SBS compared to infants with surgical NEC ( $p=0.5$ ) or infants with medical NEC ( $p=0.6$ ). In each group, most infants (~80%) had no proven infections prior to diagnosis and 20% had 1-3 infections. At the time of diagnosis, the proportion of infants with one or more infections did not differ significantly between infants with SBS and surgical NEC ( $p=0.06$ ), but was higher for infants with SBS compared to infants with medical NEC (43% vs. 20%,  $p<0.001$ ) (Table 1).

The mortality rate varied across the groups (SBS: 20%, surgical NEC: 53%, medical NEC: 19%) with death occurring earlier among infants with surgical NEC [2]. Among infants with NEC, 208 (22%) either died or were discharged home within 7 days of their NEC diagnosis and thus could not be compared on number of BSI after diagnosis (surgical NEC - 160 died, 2 discharged home; medical NEC - 43 died, 3 were discharged home). Among the 734 infants available for

comparison, the proportion with infections after diagnosis was higher among infants with SBS compared to infants with surgical NEC ( $p=0.005$ ) or medical NEC ( $p<0.001$ ) (Table 1). In the subset of 248 infants with at least one infection after diagnosis, a higher proportion of those with SBS had infections  $> 30$  days after diagnosis (68%) compared to infants with surgical NEC who had more infections occurring 8-30 days after diagnosis or in both periods or compared to infants with medical NEC (68% vs. 27%;  $p<0.001$ ). Due to concerns that some infants who died soon after diagnosis did not survive long enough to develop an infection, analyses were repeated among the subset who survived to discharge. Number and timing of infections within 7 days of diagnosis and after diagnosis were unchanged among the subgroup of survivors to discharge (data not shown).

Among the 626 infants with birth weight 401-1000 grams (Table 2), BSI results were similar to those in the complete cohort with no differences found in the number of infections prior to the diagnosis, more BSI identified after diagnosis for infants with SBS compared to surgical NEC, and more BSI at the time of and after diagnosis for infants with SBS compared to medical NEC. Additionally, a statistically significant difference was found between infants with SBS and surgical NEC on the number of infections at the time of diagnosis. Although trends were generally similar among infants with birth weight 1001-1500 grams (Table 2) there were no significant differences in the number of infections at the time of and after diagnosis between infants with SBS and infants with surgical NEC. However, a greater proportion of infants (1001-1500 grams birth weight) with SBS had infections after the diagnosis compared to infants with medical NEC ( $p<0.001$ ) and more of these infections tended to be  $> 30$  days after diagnosis.

#### Pathogens: Infants with SBS and/or NEC

Gram positive pathogens were most frequently identified around the time of and after diagnosis in all three groups, with CONS being the most frequently isolated pathogen (Table 3). The

proportion of infants with gram negative infections was similar among those with SBS (26%) and surgical NEC (29%), but higher in these groups than among infants with medical NEC (19%), ( $p=0.05$ ). *Klebsiella* was the most common gram negative pathogen identified (10% of infections among infants with SBS and surgical NEC, 3% of infections among infants with medical NEC). Fungal infections, primarily candida, were more frequent among infants with surgical (14%) and medical NEC (11%) than among infants with SBS (8%). More than half of the mixed infections in each group involved *E. coli* and/or *Klebsiella*.

*Outcomes by infection status and pathogen type after diagnosis: Infants with SBS*

Infants with SBS who had 2 or more infections were hospitalized longer than infants who had only 1 infection or were uninfected (median days: 310, 188, 172, respectively,  $p=0.01$ ) (Table 4). The duration of parenteral nutrition increased with the number of infections from median 94 days among those with no infection to 109 days among infants with 1 infection and 115 days among infants with 2 or more infections ( $p=0.004$ ). As a result, enteral feeds were initiated later among infants with 2 or more infections with the proportion of infants who achieved full feeds highest among infants with SBS and no infections after diagnosis (86%) compared to those with 1 (68%) and 2 or more infections (44%),  $p=0.01$ .

Among the 60 infants with SBS who weighed  $\leq 1000$  grams at birth, 13 (22%) died before discharge and 5 of the remaining 47 infants (11%) died after discharge. All 42 infants still alive at 18-22 months corrected age completed the follow-up visit (December 2003-April 2007).

Among this group of survivors, the proportion of infants with weight  $< 10^{\text{th}}$  percentile at 18-22 months corrected age increased across the groups (0 infections: 39%, 1 infection: 59%, 2+ infections: 71%) (Table 4). However, statistically significant differences on weight and other growth outcomes were not detected by number of infections in this small group of children

(weight < 10<sup>th</sup> percentile, p=0.3; length < 10<sup>th</sup> percentile, p=0.2; head circumference < 10<sup>th</sup> percentile, p=0.8).

The majority of children with SBS who had at least one infection >7 days after diagnosis (n=53) had CONS (15 infants had 1 episode involving CONS, 2 infants had 2 episodes, 2 infants had 3 episodes) or other gram positive pathogens (9 infants had 1 episode, 3 infants had 2 episodes, 1 had 3 episodes, 1 had 4 episodes) identified (Table 5). Among the 38 children who weighed <1000 grams at birth, 14 (37%) died before 18-22 months corrected age. No statistically significant differences on weight or other growth parameters at 18-22 months were detected across the pathogen groups among the small subset of 24 survivors.

## **Discussion**

Short bowel syndrome is associated with significant morbidity and mortality [2, 11]. The cost of managing children with SBS is very high, especially in the first year of life, because of the length of hospitalization and multiple readmissions associated with complications [4]. Single center studies have reported BSI as a very common complication of SBS [1, 12]. Although infections are relatively common, the distribution of the pathogens identified on blood culture of VLBW infants with SBS and whether BSI impacts the duration of PN, hospitalization, and growth have not been evaluated. This study reviewed the epidemiology of late-onset BSI in VLBW infants with SBS born between January 1, 2002 and June 30, 2005 who received cared at centers of the NRN. We evaluated the effect of recurrent late-onset BSI on the duration of PN, time to achieve full feeds and length of hospitalization.

Understanding the epidemiology of BSI in this population of infants is important because recurrent BSI has been identified as a contributor to poor outcomes in SBS infants [1]. In this study, the finding that a larger proportion of VLBW infants who subsequently developed SBS

had at least one BSI around the time of diagnosis of NEC compared to VLBW infants with medical NEC suggests that the occurrence of BSI around the time of diagnosis ( $\pm 7$  days) can be used as a marker for the severity of NEC and risk of adverse outcome. Neonates who are very ill with significant bowel necrosis and associated BSI may develop SBS after surgical resection. BSI is also more common after diagnosis in VLBW infants with SBS (60%) compared to VLBW infants with surgical NEC without SBS (42%) and medical NEC (21%), which supports the findings reported in a smaller single center study [13]. The incidence of new BSI was also significantly higher  $> 30$  days after the diagnosis of NEC in infants with SBS compared to infants in the other 2 groups. Findings were similar for infants 401- 1000 grams and those 1001-1500 grams birth weight (Table 2). Increased rates of infection among infants with SBS could be partially due to prolonged hospitalization and the continued presence of central lines needed for PN in infants with SBS. Increased intestinal permeability which develops in infants due to the lack of or inadequate enteral nutrition stimulation could also increase risk for BSI in SBS infants  $> 30$  days after diagnosis [14].

The pathogen distribution among infected infants in this study is similar to what has been reported in other studies among NICU patients [15-17]. Gram positive organisms were most frequently identified in all 3 patient groups, with CONS the single most frequently isolated pathogen [15-17]. The predominance of CONS in these patients may be due to skin colonization/contamination with prolonged hospital stay and prolonged use of intravascular devices. *Klebsiella* was the most frequently isolated Gram negative pathogen among infants with SBS and surgical NEC without SBS, while *E. coli* was the most frequent among patients with medical NEC. In some patients, infection with gram negative pathogens may have resulted from increased intestinal permeability [11, 12].



Infants with SBS who had 2 or more BSI were hospitalized longer, had a longer duration of PN, and later initiation of enteral feeds compared to those who remained uninfected or had only 1 infection reported. This finding could be due to the extent of the initial injury experienced by these infants or the need for prolonged PN. The dependence on PN for survival puts these infants at greater risk for recurrent BSI and prolonged hospitalization. Meticulous central line care, including compliance with infection control guidelines, would reduce BSI and could significantly decrease the duration of hospitalization in these children [18, 19]. Developing strategies that will decrease intestinal permeability and improve the immune status of infants with SBS could also lead to decreasing BSI incidence in those with chronic PN. The absence of statistically significant differences in growth outcomes (weight, length and head circumference) when examined by number of BSI or type of pathogen is likely due to the small numbers of children who could be evaluated in this cohort.

To our knowledge, the present study is the largest evaluation of BSI in a cohort of VLBW infants with SBS. Recurrent BSIs were common in our cohort of infants with SBS and gram positive organisms, especially CONS, were the most common infecting pathogens. The strengths of this study include the large sample size, the participation of multiple geographically and ethnically diverse clinical centers, and the ability to compare SBS infants with other infants of similar GA and BW who were diagnosed with NEC treated medically or surgically without the development of SBS. Although the number of infants in each pathogen group was too small to allow us to evaluate the impact of pathogen type on outcome, the overall sample size was sufficient to evaluate the impact of recurrent infections on the duration of hospitalization and ability to tolerate enteral feeds and be weaned off PN. Interventional trials are needed to evaluate the effect of specific therapeutic interventions aimed at reducing BSI in infants with SBS. Interventions are also needed to reduce time needed to achieve full enteral feeds and thus

decrease duration of PN, with the ultimate aim of optimizing anthropometric growth and cognitive development.

**Table 1: Blood culture confirmed infections in VLBW children with SBS and/or NEC**

	<b>SBS</b>	<b>Surgical NEC without SBS</b>	<b>Medical NEC</b>
<b>At the time of diagnosis<sup>a</sup></b>			
Number of infants	88	452	402
Number of infections, n (%)			
0	50 (57)	301 (67)	322 (80)***
≥ 1	38 (44)	151 (33)	80 (20)
<b>After diagnosis<sup>b</sup></b>			
Number of infants <sup>c</sup>	88	290	356
Number of infections, n (%)			
0	35 (40)	168 (58)**	283 (79)***
1	37 (42)	81 (28)	55 (15)
≥ 2	16 (18)	41 (14)	18 (5)
Timing of infections after the diagnosis			
8-30 days	11 ( 21)	41 ( 34)*	44 ( 60)***
>30 days	36 ( 68)	56 ( 46)*	20 ( 27)*
Both (</> 30 days)	6 ( 11)	25 ( 20)	9 ( 12)

<sup>a</sup> At the time of diagnosis is defined as ± 7 days around the diagnosis date

<sup>b</sup> After the diagnosis is defined as >7 days after the diagnosis

<sup>c</sup> 208 infants reached final status within 7 days of diagnosis and were not included in the "after" period (surgical NEC: 160 died, 2 discharged to home; medical NEC: 43 died, 3 discharged to home).

\* p ≤ 0.05, \*\*p ≤ 0.01, \*\*\* p ≤ 0.001 versus SBS by the chi-square test.

**Table 2: Blood culture confirmed infections in VLBW infants by birth weight**

(a) 401-1000 grams (b) 1001-1500 grams

<b>(a) 401-1000 grams</b>	<b>SBS</b>	<b>Surgical NEC without SBS</b>	<b>Medical NEC</b>
<b>Prior to diagnosis</b>			
Number of infants <sup>1/</sup>	49	280	212
Number of infections, n (%)			
0	39 (80)	205 (73)	151 (71)
≥1	10 (20)	75 (27)	61 (28)
<b>At the time of diagnosis<sup>2/</sup></b>			
Number of infants	60	323	243
Number of infections, n (%)			
0	30 (50)	218 (67)**	191 (79)***
1	27 (45)	99 (31)	52 (21)
≥2	3 (5)	6 (2)	0 (0)
<b>After diagnosis</b>			
Number of infants <sup>3/</sup>	60	221	203
Number of infections, n (%)			
0	22 (37)	122 (55)*	154 (76)***
1	26 (43)	65 (29)	34 (17)
≥2	12 (20)	34 (16)	15 (7)
Timing of infections after the diagnosis			
8-30 days	10 (26)	34 (34)	28 (57)**
>30 days	23 (61)	44 (44)	13 (27)
Both (</> 30 days)	5 (13)	21 (21)	8 (16)
<b>(b) 1001-1500 grams</b>	<b>SBS</b>	<b>Surgical NEC without SBS</b>	<b>Medical NEC</b>
<b>Prior to diagnosis</b>			
Number of infants <sup>4/</sup>	21	99	146
Number of infections, n (%)			
0	18 (86)	91 (92)	134 (92)
≥1	3 (14)	8 (8)	12 (8)
<b>At the time of diagnosis<sup>2/</sup></b>			
Number of infants	28	129	159
Number of infections, n (%)			
0	20 (71)	83 (64)	131 (82)
1	7 (25)	43 (33)	28 (18)
≥2	1 (4)	3 (2)	0 (0)
<b>After diagnosis</b>			
Number of infants <sup>5/</sup>	28	69	153
Number of infections, n (%)			
0	13 (46)	46 (67)	129 (84)***
1	11 (39)	16 (23)	21 (14)
≥2	4 (15)	7 (10)	3 (2)

Timing of infections after the diagnosis, n (%)			
8-30 days	1 (7)	7 (30)	16 (67)**
>30 days	13 (87)	12 (52)	7 (29)
Both (</> 30 days)	1 (7)	4 (17)	1 (4)

<sup>1</sup>85 infants diagnosed within 7 days of birth had no "prior" period.

<sup>2</sup>At the time of diagnosis is defined as  $\pm$  7 days around the diagnosis date which for most infants was the date NEC was diagnosed. (See Methods for details.)

<sup>3</sup>142 infants reached final status within 7 days of diagnosis and were not included in the "after" period.

<sup>4</sup>50 infants diagnosed within 7 days of birth had no "prior" period.

<sup>5</sup>66 infants reached final status within 7 days of diagnosis and were not included in the "after" period.

\*  $p \leq 0.05$ , \*\*  $p \leq 0.01$ , \*\*\*  $p \leq 0.001$  versus SBS by the chi-square test

**Table 3: Distribution of pathogens at the time of and after diagnosis among VLBW children with SBS and/or NEC**

Pathogen, n (%) <sup>1/</sup>	SBS	Surgical NEC without SBS	Medical NEC
<b>Gram negative</b>	<b>31 (26.1)</b>	<b>94 (28.7)</b>	<b>32 (18.8)</b>
E. coli	8 (6.7)	25 (7.6)	9 (5.3)
Klebsiella	12 (10.1)	33 (10.1)	5 (2.9)
Citrobacter	1 (0.8)	4 (1.2)	2 (1.2)
Enterobacter	6 (5.0)	18 (5.5)	7 (4.1)
Pseudomonas aeruginosa	1 (0.8)	10 (3.0)	5 (2.9)
Other <sup>2/</sup>	3 (2.5)	4 (1.2)	4 (2.4)
<b>Gram positive</b>	<b>67 (56.3)</b>	<b>156 (47.6)</b>	<b>108 (63.5)</b>
Group B streptococcus	0	3 (0.9)	3 (1.8)
Viridans streptococcus	0	2 (0.6)	1 (0.6)
Other streptococci	14 (11.8)	30 (9.1)	9 (5.3)
CONS	43 (36.1)	100 (30.5)	74 (43.5)
S. aureus	4 (3.4)	15 (4.6)	14 (8.2)
Other <sup>3/</sup>	6 (5.0)	6 (1.8)	7 (4.1)
<b>Unspecified bacteria</b>	<b>3 (2.5)</b>	<b>9 (2.7)</b>	<b>3 (1.8)</b>
<b>Fungi</b>	<b>9 (7.6)</b>	<b>45 (13.7)</b>	<b>19 (11.2)</b>
Candida albicans	6 (5.0)	20 (6.1)	10 (5.9)
Candida parapsilosis	1 (0.8)	14 (4.3)	4 (2.4)
Candida sp.	1 (0.8)	7 (2.1)	2 (1.2) <sup>6/</sup>
Other <sup>4/</sup>	1 (0.8)	4 (1.2)	3 (1.8)
<b>Mixed infections (&gt;1 pathogen)<sup>5/</sup></b>	<b>9 (7.6)</b>	<b>24 (7.3)</b>	<b>8 (4.7)</b>
Number of infections	119 (100%)	328 (100%)	170 (100%)
Number of infants	69	231	136

<sup>1/</sup> Infections involving CONS and one other organism were classified under the other organism. All other infections involving > 1 organism (including infections with CONS and 2 other organisms) were classified as mixed infections. Four infants each with one episode of LOS and no information about infecting pathogens were excluded, as well as one episode each for two infants missing pathogen information.

<sup>2/</sup> **SBS:** serratia marcescens (2 infections) and acinetobacter (1 infection); **surgical NEC:** serratia marcescens (3 infections), acinetobacter (1); **medical NEC:** serratia marcescens (3), acinetobacter (1).

<sup>3/</sup> **SBS:** Staphylococcus species not further identified (6 infections); **surgical NEC:** Staphylococcus species not further identified (5), clostridia (1); **medical NEC:** Staphylococcus species not further identified (4), bacillus (2), clostridia (1).

<sup>4/</sup> **SBS:** Torulopsis glabrata (1 infection); **surgical NEC:** Torulopsis glabrata (2), saccharomyces (1), other fungi not further identified (1); **medical NEC:** malassezia fur fur (1), saccharomyces (1), aureobasidium (1).

<sup>5/</sup> **SBS:** E. coli + streptococcus (1 infection), E. coli + streptococcus + CONS (1 infection), E. coli + S. aureus (1), Enterobacter + Group D strep (1), Enterobacter + Candida albicans (1), Klebsiella + unspecified bacteria (1), serratia marcescens + Group D faecalis streptococcus (1), Klebsiella + proteus + unspecified bacteria (1), Candida albicans + unspecified bacteria (1); **surgical NEC:** E. coli + S. aureus (1), E. coli + Group D faecalis strep + CONS (1), E. coli + Group D faecalis strep (2), E. coli + Klebsiella (1), E. coli + enterobacter (2), E. coli + candida albicans (1), Klebsiella + strep pneumoniae (1), Klebsiella + citrobacter (1), Klebsiella + enterobacter (1), Klebsiella + proteus (1), Klebsiella + pseudomonas (2), Klebsiella + bacteroides (1), Klebsiella + enterobacter cloacae + strep (1), enterobacter + torulopsis glabrata (1), pseudomonas aeruginosa + enterobacter cloacae (1), serratia marcescens + strep viridans + CONS (1), serratia marcescens + Group D strep + unspecified bacteria (1), serratia marcescens + candida albicans (1), neisseria + strep viridans + bacillus (1), Group D strep + candida parapsilosis (1), strep + bacillus (1); **medical NEC:** E. coli + Klebsiella (1), E. coli + pseudomonas (1), E. coli + candida albicans + CONS (1), Klebsiella + strep (1), Klebsiella + strep + CONS (1), Klebsiella + malassezia fur fur (1), Enterobacter + strep (1), Group A strep + candida albicans (1).

<sup>6/</sup> Includes one infection involving both candida albicans and parapsilosis.

**Table 4:** Clinical, nutritional, and growth outcomes for children with SBS by infection status after diagnosis<sup>1/</sup>

	<b>No blood culture positive infections after diagnosis</b>	<b>1 infection</b>	<b>≥ 2 infections</b>
<b>Initial hospitalization</b>	<b>N=35</b>	<b>N=37</b>	<b>N=16</b>
<b>Hospital course</b>			
Days of hospitalization**			
Median (25 <sup>th</sup> -75 <sup>th</sup> percentile)	172 (135-216)	188 (149-234)	310 (221-365)
Died before discharge, n (%)	6 ( 17)	6 ( 16)	6 ( 38)
<b>Clinical, n (%)</b>			
PDA	23 ( 66)	16 ( 43)	11 ( 69)
RDS	16/34 ( 47)	21/36 ( 58)	10/16 ( 63)
BPD <sup>2/</sup>	24/33 ( 73)	24/37 ( 65)	12/15 ( 80)
ROP exam done	31 (89)	35 (95)	16 (100)
ROP	22/31 ( 71)	25/35 ( 71)	14/16 ( 88)
<b>Nutritional</b>			
Days of parenteral nutrition**			
Median (25 <sup>th</sup> -75 <sup>th</sup> percentile)	94 (51-108)	109 (91-116)	115 (108-117)
Enteral feeds started, n (%)	35 (100)	36 ( 97)	15 ( 94)
Age at first enteral feed (days)**			
Median (25 <sup>th</sup> -75 <sup>th</sup> percentile)	6 (3-12)	4 (2-7)	7 (3-47)
Full enteral feeds achieved, n (%)**	30 ( 86)	25 ( 68)	7 ( 44)
Age when full feeds achieved (days)			
Median (25 <sup>th</sup> -75 <sup>th</sup> percentile)	26 (18-48)	18 (14-39)	14 (13-20)
<b>Follow-up at 18-22 m</b>	<b>N=18</b>	<b>N=17</b>	<b>N=7</b>
<b>Growth</b>			
Weight <10 <sup>th</sup> percentile	7 ( 39)	10 ( 59)	5 ( 71)
Length <10 <sup>th</sup> percentile	10 ( 56)	8 ( 47)	6 ( 86)
Head circumference <10 <sup>th</sup> percentile	11 ( 61)	9 ( 53)	3 ( 43)

PDA=patent ductus arteriosus; RDS=respiratory distress syndrome; BPD=bronchopulmonary dysplasia; ROP=retinopathy of prematurity.

<sup>1/</sup>Diagnosis date for most infants was the date of NEC diagnosis (see Methods for details). The after period was defined as >7 days after the diagnosis date.

<sup>2/</sup> Three infants who died before 36 weeks post-menstrual age could not be evaluated for BPD.

\*\*p ≤ 0.01 for a difference between the groups by the log rank test (days of hospitalization), Kruskal-Wallis test (continuous variables) or Fisher's exact test (categorical variables).

**Table 5: Outcomes for children with SBS who had at least one infection after diagnosis by pathogen group<sup>1/</sup>**

	<b>CONS</b>	<b>Other Gram-positive</b>	<b>Gram-negative</b>	<b>Fungal</b>	<b>Combinations</b>
<b>Infant characteristics</b>	<b>N=19</b>	<b>N=14</b>	<b>N=9</b>	<b>N=3</b>	<b>N=8</b>
Birth weight (grams), n (%)					
501-1000	14 (74)	9 (64)	6 (67)	1 (33)	8 (100)
1001-1500	5 (26)	5 (36)	3 (33)	2 (67)	0
Gestational age (weeks), n (%)					
23-24	3 (16)	3 (21)	0	1 (33)	2 (25)
25-28	10 (53)	7 (50)	6 (67)	1 (33)	6 (75)
29-33	6 (32)	4 (29)	3 (33)	1 (33)	0
<b>Initial hospitalization</b>					
<b>Hospital course</b>					
Days of hospitalization					
Median (25 <sup>th</sup> -75 <sup>th</sup> percentile)	221 (165-302)	192 (165-241)	194 (142-245)	149 (147-184)	310 (184-365)
Died before discharge, n (%)	6 ( 32)	5 ( 36)	0 ( 0)	0 ( 0)	1 ( 13)
<b>Nutritional</b>					
Days of parenteral nutrition					
Median (25 <sup>th</sup> -75 <sup>th</sup> percentile)	114 (95-117)	115 (109-118)	113 (99-116)	89 (71-91)	114 (92-116)
Enteral feeds started, n (%)	18 ( 95)	14 (100)	9 (100)	3 (100)	7 ( 88)
Age at first enteral feed (days)					
Median (25 <sup>th</sup> -75 <sup>th</sup> percentile)	4 (2-8)	4 (2-12)	5 (2-5)	4 (2-11)	7 (4-22)
Full enteral feeds achieved, n (%)	10 ( 53)	8 ( 57)	8 ( 89)	2 ( 67)	4 ( 50)
Age when full feeds achieved (days)					
Median (25 <sup>th</sup> -75 <sup>th</sup> percentile)	18 (13-36)	21 (17-62)	14 (13-24)	50 (33-66)	17 (14-30)
<b>Follow-up at 18-22 m</b>	<b>N=7</b>	<b>N=5</b>	<b>N=5</b>	<b>N=1</b>	<b>N=6</b>
<b>Growth</b>					
Weight <10 <sup>th</sup> percentile	6 ( 86)	2 ( 40)	2 ( 40)	1 (100)	4 ( 67)
Length <10 <sup>th</sup> percentile	5 ( 71)	2 ( 40)	1 ( 20)	1 (100)	5 ( 83)
Head circumference <10 <sup>th</sup> percentile	5 ( 71)	2 ( 40)	2 ( 40)	0 ( 0)	3 ( 50)

<sup>1/</sup>Diagnosis date for most infants was the date of NEC diagnosis. The after period was defined as >7 days after the diagnosis date. Infants were classified into one pathogen group. (See Methods for details.)



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**From:** Hale, Ellen  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: SUPPORT Follow Up  
**Date:** Friday, June 11, 2010 2:23:24 PM

---

Rose,  
See comments below. Hope you are having a good summer.  
Ellen

Ellen Hale, RN, BS, CCRC  
Neonatal Research Network  
Emory University School of Medicine  
Department of Pediatrics - Division of Neonatology  
Office: 404-778-1679  
Fax: 404-778-1467

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]  
**Sent:** Friday, June 11, 2010 2:15 PM  
**To:** Hale, Ellen; Barbara Stoll; Adams-Chapman, Ira; Ellen Hale  
**Cc:** mgantz@rti.org  
**Subject:** SUPPORT Follow Up

Hi,

We have a few missing outcomes for SUPPORT Follow Up. Let us know how you are doing.

Thanks for all the hard work and effort!!!  
Rose

9 (b) FU window has closed but NF05 and NF09a have not been completed.  
Lost to follow-up (NF10 entered)

9 (b) FU window has closed but NF09a has not been completed.  
Child sick and unable to do or reschedule.

9 (b) FU marked as complete (per NF10/SF10) but NF05 has not been completed.  
Exam done and awaiting form to enter.

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 20592

301-435-7909

301-496-5575

301-496-3790 (FAX)

[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

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**From:** Michael Cotten  
**To:** Cunningham, Meg  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Robert W Lenfestey; Das, Abhik; Wally Carlo, M.D.; Ronald N Goldberg  
**Subject:** Re: SUPPORT Secondary Analysis Reviews  
**Date:** Friday, June 11, 2010 12:25:29 PM

---

Thanks. We appreciate the subcommittee's comments.

we will revise the protocol looking at ctr differences per Wally and Abhik's suggestions, using logistic regression models for each center that randomized > 60 infants (n = 11 centers) to assess control vs. intervention w/in center. The regression model would include the GA and familial clustering as covariables (as included in the main trials multivariable analysis).

The review did not comment on the learning Aim, to see if kids enrolled in the CPAP arm early in the trial were more likely to survive til 14 postnatal days, and have more of those 14 days spent off mechanical ventilation than kids enrolled later in the trial. Would you suggest we submit this as a separate query?

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: 919-681-6024  
fax: 919-681-6065  
email: cotte010@mc.duke.edu

"Cunningham, Meg" <mcunningham@rti.org>

06/11/2010 10:43 AM

To <cotte010@mc.duke.edu>

cc "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>,  
"Zaterka-Baxter, Kristin" <kzaterka@rti.org>

Subject SUPPORT Secondary Analysis Reviews

Hi Dr. Cotten,

Attached are the reviews for:

***Oxygen saturations and risk of mortality and morbidity in the SUPPORT trial.***  
***Center Effects within the SUPPORT Trial***

Can you please send these along to Drs. Smith and Lenfestey?

Thanks,  
Meg

*Meg Cunningham  
RTI International  
701 13th St. NW, Ste. 750  
Washington, DC 20005  
tel: 202-974-7837  
fax: 202-728-2095  
[www.rti.org](http://www.rti.org)[attachment "SUPPORT\_Secondary\_Cotten.docx" deleted by Michael  
Cotten/Pediatrics/mc/Duke]*

**From:** [Cunningham, Meg](#)  
**To:** [cotte010@mc.duke.edu](mailto:cotte010@mc.duke.edu)  
**Cc:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Zaterka-Baxter, Kristin](#)  
**Subject:** SUPPORT Secondary Analysis Reviews  
**Date:** Friday, June 11, 2010 10:43:09 AM  
**Attachments:** [SUPPORT\\_Secondary\\_Cotten.docx](#)

---

Hi Dr. Cotten,

Attached are the reviews for:

***Oxygen saturations and risk of mortality and morbidity in the SUPPORT trial.  
Center Effects within the SUPPORT Trial***

Can you please send these along to Drs. Smith and Lenfestey?

Thanks,

Meg

*Meg Cunningham  
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[www.rti.org](http://www.rti.org)*

***Smith/Cotten: Oxygen saturations and risk of mortality and morbidity in the SUPPORT trial.***

***Subcommittee Consensus: Rejected; there is too much overlap with primary study.***

***Lenfestey/Cotten: Center Effects within the SUPPORT Trial***

***Subcommittee Consensus: Rejected; the subcommittee does not want to encourage subset analysis design due to the concerns discussed unless there is some type of method to explain potential differences rather than just identify potential differences.***

Additional comments: This is a proposal regarding center affects (delivery room approach); the subcommittee felt the fundamental issue is that we did a multi center trial to account for these practices and the concern of identifying/disseminating information that may differ from the primary trial based on only subgroup analyses (similar to concerns about the MRI secondary previously voices) and that in a subset analysis, the randomization design does not apply.

Dr. Carlo suggested a revision independent of the baseline. Do a regression analysis of what the outcome is in the control group versus the intervention group by centers; this would explain whether effect is the same regardless of what the baseline is. We would need to only include centers who enrolled a minimum number of infants. Dr Das said we may find some practical differences that we did not capture in the initial analysis but that we do tend to over analyze center differences.



**From:** [Cunningham, Meg](#)  
**To:** [Luc.Brion@utsouthwestern.edu](mailto:Luc.Brion@utsouthwestern.edu); [Pablo.Sanchez@UTSouthwestern.edu](mailto:Pablo.Sanchez@UTSouthwestern.edu)  
**Cc:** [Zaterka-Baxter, Kristin](#); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Subject:** SUPPORT Secondary Analysis Review  
**Date:** Friday, June 11, 2010 10:39:24 AM  
**Attachments:** [SUPPORT\\_Secondary\\_Brion.docx](#)

---

Hi Drs. Sanchez and Brion,

Attached is the review of Dr. LeVan's **Changes in Therapy and Outcomes Associated with The SUPPORT Trial** protocol. I do not have an email address for Dr. LeVan, please forward her this message.

Thanks,  
Meg

*Meg Cunningham*  
*RTI International*  
*701 13th St. NW, Ste. 750*  
*Washington, DC 20005*  
*tel: 202-974-7837*  
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[www.rti.org](http://www.rti.org)

**LeVan: Changes in Therapy and Outcomes Associated with the SUPPORT Trial Subcommittee**

***Consensus: Postponed; the subcommittee is enthusiastic about the concept but felt it was about 3 years premature. They suggested the protocol remain in holding until more data becomes available (including the follow up outcomes) to better suit a phase IV/Quality Improvement cycle data analysis. The primary concern was lack of available follow up data and possible inability to answer the primary question of practice change at this point.***

Additional comments: Pre/Post GDB/Support review. Before samples size GDB 2002 – 2004; after size is GBD from May 1, 2010 thru April/May 2011 (1 yr observational). The rationale of the 2 year pre and 1 year post sampling is likely because of the time constraint to release analysis and it was felt the sample size would be adequate. In theory using as many post samples as possible in this time period compared to a larger pre sampling period is appropriate (the longer and bigger pre period the better the power may be). The committee continued to question whether the pre-sampling period of one year was a long enough sampling period. Other concerns were the lack of pulse oximetry tracking in the analysis plan; the proposal should have all of the Support interventions if the plan is to include all the Support outcomes in the secondary analyses.

When this moves forward all authors would be included (all authors who have contributed papers).

**From:** [Cunningham, Meg](mailto:Cunningham.Meg)  
**To:** [wcarlo@peds.uab.edu](mailto:wcarlo@peds.uab.edu)  
**Cc:** [Zaterka-Baxter, Kristin](#); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Archer, Stephanie \(NIH/NICHD\) \[E\]](#)  
**Subject:** SUPPORT Secondary Analysis Review  
**Date:** Friday, June 11, 2010 10:37:17 AM  
**Attachments:** [SUPPORT\\_Secndary\\_Carlo.docx](#)

---

Hi Wally,

Here are the minutes from the review of Retinopathy of prematurity and actual oxygen saturations:  
A secondary protocol of the SUPPORT Trial.

Thanks,  
Meg

*Meg Cunningham*  
*RTI International*  
*701 13th St. NW, Ste. 750*  
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**Carlo: Retinopathy of prematurity and actual oxygen saturations: A secondary protocol of the SUPPORT Trial**

***Subcommittee Consensus: This protocol can move forward and Dr. Gantz can begin the requested analysis. Dr. Carlo will create tables and figure as requested by the subcommittee. This should be a 1<sup>st</sup> priority for next PAS (for Support trial secondary analyses). In addition, the pre-specified Support secondary's should take priority over all other GDB or in coming secondary analyses. Dr. Higgins will discuss with RTI (Dr. Das) off line to prioritize RTI workload.***

Additional comments: Dr. Finer felt this proposal is essentially a follow up of the Support trial primary analysis rather than a secondary analyses. Primary interested in looking saturations and association with ROP and death (because it's the largest effect size); to look at which babies would have been predisposed and developed ROP. Dr. Finer suggested the need to look at O2 profiles to determine significant ROP and death/ROP and the need to do this sooner rather than later as part of the primary trial analysis. Dr. Higgins agreed because death is a primary. Dr. Higgins said it would be helpful for Dr. Carlo to provide tables and figures (about what the data could show us). Dr. Carlo agreed. Dr. Finer has asked Marie to run preliminary analysis for Dr. Carlo/Finer, then the committee, to review asap. It was suggested that it might be better to express data in percentiles (duration) in O2, then outcome. Also, exposure in terms of DOL and exposure duration. Whether to begin analysis of O2 in the 1<sup>st</sup> 7 days, then to 14 day, then up to 34 weeks PCA, then thru threshold Dz, then thru FU, that decision is pending and requires more discussion.

Dr. Gantz said this analysis will be exploratory in nature; ideally we will have our hypotheses going forward (increase O2 is associated with increased ROP) but we will also be looking at what the data will tell us; there will also be multivariate analyses. It was suggested to also consider FiO2 in the expanded analysis. We want to know whether and to what extent FiO2 could be causal factor (whole body oxygen) verses saturations in ROP/Death outcomes.

**From:** [Bell, Edward](#)  
**To:** [Dan Ellsbury \(gmail\)](#)  
**Cc:** [Wally Carlo](#); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Subject:** FW: Possible secondary proposal for SUPPORT  
**Date:** Thursday, June 10, 2010 3:19:40 PM

---

Dan,  
See below. Feel free to share you ideas about analysis of the SUPPORT data with Wally (and copy me), so he can tell you what is already planned.  
Ed

---

**From:** Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]  
**Sent:** Thursday, June 10, 2010 1:55 PM  
**To:** Bell, Edward  
**Cc:** Rosemary Higgins  
**Subject:** RE: Possible secondary proposal for SUPPORT

Ed:

I know of Dan's work and actually quote his work in my oxygen lectures. I would love to work with him.

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: 205 266 (b)

---

**From:** Bell, Edward [mailto:edward-bell@uiowa.edu]  
**Sent:** Thursday, June 10, 2010 1:41 PM  
**To:** Wally Carlo, M.D.  
**Cc:** Rosemary Higgins  
**Subject:** RE: Possible secondary proposal for SUPPORT

Wally,  
Dan is very interested in the issue of oxygen and ROP. He is a good thinker and a good worker. In particular, he would like to help explore the relationship, if any, between SO2 variability and ROP risk. He has published several papers related to oxygen use and monitoring, which I have attached. With your approval, I will see if he would like to join your analysis team. It would be a good way for him to get his feet wet in the Network.  
Thanks,  
Ed

---

**From:** Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]  
**Sent:** Thursday, June 10, 2010 1:14 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Bell, Edward  
**Subject:** RE: Possible secondary proposal for SUPPORT

Rose:

We have a lot of analyses proposed. I do not mind having others join us but the protocol has been written. Dan can join us if you think it is ok. We have the subcommittee already involved. Also, Roger emailed me that he is very interested in it. I am ok with having more collaborators.

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, June 10, 2010 1:04 PM  
**To:** Wally Carlo, M.D.  
**Cc:** edward-bell@uiowa.edu  
**Subject:** FW: Possible secondary proposal for SUPPORT

Wally

I think this may be covered in your secondary analysis, but do you want assistance/input with the paper??

Thanks

Rose

---

**From:** Bell, Edward [mailto:edward-bell@uiowa.edu]  
**Sent:** Tuesday, June 08, 2010 4:10 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Dan Ellsburly (gmail)  
**Subject:** Possible secondary proposal for SUPPORT

Rose,

Dan Ellsburly and I are interested in looking at the relationship between O2 sat variability and risk of severe ROP using the SUPPORT data. Do you know if such an analysis is already underway or planned? If not, would this be an appropriate topic for a proposed secondary analysis? If yes, does this come through you to the SUPPORT Subcommittee?

Thanks,

Ed

**From:** [Bell, Edward](#)  
**To:** [Wally Carlo, M.D.](#)  
**Cc:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Subject:** RE: Possible secondary proposal for SUPPORT  
**Date:** Thursday, June 10, 2010 2:41:28 PM  
**Attachments:** [Elsbury oxygen use survey - J Pediatr 2002.pdf](#)  
[Elsbury home oxygen in BPD - J Perinatol 2004.pdf](#)  
[Elsbury O2 + ROP - Clin Perinatol 2010.pdf](#)

---

Wally,

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Thanks,

Ed

---

**From:** Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]  
**Sent:** Thursday, June 10, 2010 1:14 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Bell, Edward  
**Subject:** RE: Possible secondary proposal for SUPPORT

Rose:

We have a lot of analyses proposed. I do not mind having others join us but the protocol has been written. Dan can join us if you think it is ok. We have the subcommittee already involved. Also, Roger emailed me that he is very interested in it. I am ok with having more collaborators.

Wally

Wally Carlo, M.D.  
Edwin M. Dixon Professor of Pediatrics  
University of Alabama at Birmingham  
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Cell: 205 266 (b)

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Thursday, June 10, 2010 1:04 PM  
**To:** Wally Carlo, M.D.  
**Cc:** edward-bell@uiowa.edu  
**Subject:** FW: Possible secondary proposal for SUPPORT

Wally

I think this may be covered in your secondary analysis, but do you want assistance/input with the

paper??

Thanks

Rose

---

**From:** Bell, Edward [mailto:edward-bell@uiowa.edu]

**Sent:** Tuesday, June 08, 2010 4:10 PM

**To:** Higgins, Rosemary (NIH/NICHD) [E]

**Cc:** Dan Ellsbury (gmail)

**Subject:** Possible secondary proposal for SUPPORT

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Thanks,

Ed



# Variability in the use of supplemental oxygen for bronchopulmonary dysplasia

Dan L. Ellsbury, MD, Michael J. Acarregui, MD, Gail A. McGuinness, MD, and Jonathan M. Klein, MD

Despite the use of "oxygen dependence at 36 weeks postmenstrual age" to define bronchopulmonary dysplasia, criteria for the use of oxygen is rarely defined. We surveyed members of the Vermont Oxford Network regarding their criteria. Pulse oximetry saturation thresholds varied widely from <84% to <96%, with only 41% of the respondents using the same criteria (<90%). This lack of uniformity in the use of oxygen casts doubt on conclusions derived from multicenter trials that use oxygen dependence at 36 weeks postmenstrual age as an outcome. (J Pediatr 2002;140:247-9)

The term bronchopulmonary dysplasia (BPD) was first used in 1967 by Northway<sup>1</sup> to describe the clinical, pathologic, and radiographic characteristics of 32 preterm infants with severe respiratory distress syndrome who were treated with prolonged mechanical ventilation and high concentrations of supplemental oxygen. A definition was refined by Bancalari<sup>2</sup> to include the use of positive pressure ventilation during the first week of life for a minimum of 3 days, clinical signs of chronic respiratory disease persisting longer than 28 days, requirement for supplemental oxygen for more than 28 days to maintain a partial pressure of arterial oxygen (PaO<sub>2</sub>) >50 mm Hg, and chest radiographic findings of persistent strands of densities alternating with areas of normal or increased lucency. Tooley<sup>3</sup> suggested that any infant requiring supplemental oxygen at 30 days of age with any radiographic abnormality of the

lung parenchyma could be considered to have BPD.

The definition of BPD as a requirement for supplemental oxygen at 28 to 30 days of age came into common use as an outcome measure in clinical trials in the 1980s.<sup>4,5</sup> In 1988, Shennan<sup>6</sup> found that extending the assessment period to 36 weeks PMA increased the predictive power of dependence on supplemental oxygen as an indicator of abnormal pulmonary outcome. Defining BPD as oxygen dependence at 36 weeks PMA

BPD	Bronchopulmonary dysplasia
P <sub>a</sub> O <sub>2</sub>	Partial pressure of arterial oxygen
PMA	Postmenstrual age
SpO <sub>2</sub>	Pulse oximeter saturation
VON	Vermont Oxford Network

has now become a frequently used outcome measure.<sup>4,7-9</sup>

The specific criteria for oxygen use at 36 weeks PMA is not clearly defined in most clinical trials.<sup>8,9</sup> Furthermore,

concern has been raised over the use of this definition as an outcome measure.<sup>10,11</sup> Assigning the diagnosis of BPD based solely on the use of oxygen, rather than on specific criteria that define the need for supplemental oxygen, potentially introduces a large element of subjectivity into the diagnosis. If criteria for the use of supplemental oxygen vary from clinician to clinician and center to center, then substantial error could be introduced into studies that use oxygen dependence as an outcome measure. This in turn would lead to invalid conclusions on the basis of center to center comparisons regarding the incidence of BPD. Our objective was to determine if substantial variations exist among neonatologists in the use of supplemental oxygen for infants at 36 weeks PMA.

## METHODS

We surveyed participants at the December 2000 meeting of the Vermont Oxford Network (VON) regarding their criteria for the treatment of infants at 36 weeks PMA with supplemental oxygen. Although permission for distribution of the survey was obtained from the VON, the VON was not involved in the design or content of the survey. An identical survey was submitted via E-mail to directors of fellowship programs in neonatal-perinatal medicine. Names and E-mail addresses were obtained from the Fellowship and Residency Electronic Interactive Database provided by the American Medical Association (<http://www.ama-assn.org/ama/pub/category/2997.html>). We chose to survey the VON because of the wide geographic

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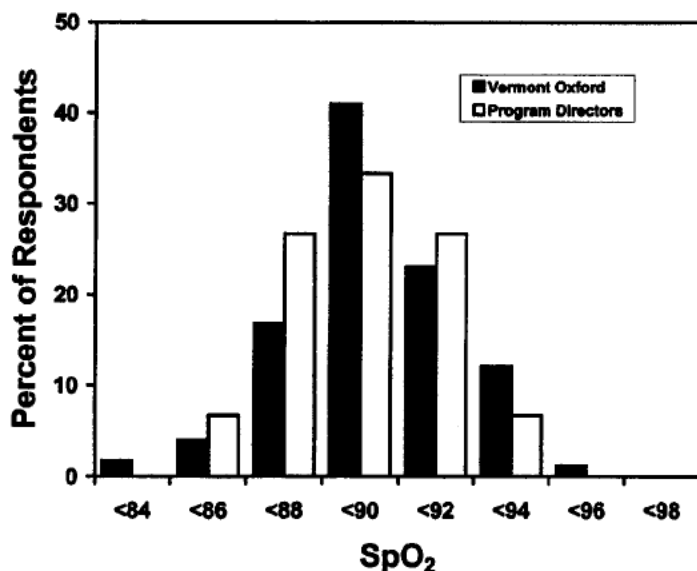
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**Figure.** Frequency distribution of SpO<sub>2</sub> thresholds for the administration of supplemental oxygen at 36 weeks' PMA by members of the Vermont Oxford Network and by neonatal-perinatal medicine fellowship program directors. SpO<sub>2</sub>, Pulse oximetry saturation.

**Table.** Indications other than hypoxemia for use of supplemental oxygen for infants at 36 weeks' PMA

Indication(s)	VON (n = 181) (%)	PD (n = 30) (%)
To prevent/treat apnea, bradycardia, or desaturation during feedings	69	60
Treatment of apnea of prematurity	25	27
Decrease work of breathing	15	13
Prevention of retinopathy of prematurity	13	10
Growth enhancement	10	10

PD, Neonatal-perinatal medicine fellowship program directors.

(48 states) and clinical range (private practice to university) of its members. Neonatal-perinatal fellowship program directors were chosen for the survey as a way to gauge the current academic approach to this topic.

The survey included the following questions:

- At 36 weeks PMA, what baseline SpO<sub>2</sub> (pulse oximeter saturation) on room air would you consider low enough to warrant treatment with supplemental oxygen? Possible answers: <84%, <86%, <88%, <90%, <92%, <94%, <96%, and <98%.
- Do you currently use supplemental oxygen for infants at 36 weeks PMA for reasons other than hypoxemia? Possible answers (may select more than one): (a) To prevent/treat apnea, bradycardia, or desaturation during feedings; (b) For treatment of apnea of prematurity; (c) To decrease work of breathing; (d) For prevention of retinopathy of prematurity; or (e) To enhance growth.
- As a general practice, do you identify an infant's SpO<sub>2</sub> on room air ("room air challenge") at 36 weeks PMA? Possible answers: (a) Always; (b) Sometimes; and (c) Never.
- Do you think that hypoxemia (by a defined SpO<sub>2</sub> level) on room air

at 36 weeks PMA would be a better descriptor of chronic lung disease than "oxygen dependence at 36 weeks PMA"? Possible answers: (a) Yes; or (b) No.

## RESULTS

Surveys were completed by 181 (61%) of the 297 participants attending the VON meeting. Identification of center affiliation was not required and, therefore, some responses may have come from the same center leading to the possibility that <181 centers were actually represented. The threshold SpO<sub>2</sub> for administration of supplemental oxygen at 36 weeks PMA ranged widely (Figure) with <90% being the threshold most frequently chosen (41%). Of the 100 program directors in the directory, 12 did not have an E-mail address listed and 17 had addresses that were undeliverable. Of the remaining 71 program directors, 30 (42%) returned surveys, 14 of whom also belong to the VON. Program director results were consistent with the VON, with <90% as the most frequently chosen threshold (33%), however, the range was not as wide (Figure). Supplemental oxygen was also used for reasons other than hypoxemia (82% of VON and 77% of program director respondents) with the most frequent reason being the prevention or treatment of apnea, bradycardia, or desaturation during feedings (Table).

We found a wide variation in the practice of determining an infant's SpO<sub>2</sub> on room air at 36 weeks PMA. The frequency of determining a room air SpO<sub>2</sub> by the VON respondents was as follows: always (19%), sometimes (53%), or never (28%) performed. Program director responses in determining room air SpO<sub>2</sub> were similar: always (20%), sometimes (43%) or never (37%) performed. Evaluation of SpO<sub>2</sub> by trending over time rather than by an isolated "spot" reading was added as an important clarification by 15% of VON respondents.

We found that hypoxemia, as defined by a specific SpO<sub>2</sub> level on room air at 36 weeks PMA, was considered to be a better descriptor of chronic lung disease than "oxygen dependence at 36 weeks PMA" by 60% of both VON and program director respondents. In addition, 12% of VON respondents expressed concern that a specific SpO<sub>2</sub> level on room air required additional clarification for infants cared for at high altitudes.

## DISCUSSION

Our findings reinforce concerns regarding the use of oxygen dependence at 36 weeks PMA as a definition of BPD.<sup>10,11</sup> The threshold SpO<sub>2</sub> for administration of supplemental oxygen to infants at 36 weeks PMA was not uniform. In fact, less than half of the VON neonatologists surveyed used the same criterion (41% used SpO<sub>2</sub> <90%), and only 13% were consistent with recent recommendations to use supplemental oxygen to keep SpO<sub>2</sub> >93%.<sup>12</sup> Furthermore, as many as 23% would not use supplemental oxygen unless the SpO<sub>2</sub> was <88%. If these data are consistent with the way in which supplemental oxygen is used in multicenter clinical trials, then significant concerns can be raised regarding the effects of various interventions on the incidence of BPD.

Our data demonstrate that supplemental oxygen is often used in premature infants for conditions (Table) other than hypoxemia. In these cases, the use of supplemental oxygen could lead to an infant being misrepresented as having BPD. The use of a specific threshold SpO<sub>2</sub> level on room air at 36 weeks PMA was considered by 60% of respondents to be a better descriptor of BPD than just the need for oxygen. Thus, regardless of the exact level chosen, the use of a consistent value for maintaining or discontinuing oxygen therapy would bring substantial clarity

to the interpretation of multicenter trials using BPD, as defined by oxygen dependence, as an outcome measure.

Our study has several limitations. Responses were self-reported perceptions subject to both recall bias and selective participation. The survey was completed by only 61% of the targeted VON audience and views of the nonresponders may potentially have influenced the results. The targeted audience, the VON, may not be representative of all groups involved in multicenter clinical trials investigating BPD. However, the similarity of the results to those of the program directors makes this less likely. Although the response rate for the program directors survey was low (42%), the agreement in the responses with those of the VON suggests that criteria that are taught in academic centers are reflected in the current practice of neonatology.

We conclude that oxygen use at 36 weeks PMA is a poor definition for BPD, and we speculate that center-to-center variability in criteria for the use of supplemental oxygen may contribute to differences in the incidence of BPD. These findings raise serious concerns regarding the interpretation of multicenter studies employing "oxygen dependence at 36 weeks PMA" as an outcome measure. The concern over a consistent definition of BPD was also recently emphasized in a workshop held by the National Institutes of Health on this disease.<sup>13</sup> In the future, a physiologic definition of BPD based on oxygen saturation, as suggested by Walsh-Sukys et al,<sup>14</sup> would help to bring consistency to this diagnosis.

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## Controversy Surrounding the Use of Home Oxygen for Premature Infants with Bronchopulmonary Dysplasia

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### OBJECTIVE:

To determine the criteria used in the current practice of neonatology for the initiation of home oxygen therapy in premature infants with bronchopulmonary dysplasia and to compare these criteria with the available literature regarding the use of home oxygen therapy.

### STUDY DESIGN:

Participants in the December 2000 meeting of the Vermont Oxford Network were surveyed regarding their current use of home oxygen therapy for infants with bronchopulmonary dysplasia.

### RESULTS:

Surveys were returned by 181 out of 297 participants. Pulse oximetry saturation (SpO<sub>2</sub>) thresholds for the initiation of home oxygen therapy varied widely from <84% to <98%. The most common threshold was <90% chosen by only 43% of the respondents. Additionally, 22% of the respondents did not initiate therapy until the oxygen saturation in room air was below 88%. Once on oxygen therapy, the target SpO<sub>2</sub> also varied widely from >84% to >98%, with only 27% of respondents aiming for an SpO<sub>2</sub> of >94%.

### CONCLUSIONS:

There is a clear lack of consensus among neonatologists regarding the initiation of home oxygen therapy for bronchopulmonary dysplasia. Furthermore, the criteria used for home oxygen therapy varies widely with the majority of neonatologists surveyed using oxygen saturation levels not supported by the literature. We speculate that a significant underutilization of home oxygen therapy exists for infants with bronchopulmonary dysplasia.

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### INTRODUCTION

Considerable uncertainty exists regarding the specific criteria for the initiation of home oxygen therapy for infants with chronic lung disease. Despite over 20 years of experience with home oxygen therapy for infants with bronchopulmonary dysplasia (BPD), no consensus exists regarding specific indications for its use.<sup>1,2</sup> In a previous study, we found large variations in criteria for the use of oxygen to treat premature infants at 36 weeks postmenstrual age (PMA).<sup>3</sup> In this current study, we wanted to determine if this same variability in practice extended into the use of home oxygen.

No randomized controlled trials have been performed to determine what pulse oximeter saturation (SpO<sub>2</sub>) criteria should be used for the initiation and management of home oxygen therapy for BPD. In the absence of controlled studies regarding the effects of oxygen therapy to achieve a specific SpO<sub>2</sub> level in infants with BPD, recommendations can only be based on reference values from healthy infants and on observational studies regarding the pathophysiological effects of acute and chronic hypoxia.

In healthy term infants, the median baseline SpO<sub>2</sub> was found by Hunt et al.<sup>4</sup> to be 98%, with the 10th percentile being 95.2%.<sup>4</sup> Poets et al.<sup>5</sup> described similar levels of oxygen saturation (median SpO<sub>2</sub> of 99.5% with the fifth percentile being 95.7%) in healthy preterm infants at the time of hospital discharge (median gestational age 32.8±2.5 weeks). In a cohort of preterm infants (median gestational age 35 weeks) with no previous history of respiratory distress, Richard et al.<sup>6</sup> also found similar room air oxygen saturation levels with a mean SpO<sub>2</sub> of 99.4% and a fifth percentile of 99.5%. Ng et al.<sup>7</sup> demonstrated similar findings in a group of preterm infants (median gestational age 33 weeks, range 30 to 34 weeks) who had a mean SpO<sub>2</sub> of 97%. Both the Hunt and Ng studies used Ohmeda oximeters which yielded results 1.6% lower than the Nellcor oximeters used in the Richard and Poets studies.<sup>8</sup> Overall, the vast majority of healthy term and preterm infants at discharge have an oxygen saturation greater than 95% in room air with a median value of 99%.

Studies of infants with BPD have shown benefits from the use of oxygen at home. For example, home oxygen therapy has been shown to affect growth. In a retrospective study of infants with BPD, Groothuis and Rosenberg<sup>9</sup> found that home oxygen therapy targeted to maintain SpO<sub>2</sub> ≥ 93% resulted in appropriate weight gain. However, when parents prematurely discontinued supplemental oxygen against medical advice, mean daily weight gain fell from 27.3 to 1.4 g/day. When home oxygen therapy was

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resumed, weight gain increased to 18.3 g/day. Hudak et al.<sup>10</sup> also observed a similar effect on catch-up growth in 30 extremely low-birth-weight infants with BPD (birth weight  $783 \pm 24$  g, gestational age  $26 \pm 0.3$  weeks). At hospital discharge, 77% of the infants were below the fifth percentile for weight. Home oxygen therapy was given to maintain  $SpO_2 \geq 95\%$ . At the time of discontinuation of home oxygen therapy (median of 4.5 months), only 23% of the infants were still below the fifth percentile for weight. Moyer-Mileur et al.<sup>11</sup> prospectively evaluated 48 preterm infants with baseline  $SpO_2$  levels of 88 to 91% versus  $\geq 92\%$  at the time of discontinuation of home oxygen therapy. Infants in both groups showed a decrease in growth after oxygen was stopped. In the 88 to 91% group, weight gain decreased from 17.3 to 3.7 g/kg/day, whereas in the  $\geq 92\%$  group weight gain decreased only slightly from 19.3 to 17.3 g/kg/day.

Supplemental oxygen therapy for infants with BPD has benefits beyond growth. The use of oxygen in infants with BPD to correct mild hypoxemia ( $SpO_2$  89%) results in a 50% decrease in airway resistance, a significant increase in dynamic compliance and a decreased work of breathing.<sup>12</sup> Abman et al.<sup>13</sup> demonstrated a 50% decrease in pulmonary artery pressure when supplemental oxygen was used to increase  $SpO_2$  from 82 to 93% in infants with severe BPD. The frequency of intermittent desaturation episodes ( $SpO_2 < 80\%$ ) in infants with BPD was reduced from 5 to 0.2% by the use of oxygen targeted to maintain  $SpO_2$  94 to 96%, compared to maintaining  $SpO_2$  from 87 to 91%.<sup>14</sup> Furthermore, the incidence of sudden infant death syndrome in infants with BPD may be decreased by use of home oxygen therapy to keep  $SpO_2 \geq 93\%$ .<sup>15,16</sup>

A review on the use of supplemental oxygen by Poets<sup>17</sup> suggests that home oxygen therapy should be considered in infants whose room air  $SpO_2$  is  $< 93\%$ , and that once started on home oxygen the  $SpO_2$  should be maintained at  $\geq 95\%$ . A second review by Kotecha and Allen<sup>18</sup> states that an  $SpO_2 < 92\%$  should be avoided, and a target range of at least 94 to 96% should be maintained. A third review by Abman<sup>19</sup> suggests maintaining the  $SpO_2 > 92\%$  in infants with BPD without pulmonary hypertension, and 94 to 96% in infants with BPD complicated by pulmonary hypertension. The American Academy of Pediatrics' *Guidelines for Pediatric Home Health Care* suggest use of oxygen in infants with BPD having baseline  $SpO_2$  values  $< 95\%$  and targeting therapy to maintain  $SpO_2$  95 to 98%.<sup>20</sup>

The American Thoracic Society in a recent *Statement on the Care of the Child with Chronic Lung Disease of Infancy and Childhood* recommends that infants with BPD who are past the age of oxygen-induced retinopathy be provided with supplemental oxygen to achieve a saturation  $\geq 95\%$ .<sup>21</sup> As a whole, the above reviews would suggest a threshold  $SpO_2$  of  $< 92$  to  $< 95\%$  for the initiation of home oxygen therapy in infants with BPD, with a target saturation of at least  $\geq 94\%$ . Whether any of the above practices or another standard is employed among neonatologists is unknown. Thus, our objective was to determine

the current practice among neonatologists regarding the use of supplemental oxygen at home and compare these criteria with the available literature regarding home oxygen use in infants with BPD.

## METHODS

We surveyed participants at the December 2000 meeting of the Vermont Oxford Network (VON) regarding their criteria for the use of home oxygen therapy for treatment of infants with BPD. BPD was defined as oxygen dependence at 36 weeks PMA.<sup>22</sup> We chose to survey the VON because of the wide geographic (48 states and 20 countries) and clinical range (private practice to university) of its members. Although permission for distribution of the survey was obtained from the VON, it was not involved in the design or content of the survey. The survey included the following questions:

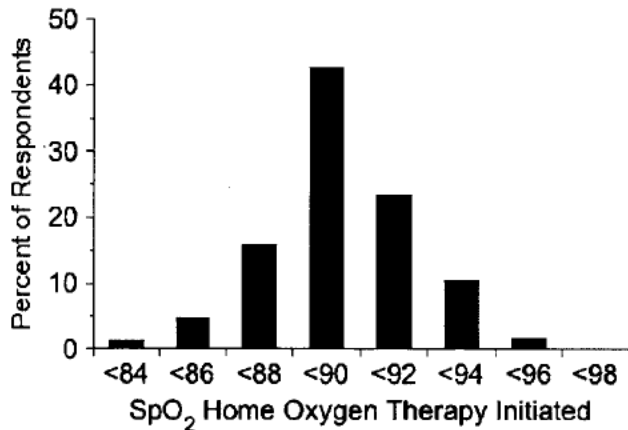
- (1) What baseline  $SpO_2$  on room air would you consider low enough to warrant home supplemental oxygen therapy? Possible answers:  $< 84$ ,  $< 86$ ,  $< 88$ ,  $< 90$ ,  $< 92$ ,  $< 94$ ,  $< 96$  and  $< 98\%$ .
- (2) What  $SpO_2$  level do you seek to maintain in an infant on home oxygen therapy? Possible answers:  $> 84$ ,  $> 86$ ,  $> 88$ ,  $> 90$ ,  $> 92$ ,  $> 94$ ,  $> 96$  and  $> 98\%$ .
- (3) If an infant has a "normal  $SpO_2$ " on room air but is tachypneic (respiratory rate  $> 60$  bpm) tachycardic (heart rate  $> 160$  bpm) and/or showing poor growth ( $< 10$  g/day) — would you consider home oxygen therapy? (a) Yes. (b) No.

## RESULTS

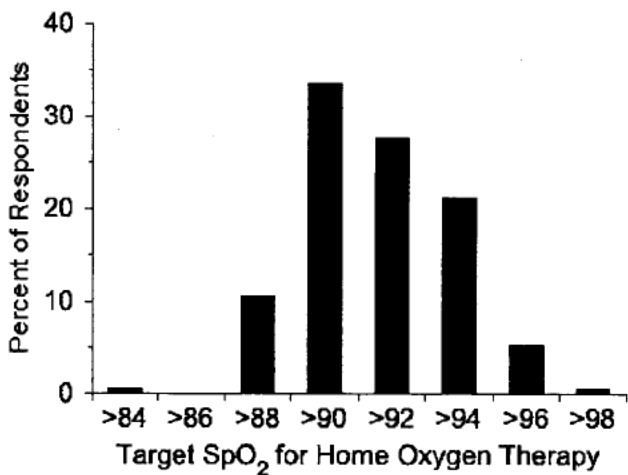
Home Oxygen Therapy Surveys were completed and returned by 181 of the 297 participants (61%) attending the December 2000 meeting of the Vermont Oxford Network. The VON did not allow identification of center affiliation and thus some responses may have come from the same center leading to the possibility that less than 181 centers were represented.

We found a wide range in the threshold  $SpO_2$  for the administration of home oxygen, from  $< 84$  to  $< 96\%$ , with 64% of respondents not initiating home oxygen until the  $SpO_2$  was below 90% (Figure 1). If Poets'<sup>17</sup> recommended threshold of 93% is used as a reference, then up to 88% of all respondents would not initiate home oxygen therapy (Figure 1). An oxygen saturation level of  $< 90\%$  was most often chosen as the threshold at which home oxygen was initiated, however, this same target was chosen by only 43% of the respondents.

Once on home oxygen therapy, the goal  $SpO_2$  also varied widely, ranging from a target  $SpO_2$  of  $> 84$  to  $> 98\%$ , with only 27% of respondents targeting an  $SpO_2$  of  $> 94\%$  (Figure 2). Again, there was therapeutic inconsistency among the respondents with only 34% using the same target saturation of  $> 90\%$ .



**Figure 1.** Frequency distribution of SpO<sub>2</sub> thresholds for treatment of BPD with supplemental home oxygen by members of the VON.



**Figure 2.** Frequency distribution of the SpO<sub>2</sub> levels targeted by members of the VON during treatment of BPD with home oxygen.

There were reasons other than abnormal SpO<sub>2</sub> values in room air given for the use of supplemental oxygen at home. The use of home oxygen therapy was considered by 51% of the respondents for the treatment of an infant with a "normal SpO<sub>2</sub>" on room air who had tachypnea, tachycardia, and/or poor growth. Out of the remaining 49% of the respondents who would not consider oxygen for these indications; 12% advocated red blood cell transfusion as a preferred therapy, 6% listed corticosteroids, and 8% would pursue an "additional evaluation".

## DISCUSSION

Recently, a survey of departments of pediatrics in Germany of criteria for the use of home oxygen therapy in infants found that the SpO<sub>2</sub> thresholds for oxygen varied widely (80 to 94%) with 93% of respondents using SpO<sub>2</sub> thresholds lower than Poets'

recommendation (<93% saturation to initiate or continue supplemental oxygen in premature infants with BPD). The targeted SpO<sub>2</sub> goal once on oxygen therapy was also found to vary widely from 86 to 100% saturation, with 68% using a target SpO<sub>2</sub> that was again less than Poets'<sup>1</sup> recommendation of ≥95%. A separate study in the United Kingdom and Ireland also addressed criteria for the discontinuation of home oxygen therapy in infants with BPD. Consistent with the study from Germany, they found a wide range of SpO<sub>2</sub> thresholds (85 to 98%) with 46% again using a threshold less than Poets' recommendation.<sup>2</sup> It is clear that this practice pattern is not unique to a specific country and may actually be representative of a global inconsistency in the use of home oxygen therapy.

We found, in agreement with the above studies, that the majority of Vermont Oxford Network neonatologists surveyed also used SpO<sub>2</sub> criteria well below the recommendations of Poets, Kotecha, Abman and the American Academy of Pediatrics.<sup>17-19</sup> Despite observational data spanning nearly 20 years, nearly 90% of respondents used SpO<sub>2</sub> thresholds for the initiation and maintenance of home oxygen therapy below the levels recommended by the medical literature. The reasons for the discrepancy between the SpO<sub>2</sub> thresholds currently supported by the literature and thresholds commonly used in clinical practice for home oxygen therapy are unclear.

Our survey did not explore the rationale for the reluctance to use home oxygen therapy for infants with BPD. Factors possibly affecting the decision to continue or initiate home oxygen therapy could include cost, parental stress or anxiety and oxygen toxicity. Concerns over home oxygen therapy increasing the overall costs of medical care have not been substantiated. In fact, home oxygen therapy has been shown to decrease health-care costs. Thilo et al.<sup>23</sup> calculated an average estimated savings of \$33,370 for each infant discharged on home oxygen therapy. McAleese et al.<sup>24</sup> found a similar savings of \$41,725 per infant, although the cost savings were primarily for third-party payors and hospitals with an increase in out-of-pocket costs to the patients.

Physicians may be reluctant to prescribe home oxygen therapy because it may increase parental stress. It is true that parental stress, anxiety and inconvenience are increased transiently with home oxygen therapy, but overall this form of outpatient therapy is well accepted by parents and is in fact preferred to ongoing hospitalization.<sup>23-27</sup>

Physician concern over oxygen toxicity may be another reason limiting the use of home oxygen. The acceptance of lower SpO<sub>2</sub> values rather than starting home oxygen therapy could possibly be related to the use of SpO<sub>2</sub> levels <94% early in a premature infant's course to minimize both the risk of retinopathy of prematurity (ROP) and pulmonary oxygen toxicity from exposure to high levels of oxygen.

An observational study by Tin et al.<sup>28</sup> has shown that by maintaining oxygen saturations 70 to 90% versus 88 to 98%, the incidence of ROP and BPD was reduced and growth was less

impaired. This practice was primarily used in the first 2 months of life and is not relevant for home oxygen therapy. In fact, liberal oxygen supplementation was employed by Tin et al,<sup>28</sup> in infants with BPD who were older than 8 weeks with mature retinal vasculature. The above concern over SpO<sub>2</sub> levels >94% increasing the risk for ROP is not supported at the older PMA at which an infant would be considered for discharge on home oxygen. In fact, the STOP-ROP study, with a mean PMA at entry of 35 weeks, demonstrated no worsening to a slight decrease in progression from prethreshold to threshold ROP when SpO<sub>2</sub> was kept >94% (96 to 99% versus 89 to 94%). However, pulmonary oxygen toxicity was slightly increased in the high-saturation group, possibly reflecting elevated inspired oxygen concentrations for a subset of these patients, as the mean fractional inspired oxygen concentration in this group was relatively high at 0.46±0.20 after randomization.<sup>29</sup> Thus, the potential for exposure to toxic concentrations of oxygen could be minimized during home oxygen therapy by limiting nasal cannula flow rates.<sup>30</sup>

The recently completed BOOST trial studied infants requiring oxygen at 32 weeks PMA with the SpO<sub>2</sub> targeted to either 91 to 94% or 95 to 98%. No beneficial differences were seen between groups at 1 year of age from targeting a higher saturation level.<sup>31</sup> However, this population is not comparable to patients discharged on home oxygen since the BOOST trial reflects a much younger hospitalized group of patients at 32 weeks PMA versus the much older, at least 36 weeks PMA, patient with BPD. Furthermore, the BOOST trial did not include a group in which SpO<sub>2</sub> levels of 90% or less were tolerated. A saturation level at which the majority (64%) of the neonatologists in our survey (Figure 1) would not implement home oxygen therapy.

Our study has several limitations. Responses were self-reported perceptions subject to recall bias and selective participation. There were no standardized conditions required for the state of the infant at the time at which the SpO<sub>2</sub> was measured. The survey was completed by only 61% of the targeted VON audience, views of the nonresponders may potentially have influenced the results and there may have been multiple responders from the same institution.

We found a wide variation in the oxygen saturation levels used for the implementation of home oxygen therapy for infants with BPD. The majority of neonatologists surveyed used SpO<sub>2</sub> levels not well supported by the available literature. Furthermore, even when employed, home oxygen therapy is not optimized. We speculate that a significant underutilization of home oxygen therapy exists for infants with BPD. The decision to use supplemental home oxygen therapy to keep saturations ≥94 versus ≥90% remains controversial. Clear guidelines in this area would require large, randomized clinical trials to examine the impact of these different saturation levels on long-term outcomes. In lieu of such trials, one should consider the potential benefits versus risks of utilizing home oxygen for infants with BPD whose room air saturations are <94%.

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# Comprehensive Oxygen Management for the Prevention of Retinopathy of Prematurity: The Pediatrix Experience

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## KEYWORDS

- Comprehensive Oxygen Management • Quality Improvement
- Retinopathy of prematurity • Very low birth weight infants

In 2003, Chow and coworkers<sup>1</sup> described a striking reduction in retinopathy of prematurity (ROP) after implementation of a structured oxygen management protocol, focused on avoiding hyperoxia and repeated episodes of hypoxia-hyperoxia in very low birth weight infants. This publication generated much interest and discussion in the neonatology community including practices within Pediatrix Medical Group. Some Pediatrix Physician Groups adopted the general approach proposed by Chow and coworkers<sup>1</sup> with similar results,<sup>2-4</sup> as did a number of centers outside of Pediatrix.<sup>5-7</sup> Within Pediatrix Medical Group, discussions continued by intranet discussion forums and presentations at Pediatrix quality improvement conferences. In 2006, the basic principles of avoiding hyperoxia and repeated episodes of hypoxia-hyperoxia were expanded into a Pediatrix quality improvement initiative called "Comprehensive Oxygen Management for the Prevention of Retinopathy of Prematurity" (COMP-ROP).

COMP-ROP was enthusiastically received. Eighty neonatal intensive care units (NICU) formally participated in the initiative, with many more informally participating. The COMP-ROP Collaborative was loosely structured. NICUs were provided with a toolkit containing a basic description of the oxygen management process and multiple tools to facilitate rapid adaptation and implementation of the program within their centers.

Because of the uncertainties and controversies surrounding the definition of "optimal oxygen saturation" in extremely premature infants, rigid oxygen saturation

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limits were not mandated.<sup>8,9</sup> Emphasis was placed on NICU staff education, system-based approaches to decreasing hyperoxia, avoidance of large fluctuations in oxygen saturation, ensuring compliance with oximeter alarm use, and using oxygen saturation trending to assist and guide oxygen management efforts.

Between 2003 and 2008, a striking decrease in severe ROP (stage 3, 4, 5, or surgical) was seen in the Pediatrix Network. In infants with birth weights of 400 to 1500 g, severe ROP dropped from 11% in 2003 to 5.8% in 2008 (Fig. 1). During this time period, mortality rates remained stable. Necrotizing enterocolitis decreased, then increased during this time period, with 2008 rates very similar to 2003. This pattern was also seen in infants with birth weights greater than 1500 g, who were not included in COMP-ROP. Patent ductus arteriosus and patent ductus arteriosus ligation rates also fluctuated, with 2008 rates remaining similar to 2003. Oxygen use at 28 days of life and at 36 weeks postmenstrual age decreased from 2003 to 2008.

#### WHY WAS COMP-ROP SUCCESSFUL?

Why did this initiative succeed? Early adopters started the process after Chow and coworkers<sup>1</sup> publication. The quality improvement infrastructure within Pediatrix Medical Group fostered the spread of this information, eventually formalizing the process as the COMP-ROP program. Berwick<sup>10</sup> describes seven guiding rules for diffusion of innovations, all of which were used in the events leading up to the COMP-ROP initiative and continued in the implementation of the program:

1. Find sound innovations: The structure of the Pediatrix system encourages, by intranet and conferences, continuous discussion and debate of new innovations found in the medical literature.
2. Find and support innovators: The ongoing communication and debate of new innovations includes discussion of the initial successes and difficulties with implementation of new ideas. Successful innovators could be identified despite the size of the network (almost 1000 physicians in 33 states, providing care for approximately 20% of infants receiving neonatal intensive care in the United States).

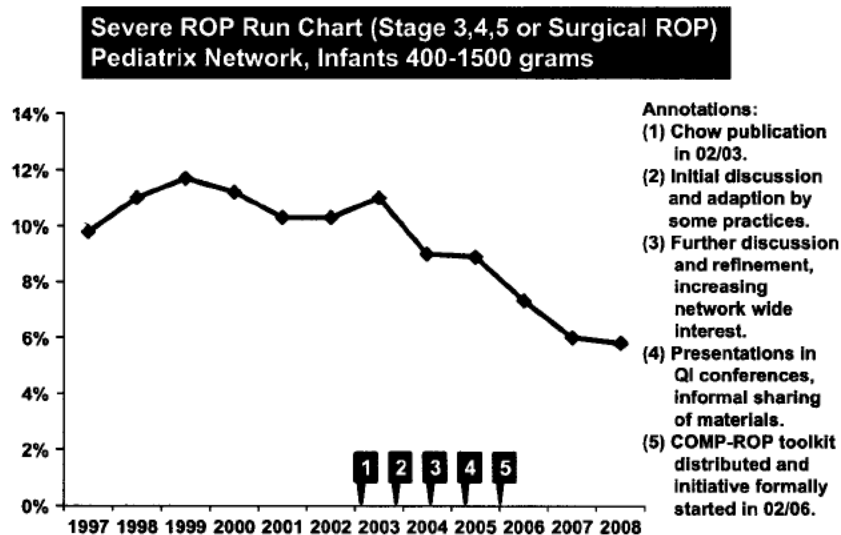


Fig. 1. COMP-ROP severe ROP annotated run chart.

3. Invest in early adopters: The early adopters were identified in these ongoing intranet discussions and quality conferences. Corporate support including mentorship, education materials, conference calls, and so forth was provided to assist these early adopters in effectively implementing the COMP-ROP program.
4. Make early adopter activity observable: The COMP-ROP program was encouraged and promoted by corporate staff in a variety of settings. Although participation was encouraged, it was not mandated.
5. Trust and enable reinvention: As the program was implemented, objections to some components of the program were raised. Elements that were completely acceptable in one center were not accepted in others. All participating centers were encouraged to adapt the program to fit the culture and workflow of their centers.
6. Create slack for change: Center participation was valued at the corporate level and viewed as an important contribution to the practice and the patients. Quality improvement activity was considered a vital part of the practice, not an extracurricular activity.
7. Lead by example: Leaders of the COMP-ROP program were practicing neonatologists who shared their ongoing successes and difficulties with implementation in their own centers.

#### **THE COMP-ROP PROGRAM**

This article describes the components of the COMP-ROP toolkit and lessons learned from its dissemination within the Pediatrix network. The toolkit was provided to all Pediatrix practices in electronic format. Educational presentations, sample order sets, bedside signs, surveys to assess knowledge gaps, and other materials were provided. Local adaptation and modification of the materials was encouraged to facilitate acceptance and use in a variety of NICU settings.

##### ***Basic Principles***

The guiding principles of the COMP-ROP program included the following: (1) the avoidance of hyperoxia and repeated episodes of hypoxia-hyperoxia is associated with reduced incidence of ROP; (2) systems should be redesigned to minimize or eliminate practices that result in periods of hyperoxia; (3) NICU staff should be educated regarding the risks and benefits of supplemental oxygen administration in premature infants, including the limitations of pulse oximetry in detecting hyperoxia; and (4) auditing compliance with oximeter alarm settings, and the percentage of time patients spend below, within, and above the targeted oxygen saturation parameters, should be used to provide short-term feedback on the success of oxygen management practices.

##### ***Program Structure***

The program was structured to assess baseline ROP outcomes, oxygen management practices, and staff beliefs concerning ROP pathophysiology. Further, the program provided basic instruction in team building, multidisciplinary NICU staff education, and facilitated system-based changes designed to optimize oxygen management. After implementation, periodic review of process, outcome, and balancing measures was followed to assess the impact of COMP-ROP (Fig. 2).

##### ***The Multidisciplinary COMP-ROP Team***

The COMP-ROP toolkit advocated for each unit to create a multidisciplinary ROP team. Ideally, this group would include physicians, nurses, nurse practitioners, and respiratory therapists; inclusion of leadership with the authority to make system-based

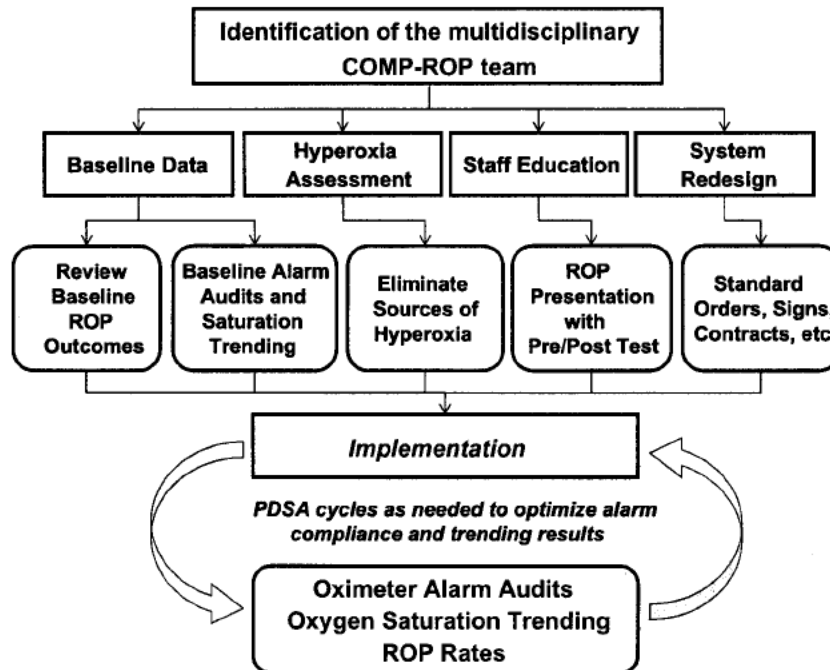


Fig. 2. Structure of the COMP-ROP program.

changes was encouraged. Emphasis was placed on including individuals from different work shifts (days, nights, weekend shifts). Additionally, it was emphasized that COMP-ROP was not a clinical trial or research project, and that the program was meant as a starting point, with adaptation to each center's culture and work flow provided by each project team. Review by an institutional review committee or hospital quality improvement committee was governed by each center's guidelines and regulations for quality improvement activities.

#### **Baseline Data Collection**

Certain baseline data were obtained, including ROP outcomes, and several measures of oxygen and oximetry use. These measures were followed throughout the project.

#### **ROP outcomes**

ROP data were available through the Pediatrix Clinical Data Warehouse (discussed elsewhere in this issue). The reports provided data on clinical outcomes and certain process measures related to ROP and could be stratified by birth weight, gestational age, NICU patient volume, and inborn-outborn status.

#### **Baseline oximeter alarm audits**

A sample oximeter alarm audit tool (Fig. 3) was provided to facilitate collection of oximeter alarm settings by bedside audits. The experience was that many centers had poor compliance in setting oximeter alarms in a fashion to minimize exposure to hyperoxic environments. Many centers had no process to consistently order oximeter alarm settings in the population at risk for ROP. Further, many oximeters have a factory

### Pulse Oximetry Alarm Audit Tool

Please review the oximeter alarm settings and mark “correct” if they are set appropriately, and “incorrect” if not, according to:

- the standard oximeter alarm setting orders, OR
- a specific order in the chart

Determine reasons for non-compliance when they occur, and address these as indicated, especially system issues

- use episodes of non-compliance as educational opportunities

The overall percent correct should be recorded on a spreadsheet (use the oximeter alarm audit run chart, in excel)

Patient	1	2	3	4	5	6	7	8	9	10
Correct										
Incorrect										

Fig. 3. Sample oximeter alarm compliance audit tool.

default high-saturation alarm setting of 100%. If this default setting is not noticed and altered, infants receiving supplemental oxygen are at risk for excess time in a hyper-oxic environment.

#### **Baseline oxygen saturation trend audits**

This audit was designed to provide an estimate of the amount of time an infant spent at various oxygen saturations, with emphasis on the proportion of time the oxygen saturation is greater than 95% and the general distribution of saturation values, both high and low. Ongoing measurement of saturation trends was suggested as an important ongoing process measure. Four methods were suggested, discussed next.

**Flow-sheet review** Nursing or respiratory therapy flow-sheets typically capture oxygen saturations levels. Although flow sheets may provide a general sense of oxygen saturation trends, they are of limited use because of the small number of data points and the potential bias of the documenter; the provider may choose to document the “best” number over the last hour, not the “most representative.”

**Monitor trend review** Many bedside monitors have features that allow trending of vital sign data. Capabilities among monitors vary; however, many machines allow the data of the time spent at various oxygen saturations to be presented graphically, downloaded to a computer, or printed. Rapid feedback of oximetry trends to front-line providers is a powerful behavior change agent.

**Peak Po<sub>2</sub> in the first 24 hours** As a supplement to the previously mentioned techniques, the Po<sub>2</sub> trend, as determined by arterial blood gases, can be reviewed from the medical record. This observation is limited to babies with arterial catheters, but may be useful for some babies in the first days of life.

**Saturation level and oximeter alarm random spot checks** This supplementary technique involves simply walking to the bedsides of infants at risk for ROP at a random

time and auditing the oxygen saturation, the fraction of inspired oxygen ( $F_{iO_2}$ ), and the oximeter alarm settings to determine if they are appropriate at that point in time. This "spot check," although not precise, is an additional method to determine general compliance with the desired oxygen management strategies. This technique can be informally used during clinical rounds as part of a random safety audit program.<sup>11</sup>

### ***Hyperoxia Assessment***

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A hyperoxia assessment survey was provided to enable teams to review the manner in which oxygen is used in their unit. This survey facilitated identification of common sources of hyperoxia, including equipment and practice style issues. Once identified, system reengineering and focused education efforts could address sources of hyperoxic exposure.

Common problem areas include use of unblended (100%) oxygen; use of high oxygen concentrations during routine procedures and handling; overtitration of oxygen in response to alarms; and therapeutic use of hyperoxia, the intentional use of high  $F_{iO_2}$  as a treatment.

### ***Delivery room***

Determine if blended oxygen is available for infants less than 32 weeks' gestational age, per the 2006 Neonatal Resuscitation Program recommendations.<sup>12</sup> If blended oxygen was not available in the delivery room, a simple mobile cart was suggested that included an air and oxygen tank connected to an oxygen blender.

### ***Transport***

Some NICUs historically have used 100% oxygen during both "in-house" and "out-of-house" transports. Neonatal transport incubators are commonly designed to provide blended oxygen. If not, most systems can be adapted to include an air tank and an oxygen blender. Oximetry should be used during transports to enable titration of inspired oxygen.

### ***Nebulizers***

100% oxygen is often used as the gas source for nebulizer treatments, creating a significant exposure to hyperoxia for some patients. This issue can be addressed by providing blended oxygen as the nebulizer gas source, or changing to administration by a metered dose inhaler.

### ***Preoxygenation for procedures and cares***

Because some infants desaturate when exposed to noxious stimulation (eg, suctioning, heelsticks, diaper changes, and so forth), providers may prophylactically increase the  $F_{iO_2}$  to "preoxygenate" the infant. This practice may result in hyperoxia, especially if large increases in oxygen concentration are given. This problem can be addressed by education and modification of nursing protocols focused on minimizing this practice, and using only small incremental increases  $F_{iO_2}$  when indicated.

### ***Treatment of apnea***

Infants at risk for ROP often desaturate when apneic. Although stimulation of effective breathing typically corrects the transient hypoxia, the initial response of many providers is to increase the patient's  $F_{iO_2}$ . Not only is increasing the  $F_{iO_2}$  typically ineffective as an initial intervention, it places the infant at risk for an "overdose" of oxygen once respirations are reestablished. This problem can be addressed by education and modification of nursing protocols focused on minimizing this practice, and using only small incremental increases in  $F_{iO_2}$  when indicated.

### ***Therapeutic use of hyperoxia***

Excess oxygen is given, at times, to intentionally cause hyperoxia for a specific therapeutic purpose. Many of these practices are of little benefit, and may risk significant hyperoxic injury.

**Initial transition after delivery** Some believe that it is better to give extra oxygen during the first hours after delivery to “enhance transition” or “help the baby recover” from a stressful delivery. There is no evidence that supports this practice. There is evidence that this is detrimental, especially in the preterm infant.<sup>13</sup> This practice should be abandoned.

**Pneumothorax** A 100% oxygen is sometimes used as a treatment for a nontension pneumothorax (“nitrogen washout”). This practice places a preterm infant at very high risk of significant and severe hyperoxia. Conservative management is often very effective.<sup>14,15</sup> This practice should be abandoned.

**Pulmonary hypertension (early)** Oxygen is a pulmonary vasodilator and can be beneficial in the management of persistent pulmonary hypertension of the newborn. Maintaining high oxygen saturation levels (>95%) in these infants incurs a significant risk of hyperoxic injury, however, including ROP. This practice should be restricted, and alternative treatment strategies should be used as indicated. Additionally, early pulmonary hypertension should be clearly distinguished from pulmonary hypertension that develops later in the hospital stay in infants with severe bronchopulmonary dysplasia. The infant’s retina may be mature in this latter circumstance, or at least past the stage of retinal development where higher oxygen saturations might be detrimental.<sup>16,17</sup>

### ***Staff ROP Education***

A major component of COMP-ROP is the educational program. Most health care providers want to provide high-quality clinical care. It was observed that many providers including physicians, nurses, and respiratory therapists had knowledge gaps concerning the pathophysiology of ROP, the physiologic impact of oxygen management practices, and the principles of oximetry. Further, NICU nursing staff and respiratory therapy staff commonly had the foundation of their training in adult medicine, providing a basic knowledge set about the risks and benefits of oxygen that is not fully applicable to premature infants. Oxygen was commonly perceived as a “safe drug” and high oxygen levels were thought to be physiologically beneficial.

The educational program consisted of a premade slide set that discussed the pathophysiology of ROP, risks and benefits of oxygen use in premature infants, and the limitations of pulse oximetry. The educational program also included a discussion of the targeted oxygen management practices described by Chow and coworkers<sup>1</sup> (avoiding hyperoxia and repeated episodes of hypoxia-hyperoxia).

A brief pretest and posttest was provided to determine if adequate knowledge transfer occurred with the educational program, with remedial action if gaps remained. It was suggested to centers that the educational program should be considered mandatory or at least heavily recommended for all NICU staff that manage oxygen, including physicians, nurse practitioners, nurses, and respiratory therapists. The compliance rate with completing the educational program was considered one of the process measures of the project.

### ***System Redesign***

As discussed elsewhere in this issue, system reengineering is more likely to achieve sustainable improvement than telling people to “be careful” or to “try harder.” The

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hyperoxia assessment and educational testing typically highlighted systems or processes for reengineering. To effect change in ROP outcomes, development of a structured approach to the use of oxygen and oximetry was emphasized. This process included developing standardized orders for oximeter settings and alarm limits, creating or modifying specific oxygen management nursing protocols, bedside signs, and the use of “oxygen management contracts.”

**Standardized oximeter alarm orders**

Centers were encouraged to develop center-specific oximeter alarm limits to use for all infants at risk for ROP. Two general approaches to use of alarm limits emerged. The alarm limit approach consisted of the alarm limits being placed at the precise borders of the acceptable saturation range (eg, lower alarm at 85%, upper alarm at 93%).<sup>18</sup> Alternatively, other centers preferred to use a targeting approach, which used wide alarm limits, with the staff titrating the inspired oxygen to keep the saturation level within a narrower limit (eg, alarm limits at 80% and 95%, with saturations targeted at 88%–92%). It was believed by some centers that the targeting approach resulted in fewer alarm events and hence fewer opportunities to overadjust the oxygen concentration.

The specific alarm limits and the specific approach (alarm or targeting) was determined by each center. The guiding principles were to use a strategy to minimize hyperoxia by avoidance of saturation levels above 95% when receiving supplemental oxygen and avoiding large fluctuations of the oxygen saturation levels into hyperoxic and hypoxic ranges. Development of standardized orders to reflect the center's chosen approach was recommended.

Further, emphasis was given to ongoing saturation trending as an important process measure to assess the effectiveness of the system redesign and educational interventions. Oxygen management is a complex task. The target saturations and alarm limits are the proverbial tip of the iceberg in oxygen management (**Fig. 4**). As Greenspan and Goldsmith<sup>19</sup> very importantly and astutely observed, “Providers need to understand that cumulative oxygen saturations over time represent a bell-shaped curve, and the role of the health care team is to minimize the tails in both directions.”

**Default oximeter alarm limits**

Many oximeters have a default high saturation alarm setting of 100%. These oximeters typically revert to this 100% default setting each time they are turned off and back on, adversely affecting compliance with the center's agreed on alarm settings. Fortunately, many oximeter default settings can be altered by hospital biomedical engineering personnel to comply with the center's desired alarm settings. This system-based intervention can dramatically increase compliance with desired alarm limits in many centers.

**Nursing protocols**

Commonly, nursing and respiratory therapy protocols required modifications to be consistent with the desired changes in oxygen management. These modifications commonly included specific details of responding to an oximeter alarm (eg, determine if it is real or motion artifact, observe for spontaneous recovery, assess for a loose probe, and so forth before adjusting the oxygen concentration). Guidelines were often provided on the magnitude of oxygen titration (eg, increase by 2%–5% and observe).

**Bedside signs**

Bedside signs were frequently used to reinforce desired oximeter alarm limits and the approach to titrating oxygen. Sample signs were provided for customization and



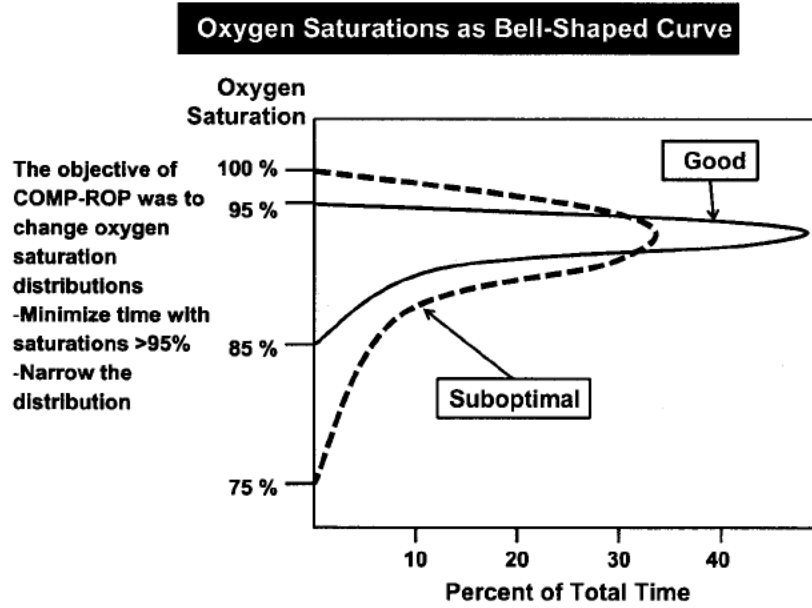


Fig. 4. Oxygen saturation trending curves. While the average oxygen saturation for each curve is similar, the wide distribution seen in the suboptimal curve should be avoided.

personalization at each center. These simple signs were often quite effective, especially in the initial stages of the program, when the oxygen management strategies were still new to the staff (Fig. 5).

**Oxygen management contract**

Chow and coworkers<sup>1</sup> described use of a written oxygen management agreement, or contract, that summarized the approach to oxygen and oximetry use, and was designed to be signed by all NICU staff members. The contract clarifies and reinforces

**Sample Bedside Oximeter Sign**

<b>OXIMETER ALARM LIMITS</b>
<b>85 to 95%</b>
<i>Before adjusting the oxygen:</i> <b><i>Is it real or artifact?</i></b>
<i>Check for excessive motion, waveform, probe placement</i>
<b><i>Adjust oxygen in small amounts (2 to 5%) to avoid overshooting</i></b>

Fig. 5. Sample bedside oximeter alarm sign. These were typically modified to reflect the center's preferred oximeter alarm limits. Additional personalization (animals, logos, catch-phrases) was often added to draw attention to the sign and reinforce oxygen management principles.

the goals of the program and provides an additional opportunity to discuss any disagreements with the practice changes. It can be used as a motivational tool, to clearly demonstrate the institution's and an individual's commitment to improve oxygen management. Use of the contract was well received in many NICUs, but some centers had staff that reacted negatively to this concept, and elected not to use the contract.

#### ***Ongoing Implementation***

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After the initial assessment and implementation, maintenance efforts were focused on compliance with the oxygen management guideline. Random safety auditing<sup>11</sup> of saturation trends and oximeter alarm settings were suggested process measures to evaluate the short-term efficacy of COMP-ROP implementation. The primary clinical outcome measure was severe ROP. If concerning trends in process or outcome measures were noted, serial plan-do-study-act cycles were to be initiated until the system provided the desired results.

#### **QUESTIONS AND BARRIERS ENCOUNTERED DURING THE IMPLEMENTATION OF COMP-ROP**

##### ***What About the Infants that have Oxygen Saturation Levels Greater than 95% in Room Air or in Very Low Concentrations of Supplemental Oxygen?***

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Significant hyperoxia in room air is unlikely. The difficulty in this scenario is that these infants continuously trigger the upper oximeter limit alarm; the alarm limit is then adjusted upward to prevent continuous triggering of the alarm. Unfortunately, many of these infants will require supplemental oxygen again, but the upper alarm limit (now functionally turned off) may not always be reset, creating an opportunity for hyperoxia. There is not a clear system solution to this problem.

##### ***What About Infants Whose Oxygen Saturation Level Rapidly Fluctuates and Triggers Alarms Continuously?***

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###### ***Respiratory issues***

After ruling out common causes of artifact (eg, soiled or loose probes, motion), one should assess for airway obstruction. Malposition of the endotracheal tube, secretions, and loose taping of the endotracheal tube are common problems. Infants on continuous positive airway pressure may have nasal obstruction or malposition of the prongs or the head. Any infant with marginal lung inflation may show substantial lability in oxygenation because of decreased functional residual capacity. Attention to these issues can minimize the variability of the oxygen saturation levels.

###### ***Oximeter issues***

Each brand of oximeter has slightly different methods of acquiring and sampling SpO<sub>2</sub> levels. These subtle differences can affect the lability of oxygen saturation levels. Increasing averaging time and use of alarm delays may both be useful in filtering out "nuisance alarms," but may result in a less sensitive alarm system. The optimal use of these techniques is not known.<sup>20-22</sup>

#### **SUMMARY**

Comprehensive oxygen management, focused on avoiding hyperoxia and repeated episodes of hypoxia-hyperoxia in very low birth weight infants, has been successfully used for the reduction of ROP. Building on this experience, the COMP-ROP quality improvement initiative was developed to facilitate the spread and refinement of these techniques. The initiative focused on staff education, evaluation and redesign of the processes, and practices involving oxygen use. Monitoring of the effectiveness of

the system changes was supported through audits of clinical practice changes, use of oxygen saturation trending data, and the incidence of ROP.

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**From:** Kristi Watterberg  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: concept and protocol (Out of the office)  
**Date:** Thursday, June 10, 2010 1:51:55 PM

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I will be out of the office from June 4 - June 20, without email access. If you need assistance before then, please contact Heather Shinn at 505-272-0180, or Mary Merchant at 505-272-8609. (HShinn@salud.unm.edu or Mmerchant@salud.unm.edu).

>>> "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> 06/10/10 11:51 >>>

I am also trying to see if Seetha/Krisa can join at the beginning

From: Poindexter, Brenda B [mailto:bpoindex@iupui.edu]  
Sent: Thursday, June 10, 2010 1:46 PM  
To: Poindexter, Brenda B; Higgins, Rosemary (NIH/NICHD) [E]; 'richard.ehrenkranz@yale.edu'; 'kwatterberg@salud.unm.edu'; 'ifrantz@tuftsmedicalcenter.org'; 'jon.e.tyson@uth.tmc.edu'; 'kurt.schibler@cchmc.org'; 'Roger.Faix@hsc.utah.edu'; 'Wallace, Dennis'; 'Das, Abhik'  
Cc: 'Webb, Robin E.'; Archer, Stephanie (NIH/NICHD) [E]; 'Zaterka-Baxter, Kristin'  
Subject: RE: concept and protocol

Kristi is out of the office until June 20th. I am happy to review the aEEG protocol instead - as long as no one thinks this is a conflict since I'm on the subcommittee. I am not one of the authors on the study, so I think it will be okay. Let me know if you think otherwise. Brenda

From: Poindexter, Brenda B  
Sent: Thursday, June 10, 2010 1:05 PM  
To: 'Higgins, Rosemary (NIH/NICHD) [E]'; richard.ehrenkranz@yale.edu; kwatterberg@salud.unm.edu; ifrantz@tuftsmedicalcenter.org; jon.e.tyson@uth.tmc.edu; kurt.schibler@cchmc.org; Roger.Faix@hsc.utah.edu; Wallace, Dennis; Das, Abhik  
Cc: Webb, Robin E.; Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin  
Subject: RE: concept and protocol

All,

Our next protocol review conference call is on Monday from 11 am - 1 pm EST. I am attaching both of the protocols that we will be discussing. Kurt and Ivan will be the primary reviewers of the ROP genomics protocol and I need to assign reviewers for the aEEG protocol. Since Richard, Jon, Kurt, and I are on the optimizing cooling subcommittee, I'd like to ask Roger and Kristi if they could review this study. Sorry for the late notice - I'm afraid I let this one slip through without assigning reviewers. Talk to you all on Monday - Brenda

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
Sent: Monday, May 10, 2010 3:54 PM  
To: Poindexter, Brenda B; richard.ehrenkranz@yale.edu; kwatterberg@salud.unm.edu; ifrantz@tuftsmedicalcenter.org; jon.e.tyson@uth.tmc.edu; kurt.schibler@cchmc.org; Roger.Faix@hsc.utah.edu; Wallace, Dennis; Das, Abhik  
Cc: Webb, Robin E.; Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin  
Subject: RE: concept and protocol

We will need a second call for the attached protocol (or one 2 hour call)

Rose

---

From: Poindexter, Brenda B [mailto:bpoindex@iupui.edu]  
Sent: Wednesday, May 05, 2010 2:06 PM

To: richard.ehrenkranz@yale.edu; kwatterberg@salud.unm.edu; ifrantz@tuftsmedicalcenter.org;  
jon.e.tyson@uth.tmc.edu; kurt.schibler@cchmc.org; Roger.Faix@hsc.utah.edu; Wallace, Dennis; Das, Abhik  
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Webb, Robin E.; Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter,  
Kristin  
Subject: FW: concept and protocol

Protocol Review Subcommittee-

Robin will be setting up a call to discuss the attached protocol - depending on availability we could even consider trying to meet in DC during the upcoming meeting. Kurt, given your genomics expertise I'd like to ask you to review this one (promise you'll get a break next time-I know you just reviewed the other SUPPORT secondary as well) and would also like to ask Ivan to review. Let me know if either of you have any conflicts. Thanks, Brenda

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
Sent: Wednesday, May 05, 2010 12:15 PM  
To: Poindexter, Brenda B; Robin E. 'Webb  
Cc: Archer, Stephanie (NIH/NICHD) [E]; Das, Abhik; kristin zaterka  
Subject: FW: concept and protocol

Robin-

Can you set up a protocol review call?  
Brenda - can you assign reviewers?

Thanks

Rose

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network

---

From: Michael Cotten [mailto:cotte010@mc.duke.edu]  
Sent: Saturday, May 01, 2010 5:45 PM  
To: Higgins, Rosemary (NIH/NICHD) [E]  
Cc: 'goldb008@mc.duke.edu'; John  
Subject: Re: concept and protocol

Hi Rose...

here's the protocol submission for the SUPPORT secondary to test for associations between genetic variants in angiogenesis and oxygen response pathway genes and ROP, w/ assessment of interactions with the oxygen sat target.

thanks

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: 919-681-6024  
fax: 919-681-6065

email: cotte010@mc.duke.edu  
"Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>

05/01/2010 09:14 AM

To

"cotte010@mc.duke.edu" <cotte010@mc.duke.edu>

cc

"goldb008@mc.duke.edu" <goldb008@mc.duke.edu>

Subject

Re: concept and protocol

Mike

We are currently tracking the neuroimaging cohort (approx 560). There is a protocol to follow the breathing outcomes infants, but this requires revisions and needs to go back to protocol review. This also would exclude the deaths from the study (slightly over 200).

Hope this helps

Rose

---

From: Michael Cotten <cotte010@mc.duke.edu>  
To: Higgins, Rosemary (NIH/NICHD) [E]  
Sent: Sat May 01 01:55:41 2010  
Subject: Re: concept and protocol

Hi Rose..in finalizing the SUPPORT secondary to submit, I've come to realize that the follow up is complete for the study kids....except maybe about 100 still missing....per the montly report....is there longer term followup in the works for the SUPPORT cohort?

I've asked John Dagle whether or not they are sending out buccal swabs to homes for samples from kids and if they've had success...otherwise..w/o further followup for the SUPPORT kids, I don't think we'll be able to do the oxygen-genomics proposal....

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: 919-681-6024  
fax: 919-681-6065  
email: cotte010@mc.duke.edu  
"Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>

04/05/2010 04:18 PM

To

"Michael Cotten" <cotte010@mc.duke.edu>

cc

"Archer, Stephanie (NIH/NICHD) [E]" <archerst@mail.nih.gov>, "Ron Goldberg (goldb008@mc.duke.edu)" <goldb008@mc.duke.edu>

Subject

concept and protocol

Mike

We have the following concept you presented which is overdue for a protocol submission. If we do not receive a protocol by May 1, we will remove this from the pending list:

SUPPORT DNA collection for ROP risk

We also have the following protocol which is overdue for a protocol resubmission. IF we do not receive a revision by June 1, we will remove it from the list:

Prospective DNA Repository

Thanks

Rose

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network  
Pregnancy and Perinatology Branch  
Center for Developmental Biology and Perinatal Medicine  
Eunice Kennedy Shriver National Institute of Child Health and Human Development  
National Institutes of Health  
6100 Executive Blvd., Room 4B03  
MSC 7510  
Bethesda, MD 20892  
For overnight delivery use Rockville, MD 20852  
301-496-5575  
301-496-3790 (FAX)  
higginsr@mail.nih.gov

**From:** [Bell, Edward](#)  
**To:** [Gantz, Marie](#); [Das, Abhik](#)  
**Cc:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Wally Carlo](#)  
**Subject:** RE: SUPPORT Questions  
**Date:** Thursday, June 10, 2010 1:07:44 PM

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Thank you

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**From:** Gantz, Marie [mailto:[mgantz@rti.org](mailto:mgantz@rti.org)]  
**Sent:** Thursday, June 10, 2010 12:05 PM  
**To:** Das, Abhik; Bell, Edward  
**Cc:** Rosemary Higgins; Wally Carlo  
**Subject:** RE: SUPPORT Questions

To answer the second question, yes, the figure represents the distributions, by treatment group, of the median saturation for each patient. I agree that this does not fully represent the overall distribution of saturation values for each infant. We have not yet looked at these distributions in depth, but we are about to begin a more extensive analysis that will look at patients' SpO2 distributions and their relationship to patient outcomes. Wally Carlo is heading up this effort, and I believe the intention is to submit the results for presentation at PAS next year.

Marie

Marie Gantz, Ph.D.  
Research Statistician  
RTI International  
[mgantz@rti.org](mailto:mgantz@rti.org)  
828-251-6255

---

**From:** Das, Abhik  
**Sent:** Thursday, June 10, 2010 12:57 PM  
**To:** 'Bell, Edward'; Gantz, Marie  
**Cc:** Rosemary Higgins; Wally Carlo  
**Subject:** RE: SUPPORT Questions

I will let Marie respond to the 2<sup>nd</sup> item, but since the trial randomized multiples to the same treatment arm, and randomization was stratified by site and GA group, these features (sometimes called 'design variables') needed to be adjusted for in the analysis.

Thanks

Abhik

---

**From:** Bell, Edward [mailto:[edward-bell@uiowa.edu](mailto:edward-bell@uiowa.edu)]  
**Sent:** Thursday, June 10, 2010 12:46 PM  
**To:** Gantz, Marie  
**Cc:** Das, Abhik; Rosemary Higgins; Wally Carlo  
**Subject:** FW: SUPPORT Questions

Marie,

Can you help with the two questions below from Dan Ellsbury. Dan is the lead investigator for our satellite site at Mercy Hospital.

Thanks,  
Ed

---

**From:** Dan Ellsbury [mailto:(b) (6)]  
**Sent:** Thursday, June 10, 2010 10:12 AM  
**To:** Bell, Edward  
**Subject:** SUPPORT Questions

Ed,  
As we discussed, I have two questions on the SUPPORT trial (Oxygen Targeting)

1. In the major outcomes table (table 2) an adjusted relative risk was reported. Why was this adjusted, and how was it done? The baseline characteristics shown in table 1 were not different, so I'm unclear as to why this was done.
2. Figure 3. Actual Median Oxygen Saturation with Oxygen Supplementation in the Two Treatment Groups. What is being represented on this figure? Is it showing the distribution of median saturation for each patient? The median, while useful, does not represent the distribution of saturation values for each patient, which is vitally important information. Was a similar figure created showing the distribution of saturations for each group?

Any help you can provide to clarify these points would be greatly appreciated.

Thanks.

--

-Dan  
Dan Ellsbury MD  
Director, Continuous Quality Improvement  
Center for Research, Education, and Quality  
Pediatrix Medical Group, Inc  
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Phone: (515)-262-3916

e-Fax: (888)-872-4921

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**From:** [Zaterka-Baxter, Kristin](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Das, Abhik](#)  
**Subject:** Drafted SUPPORT subcom minutes  
**Date:** Monday, June 07, 2010 12:26:42 PM  
**Attachments:** [Support\\_Secondary\\_Analyses20100607.docx](#)

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Hi,

Please review and let me know whether these shod be posted to the website or not.

Thanks,

Kris

---

**From:** [Zaterka-Baxter, Kristin \[mailto:kzaterka@rti.org\]](mailto:kzaterka@rti.org)  
**Sent:** Monday, June 07, 2010 8:03 AM  
**To:** Wally Carlo, M.D.  
**Subject:** RE: SUPPORT data queries

Hi Wally,

Sorry but I am a bit confused, I thought this call was about the Support queries?

Thanks,

Kris

---

**From:** [Wally Carlo, M.D. \[mailto:WCarlo@peds.uab.edu\]](mailto:WCarlo@peds.uab.edu)  
**Sent:** Monday, June 07, 2010 8:59 AM  
**To:** [Zaterka-Baxter, Kristin](mailto:Zaterka-Baxter, Kristin); [alaptook@WIHRI.org](mailto:alaptook@WIHRI.org); [Bradley Yoder](#); [Das, Abhik](#); [Gantz, Marie](#); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [kurt.schibler@cchmc.org](mailto:kurt.schibler@cchmc.org); [mcw3@cwru.edu](mailto:mcw3@cwru.edu); [nancy newman](#); [nfiner@ucsd.edu](mailto:nfiner@ucsd.edu); [Roger Faix](#); [Wallace, Dennis](#); [wrich@ucsd.edu](mailto:wrich@ucsd.edu)  
**Cc:** [sharon.gough@hsc.utah.edu](mailto:sharon.gough@hsc.utah.edu); [Archer, Stephanie \(NIH/NICHD\) \[E\]](#); [Brenda Vecchio](#); [Cunningham, Meg](#); [Martinez, Fernando](#); [Huitema, Carolyn Petrie](#)  
**Subject:** RE: SUPPORT data queries

Kristin:

It would be good to have all submitted protocols available because there is a lot of overlap. Could you send all the others.

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: 205 266 4004

---

**From:** Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]  
**Sent:** Monday, June 07, 2010 7:52 AM  
**To:** alaptook@WIHRI.org; Bradley Yoder; Das, Abhik; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; kurt.schibler@cchmc.org; mcw3@cwru.edu; nancy newman; nfiner@ucsd.edu; Roger Faix; Wallace, Dennis; Wally Carlo, M.D.; wrich@ucsd.edu  
**Cc:** sharon.gough@hsc.utah.edu; Archer, Stephanie (NIH/NICHD) [E]; Brenda Vecchio; Cunningham, Meg; Martinez, Fernando; Huitema, Carolyn Petrie  
**Subject:** FW: SUPPORT data queries

Dear all,  
Reminder for the call this morning at 10:00 AM EST

---

**From:** Webb, Robin E.  
**Sent:** Tuesday, May 25, 2010 3:29 PM  
**To:** Webb, Robin E.; 'Abbot Laptook (alaptook@WIHRI.org)'; 'Bradley Yoder'; Das, Abhik; Gantz, Marie; 'Higgins, Rosemary (NIH/NICHD) [E]'; 'kurt.schibler@cchmc.org'; 'mcw3@cwru.edu'; 'nancy newman'; 'nfiner@ucsd.edu'; 'Roger.Faix@hsc.utah.edu'; Wallace, Dennis; 'Wally Carlo, M.D.'; 'wrich@ucsd.edu'  
**Cc:** '(sharon.gough@hsc.utah.edu)'; 'Archer, Stephanie (NIH/NICHD) [E]'; 'Brenda Vecchio'; Cunningham, Meg; 'fmartinez@ucsd.edu'; Huitema, Carolyn Petrie; Zaterka-Baxter, Kristin; 'Starlett Williams'; Carolyn.Grier@UHhospitals.org  
**Subject:** RE: SUPPORT data queries

The call to discuss the SUPPORT data queries has been scheduled for:

**Monday, 6/7**  
**10:00am ET**

Dial:  
**Within the USA**  
866-675-(b) (6)  
or

**Outside the USA**  
1-203-310-(b) (6)

Then, enter Participant Passcode:  
(b) (6)

## **SUPPORT Subcommittee Conference Call – 06/07/2010 Secondary Analyses Proposals**

**Participants:** Neil Finer, Rosemary Higgins, Marie Gantz, Abbott Laptok, Wally Carlo, Roger Faix, Kurt Schibler, Abhik Das, Nancy Newman, Stephanie Archer, Kris Zaterka-Baxter

---

***Brion/LeVan: Changes in Therapy and Outcomes Associated with the SUPPORT Trial Subcommittee Consensus: Postponed; the subcommittee is enthusiastic about the concept but felt it was about 3 years premature. They suggested the protocol remain in holding until more data becomes available (including the follow up outcomes) to better suit a phase IV/Quality Improvement cycle data analysis. The primary concern was lack of available follow up data and possible inability to answer the primary question of practice change at this point.***

Additional comments: Pre/Post GDB/Support review. Before samples size GDB 2002 – 2004; after size is GDB from May 1, 2010 thru April/May 2011 (1 yr observational). The rationale of the 2 year pre and 1 year post sampling is likely because of the time constraint to release analysis and it was felt the sample size would be adequate. In theory using as many post samples as possible in this time period compared to a larger pre sampling period is appropriate (the longer and bigger pre period the better the power may be). The committee continued to question whether the pre-sampling period of one year was a long enough sampling period. Other concerns were the lack of pulse oximetry tracking in the analysis plan; the proposal should have all of the Support interventions if the plan is to include all the Support outcomes in the secondary analyses.

When this moves forward all authors would be included (all authors who have contributed papers).

***Carlo: Retinopathy of prematurity and actual oxygen saturations: A secondary protocol of the SUPPORT Trial***

***Subcommittee Consensus: This protocol can move forward and Dr. Gantz can begin the requested analysis. Dr. Carlo will create tables and figure as requested by the subcommittee. This should be a 1<sup>st</sup> priority for next PAS (for Support trial secondary analyses). In addition, the pre-specified Support secondary's should take priority over all other GDB or in coming secondary analyses. Dr. Higgins will discuss with RTI (Dr. Das) off line to prioritize RTI workload.***

Additional comments: Dr. Finer felt this proposal is essentially a follow up of the Support trial primary analysis rather than a secondary analyses. Primary interested in looking saturations and association with ROP and death (because it's the largest effect size); to look at which babies would have been predisposed and developed ROP. Dr. Finer suggested the need to look at O2 profiles to determine significant ROP and death/ROP and the need to do this sooner rather than later as part of the primary trial analysis. Dr. Higgins agreed because death is a primary. Dr. Higgins said it would be helpful for Dr. Carlo to provide tables and figures (about what the data could show us). Dr. Carlo agreed. Dr. Finer has asked Marie to run preliminary analysis for Dr. Carlo/Finer, then the committee, to review asap. It was suggested that it might be better to express data in percentiles (duration) in O2, then outcome. Also, exposure in terms of DOL and

exposure duration. Whether to begin analysis of O2 in the 1<sup>st</sup> 7 days, then to 14 day, then up to 34 weeks PCA, then thru threshold Dz, then thru FU, that decision is pending and requires more discussion.

Dr. Gantz said this analysis will be exploratory in nature; ideally we will have our hypotheses going forward (increase O2 is associated with increased ROP) but we will also be looking at what the data will tell us; there will also be multivariate analyses. It was suggested to also consider FiO2 in the expanded analysis. We want to know whether and to what extent FiO2 could be a causal factor (whole body oxygen) versus saturations in ROP/Death outcomes.

***Smith/Cotton: Oxygen saturations and risk of mortality and morbidity in the SUPPORT trial. Subcommittee Consensus: Rejected; there is too much overlap with primary study.***

***Lenfestey/Cotton: Center Effects within the SUPPORT Trial Subcommittee Consensus: Rejected; the subcommittee does not want to encourage subset analysis design due to the concerns discussed unless there is some type of method to explain potential differences rather than just identify potential differences.***

Additional comments: This is a proposal regarding center affects (delivery room approach); the subcommittee felt the fundamental issue is that we did a multi center trial to account for these practices and the concern of identifying/disseminating information that may differ from the primary trial based on only subgroup analyses (similar to concerns about the MRI secondary previously voices) and that in a subset analysis, the randomization design does not apply.

Dr. Carlo suggested a revision independent of the baseline. Do a regression analysis of what the outcome is in the control group versus the intervention group by centers; this would explain whether effect is the same regardless of what the baseline is. We would need to only include centers who enrolled a minimum number of infants. Dr Das said we may find some practical differences that we did not capture in the initial analysis but that we do tend to over analyze center differences.

**Additional overall comments:**

Dr. Finers' secondary proposal to compare all support infants to all GDB infants enrolled at the time to compare ANS exposure is in progress and a full protocol proposal will be submitted to Dr. Higgins shortly for review, then to the committee.

The next Subcommittee conf call we be scheduled in the next month or so.

**From:** Zaterka-Baxter, Kristin  
**To:** [alaptook@WIHRI.org](mailto:alaptook@WIHRI.org); Bradley Yoder; Das, Abhik; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; [kurt.schibler@cchmc.org](mailto:kurt.schibler@cchmc.org); [mcw3@cwru.edu](mailto:mcw3@cwru.edu); nancy newman; [nfiner@ucsd.edu](mailto:nfiner@ucsd.edu); Roger Faix; Wallace, Dennis; Wally Carlo, M.D.; [wrich@ucsd.edu](mailto:wrich@ucsd.edu)  
**Cc:** [sharon.gough@hsc.utah.edu](mailto:sharon.gough@hsc.utah.edu); Archer, Stephanie (NIH/NICHD) [E]; Brenda Vecchio; Cunningham, Meg; Martinez, Fernando; Huitema, Carolyn Petrie  
**Subject:** FW: SUPPORT data queries  
**Date:** Monday, June 07, 2010 8:52:11 AM  
**Attachments:** [cpap\\_center\\_and\\_learning\\_effects\\_4-21-10final.docx](#)  
[oxygen-SUPPORT\\_secondary\\_4-21-10final.docx](#)

---

Dear all,  
Reminder for the call this morning at 10:00 AM EST

---

**From:** Webb, Robin E.  
**Sent:** Tuesday, May 25, 2010 3:29 PM  
**To:** Webb, Robin E.; 'Abbot Laptok ([alaptook@WIHRI.org](mailto:alaptook@WIHRI.org))'; 'Bradley Yoder'; Das, Abhik; Gantz, Marie; 'Higgins, Rosemary (NIH/NICHD) [E]'; 'kurt.schibler@cchmc.org'; 'mcw3@cwru.edu'; 'nancy newman'; 'nfiner@ucsd.edu'; 'Roger.Faix@hsc.utah.edu'; Wallace, Dennis; 'Wally Carlo, M.D.'; 'wrich@ucsd.edu'  
**Cc:** '([sharon.gough@hsc.utah.edu](mailto:sharon.gough@hsc.utah.edu))'; 'Archer, Stephanie (NIH/NICHD) [E]'; 'Brenda Vecchio'; Cunningham, Meg; 'fmartinez@ucsd.edu'; Huitema, Carolyn Petrie; Zaterka-Baxter, Kristin; 'Starlett Williams'; Carolyn.Grier@UHhospitals.org  
**Subject:** RE: SUPPORT data queries

The call to discuss the SUPPORT data queries has been scheduled for:

**Monday, 6/7**  
**10:00am ET**

Dial:  
**Within the USA**  
866-675-(b)  
or

**Outside the USA**  
1-203-310-(b)

Then, enter Participant Passcode:  
(b) (6)



## Center Effects within the SUPPORT Trial

Lenfestey, Cotten, Smith, Tanaka, Laughon, Goldberg, RTI, SUPPORT subcommittee (Finer)

### Abstract

The NICHD Neonatal Research Network's SUPPORT trial tested initiation of delivery room NCPAP followed by a mechanical ventilation algorithm intended to accelerate extubation if intubation was needed against use of delivery room intubation and administration of surfactant, followed by a mechanical ventilation algorithm that was less permissive of extubation. Variations in center expertise in interventions tested in clinical trials can impact overall trial outcome, as noted in the Neonatal HIFI trial.<sup>1</sup> When clinicians in the hundreds of centers caring for extremely low gestational age infants consider the results of the SUPPORT trial, they are likely to ask two questions: 1) If my centers' rate of survival free of chronic lung disease among infants of a similar demographic as the study is high, and the standard at my center is early intubation and surfactant, should I change practice and do as well and maybe better with a delivery room CPAP strategy? and 2) If I adopt NCPAP, will the first infants I try it on have as good a chance at success as the 40<sup>th</sup> or 50<sup>th</sup>? Data collected during the SUPPORT trial will be useful to address these questions. Prior to and throughout the period of enrollment in the SUPPORT trial, centers which had a standard approach of intubation and administering surfactant early in the delivery room or the first postnatal hour prior to study participation continued to have among the highest survival and lowest rates of chronic lung disease in the Network. It is unknown whether effects related to delivery room and respiratory support approach noted in the overall trial were consistently noted among the infants enrolled in the high performing centers, or if the centers with prior adoption of delivery room NCPAP saw a consistent outcome in the infants randomized to NCPAP compared to sites adopting this practice for the first time in the clinical trial. Because study randomization was stratified by site, and the 4 centers with high performance (Brown, UAB, Duke, and Miami) enrolled over 300 infants, a carefully done subgroup analysis to assess whether the effect noted in these 4 benchmark centers was consistent with overall trial results is feasible. Assessment of whether or not outcome of infants in the NCPAP arm is associated with center experience with delivery room NCPAP can be addressed with analysis of clusters of infants enrolled throughout the study at each centers, i.e., did infants enrolled in the NCPAP arm early in the study fare the same as infants enrolled later in the study at that center?

**Purpose:** The overall purpose of this proposal is to assess how adopting a new delivery room approach influenced survival and pulmonary outcomes, and whether adopting the new approach was equally successful early and late during the clinical trial.

**Aim 1:** Assess whether SUPPORT trial overall results were consistent with results in the 300+ subjects enrolled and randomized at centers with consistently good survival and low rates of chronic lung disease (Brown, UAB, Duke, Miami)

**Aim 2.** Assess whether there was a center-specific NCPAP training effect among infants enrolled in the NCPAP arm of the SUPPORT trial at sites which had not used delivery room NCPAP as usual care prior to the trial .

**Statement of the Problem:** Clinicians caring for extremely low gestational age newborn (ELGAN) infants have adopted strategies for initial respiratory support (use of surfactant after endotracheal intubation or initial use of continuous positive airway pressure and later rescue intubation and surfactant treatment) and ventilator management based on available evidence from high quality clinical trials, and the less validated but compelling single center reports and

“experience and reason.” Using this combination, there is extreme site variation in the rate of survival free of BPD at Network centers.<sup>2</sup> The NICHD neonatal Research network SUPPORT trial tested the hypothesis of whether or not initial NCPAP and subsequent stringent ventilator management parameters would improve survival free of bronchopulmonary dysplasia (BPD) compared with initial intubation with surfactant administration and more conservative ventilator management. Before initiation of the study, and throughout the study period, several centers, all of whom primarily used initial intubation and surfactant administration prior to the study, consistently had the highest survival free of BPD. It is not known whether the trend in the primary outcome noted in the overall trial was noted in the cohort of subjects enrolled and randomized at the benchmark centers that used initial intubation and surfactant for ELGANs. This query will inform potential adopters of NCPAP regarding the potential clinical and economic impact of adopting NCPAP in the delivery room in sites with high rates of survival free of BPD. It is also not known whether infants enrolled at sites which had not made initial NCPAP standard practice prior to the study start-up were as successful maintaining infants randomized to NCPAP on NCPAP throughout the first 14 postnatal days at the start of study enrollment as at the end of enrollment. This query would be important to inform new adopters of the likelihood of a learning curve for adopting NCPAP in the delivery room.

### ***Aims 1 and 2:***

Study Design: Retrospective post hoc subgroup analysis (Aim 1) and retrospective cohort study (Aim 2).

### Study population:

#### *Inclusion criteria*

1. Infants in enrolled in the SUPPORT trial

#### *Exclusion criteria*

1. None

### Study intervention:

There is no specific study intervention. This will be analysis of existing data.

### Primary and Secondary Outcomes:

Aim 1:

Primary outcome: death or BPD

Secondary outcomes: death or BPD separately.

Aim 2:

Primary Outcome: death or intubated during the first 14 postnatal days.

Secondary Outcome: death or BPD

### Statistical Plans:

#### *Outcome variables*

1. Death or BPD

2. Death
3. BPD
4. Completion of 14 days of NCPAP

*Predictor variables for multivariable analyses*

1. gestational age
2. gender
3. race
4. antenatal steroids
5. multiple birth
6. small for gestational age (SGA)

**Targeted Analyses**

**Aim 1. Testing results in 4 benchmark centers**

Consistent with recently published subgroup analysis guidelines<sup>3</sup>, We will perform two post-hoc subgroup analyses with 2 levels comparing heterogeneity of odd ratios for the primary outcomes between group 1 defined as the 4 Low BPD and High survival sites vs. Group 2, the 11 remaining centers (Cincinnati is excluded as it was a training site for NCPAP in the delivery room). We also will assess whether or not the primary outcome measured among infants enrolled at the 4 Low BPD and high survival sites before the study is homogenous with the overall outcome of the clinical trial using methodologies testing for homogeneity of study results for subgroup analysis. These analyses will involve statistical tests for interaction between the center level variable and the outcome. We plan to calculate point estimates and confidence intervals for effect size of the center level variable using the Breslow-Day test for heterogeneity of odds ratios. We will use multivariable logistic regression to determine if group has an effect on outcome. Finally we will correct p-values for multiple comparisons using the equation  $1-(1-p)^K$  where p is our accepted alpha error and K is the number of comparisons<sup>3</sup>.

**Aim 2. Testing for consistency of successful NCPAP maintenance throughout enrollment.**

We will perform two exploratory visual analyses and more traditional exploratory multivariable logistic regression models

**Visual Analysis #1.** Each center would have enrollment in the CPAP arm (X axis) and primary outcome (Y axis) plotted in two dimensions. The Y axis score of 0 for the outcome, survival without intubation in the first 14 postnatal days and a score of 1 for death or intubation within the first 14 postnatal days. The X axis would be the order of enrollment at each site. The first baby enrolled at a site would be plotted at the X axis point of '1', the second baby at '2', and so on. This would be the equivalent of a multivariable logistic regression predicting the primary outcome for NCPAP arm infants testing whether order enrolled was associated with outcome.

**Visual Analysis #2,** using each center's cohort randomized to NCPAP, would plot by month of study enrollment, to assess whether the course of the study use of NCPAP (and familiarity with the procedure overall) was associated with outcome among the NCPAP enrolled infants. Again, the score "0" would be assigned if the infant survived the first 14 postnatal days and was not intubated, and "1" would be assigned if the baby was intubated or died in the first 14 postnatal days. For example, the X axis would have a block for September 2008, 0's and 1's would be plotted, within each month of enrollment block.

These 2 visual models would be the equivalent of a logistic regression predicting the primary outcome for NCPAP arm infants testing whether order enrolled or time during the study was associated with outcome.

We will perform two exploratory analyses using multivariable logistic regression using infants assigned to the NCPAP arm to determine if centers became more successful at maintaining subjects on NCPAP as they gained experience. The outcome for these two analyses is the composite of intubation during the first 14 postnatal days or death. Analysis 1#: Each infant would be assigned a variable based on the order of enrollment at their respective site. We will then perform a multivariable logistic regression to determine magnitude of enrollment order effect, with the additional predictor variables as listed (GA, gender, race, antenatal steroids, multiple birth, and SGA)

Analysis 2: Each infant would be assigned a variable based on the study month of enrollment at their respective site. We will then perform a multivariable logistic regression to determine magnitude of enrollment order effect on the composite outcome of intubation during the first 14 postnatal days or death, with the additional predictor variables as listed (GA, gender, race, antenatal steroids, multiple birth, and SGA).

## References

1. Bryan AC, Froese AB. Reflections on the HIFI trial. *Pediatrics*. 1991;87:565-567.
2. Fanaroff, A.A., et al., Trends in neonatal morbidity and mortality for very low birthweight infants. *Am J Obstet Gynecol*. 2007;196:e1-8.
3. Lagakos SW. The challenge of subgroup analyses--reporting without distorting. *N Engl J Med*. 2006;354:1667-1669.

## **NICHD Neonatal Research Network Protocol Outline**

Title: Oxygen saturations and risk of mortality and morbidity in the SUPPORT trial.

Authors:

P. Brian Smith MD MPH MHS

C. Michael Cotten MD MHS

Ronald N. Goldberg MD

RTI and SUPPORT Subcommittee (Carlo)

for the Eunice Kennedy Shriver NICHD Neonatal Research Network

### **A. Statement of the Problem**

Previous studies demonstrated increased rates of mortality, ROP, BPD, PVL and CP among infants with higher exposures to oxygen.<sup>1-6</sup> The SUPPORT study demonstrated lower rates of severe ROP in the lower saturation group but higher rates of mortality. No difference in severe ROP/death was observed between the two groups. Because many infants in the low saturation group spent time with saturations >89% and many infants in the high saturation group spent time with saturations <91%, there was a great deal of overlap in oxygen saturations between the two groups.

The SUPPORT study's finding that higher oxygen saturation limits are associated with lower mortality but higher rates of severe ROP leaves uncertainty for clinicians. The rationale for this proposal is that evidence for determining the safest range for oxygen saturation for premature infants is conflicting.<sup>5,6</sup> In the protocol described below, we will be able to examine the association between the actual recorded oxygen saturation with the clinical outcomes of the infants. *We propose to examine the incidence of mortality and morbidities using actual oxygen saturations as a predictor for infants enrolled in the SUPPORT trial.*

### **B. Hypothesis**

*Hypothesis:* Higher oxygen saturations are associated with an increased risk of death, ROP, BPD, death/ROP, or death/BPD for infants receiving supplemental oxygen.

### **C. Specific Aim**

*Specific Aim:* Determine whether oxygen saturations for infants receiving supplemental oxygen are related to death, ROP, BPD, death/ROP, or death/BPD.

### **D. Method/ Procedures**

1. Study Design: Retrospective cohort study.
2. Study population:
  - Inclusion criteria*
    1. 1316 infants in enrolled in the SUPPORT trial

*Exclusion criteria*

1. None
  
3. Study intervention:  
There is no specific study intervention. This will be analysis of existing data.
  
4. Primary and Secondary Outcomes:  
Primary outcome: Death  
Secondary outcomes: ROP, BPD, death/ROP, death/BPD
  
5. Statistical Plans:  
*Outcome variables*
  1. death
  2. ROP
  3. BPD
  4. death/ROP
  5. death/BPD

*Predictor variables*

Oxygen saturation for each infant while receiving supplemental oxygen

*Confounding variables*

1. saturation group (low vs. high)
2. gestational age
3. birth weight
4. sex
5. singleton vs. multiple birth

*Observations for analysis*

Observations recorded when the infant's SaO<sub>2</sub> could not be altered will not be used in the analysis.

1. Infant receiving 21% FiO<sub>2</sub> with SaO<sub>2</sub> > than upper target limit range
2. Infant receiving 100% FiO<sub>2</sub> with SaO<sub>2</sub> < than lower target limit range

*Weighting of observations*

Although the number of observations varied by subject in the dataset, each infant will contribute equally to the overall statistical calculations.

*Bivariable analysis*

We will compare mean oxygen saturations for infants that died vs. those that lived using the Student's t-test. The comparison will be repeated for each of the secondary outcomes: ROP, BPD, death/ROP, and death/BPD.

*Multivariable analysis*

We will build a multivariable logistic regression model to determine the relationship between outcome variables and mean oxygen saturation for each infant (continuous variable) controlling for saturation group (low vs. high), mean FiO<sub>2</sub> (continuous variable), gestational age, birth weight, sex, and singleton birth.

## E. References

1. Jobe, A.H. and Bancalari, E., Bronchopulmonary dysplasia. *Am J Respir Crit Care Med.* 163, 1723-9(2001).
2. Flynn, J.T., Bancalari, E., Snyder, E.S., Goldberg, R.N., Feuer, W., Cassady, J., Schiffman, J., Feldman, H.I., Bachynski, B., Buckley, E., and et al., A cohort study of transcutaneous oxygen tension and the incidence and severity of retinopathy of prematurity. *N Engl J Med.* 326, 1050-4(1992).
3. Saugstad, O.D., Bronchopulmonary dysplasia-oxidative stress and antioxidants. *Semin Neonatol.* 8, 39-49(2003).
4. Haynes, R.L., Baud, O., Li, J., Kinney, H.C., Volpe, J.J., and Folkerth, D.R., Oxidative and nitrative injury in periventricular leukomalacia: a review. *Brain Pathol.* 15, 225-33(2005).
5. Anderson, C.G., Benitz, W.E., and Madan, A., Retinopathy of prematurity and pulse oximetry: a national survey of recent practices. *J Perinatol.* 24, 164-8(2004).
6. Tin, W., Milligan, D.W., Pennefather, P., and Hey, E., Pulse oximetry, severe retinopathy, and outcome at one year in babies of less than 28 weeks gestation. *Arch Dis Child Fetal Neonatal Ed.* 84, F106-10(2001).

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Subject:** RE: PEDIATRICS: Decision Letter on MS# 2009-3353.R2  
**Date:** Wednesday, May 26, 2010 2:52:00 PM

---

Real message in this paper is - antenatal consent is hard and takes more time per baby enrolled

-----Original Message-----

From: Bock, Robert (NIH/NICHD) [E]  
Sent: Wednesday, May 26, 2010 2:49 PM  
To: Higgins, Rosemary (NIH/NICHD) [E]  
Subject: RE: PEDIATRICS: Decision Letter on MS# 2009-3353.R2

The point behind it is that we'd all benefit if more people volunteered for studies. Unfortunately, I don't think we could make the leap from the paper alone.

-----Original Message-----

From: Higgins, Rosemary (NIH/NICHD) [E]  
Sent: Wednesday, May 26, 2010 2:48 PM  
To: Bock, Robert (NIH/NICHD) [E]  
Subject: RE: PEDIATRICS: Decision Letter on MS# 2009-3353.R2

OK

This sounds reasonable not to do it

Rose

-----Original Message-----

From: Bock, Robert (NIH/NICHD) [E]  
Sent: Wednesday, May 26, 2010 2:43 PM  
To: Higgins, Rosemary (NIH/NICHD) [E]  
Subject: RE: PEDIATRICS: Decision Letter on MS# 2009-3353.R2

At first glance, I'd think it's too inside for a release. Am I missing something?

-----Original Message-----

From: Higgins, Rosemary (NIH/NICHD) [E]  
Sent: Wednesday, May 26, 2010 1:33 PM  
To: Bock, Robert (NIH/NICHD) [E]  
Subject: FW: PEDIATRICS: Decision Letter on MS# 2009-3353.R2

Here is the SUPPORT antenatal consent paper for the early release

Rose

-----Original Message-----

From: Rich, Wade [mailto:wrich@ucsd.edu]  
Sent: Thursday, March 18, 2010 3:49 PM  
To: Rich, Wade; Kathy J Auten; Gantz, Marie; Hale, Ellen; Hensman, Angelita; Nancy Newman; Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil  
Subject: RE: PEDIATRICS: Decision Letter on MS# 2009-3353.R2

Just noticed what I sent you all was the ORIGINAL submission, not the final one. Here is the final submitted one that was accepted.

wade



-----Original Message-----

From: Rich, Wade

Sent: Thursday, March 18, 2010 12:39 PM

To: 'Kathy J Auten'; 'Gantz, Marie'; 'Hale, Ellen'; 'Hensman, Angelita'; 'Nancy Newman'; 'Higgins, Rosemary (NIH/NICHD) [E]'; 'Finer, Neil

Subject: FW: PEDIATRICS: Decision Letter on MS# 2009-3353.R2

FYI

-----Original Message-----

From: onbehalfof+PediatricsEditorial+aap.org@manuscriptcentral.com

[mailto:onbehalfof+PediatricsEditorial+aap.org@manuscriptcentral.com] On Behalf Of

PediatricsEditorial@aap.org

Sent: Thursday, March 18, 2010 12:27 PM

To: Rich, Wade

Subject: PEDIATRICS: Decision Letter on MS# 2009-3353.R2

18-Mar-2010

RE: MS#: 2009-3353.R2

Title: Antenatal consent in a trial of immediate neonatal management: Challenges, costs and representative enrollmentc

Authors: Rich, Wade; Auten, Kathy; Gantz, Marie; Hale, Ellen; Hensman, Angelita; Newman, Nancy; Finer, Neil

Dear Mr. Rich:

Thank you for your revised manuscript, which has been accepted by Pediatrics. All accepted papers are published online at [www.pediatrics.org](http://www.pediatrics.org), which is the journal of record. The online publication date for your paper is not known at this time. Page proofs will be sent to you shortly before publication. Your paper could also be selected for print publication, but that decision will be made at a later date.

Thank you for submitting your manuscript to Pediatrics and congratulations on its acceptance.

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  
Email: [PediatricsEditorial@aap.org](mailto:PediatricsEditorial@aap.org)

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Subject:** FW: PEDIATRICS: Decision Letter on MS# 2009-3353.R2  
**Date:** Wednesday, May 26, 2010 1:33:00 PM  
**Attachments:** s1-ln75428481662147082-1939656818Hwf-366051043IdV21106686617542848PDF\_HI0001.pdf

---

Here is the SUPPORT antenatal consent paper for the early release

Rose

-----Original Message-----

**From:** Rich, Wade [mailto:wrich@ucsd.edu]  
**Sent:** Thursday, March 18, 2010 3:49 PM  
**To:** Rich, Wade; Kathy J Auten; Gantz, Marie; Hale, Ellen; Hensman, Angelita; Nancy Newman; Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil  
**Subject:** RE: PEDIATRICS: Decision Letter on MS# 2009-3353.R2

Just noticed what I sent you all was the ORIGINAL submission, not the final one. Here is the final submitted one that was accepted.

wade

-----Original Message-----

**From:** Rich, Wade  
**Sent:** Thursday, March 18, 2010 12:39 PM  
**To:** 'Kathy J Auten'; 'Gantz, Marie'; 'Hale, Ellen'; 'Hensman, Angelita'; 'Nancy Newman'; 'Higgins, Rosemary (NIH/NICHD) [E]'; Finer, Neil  
**Subject:** FW: PEDIATRICS: Decision Letter on MS# 2009-3353.R2

FYI

-----Original Message-----

**From:** onbehalfof+PediatricsEditorial+aap.org@manuscriptcentral.com  
[mailto:onbehalfof+PediatricsEditorial+aap.org@manuscriptcentral.com] On Behalf Of  
PediatricsEditorial@aap.org  
**Sent:** Thursday, March 18, 2010 12:27 PM  
**To:** Rich, Wade  
**Subject:** PEDIATRICS: Decision Letter on MS# 2009-3353.R2

18-Mar-2010

RE: MS#: 2009-3353.R2

**Title:** Antenatal consent in a trial of immediate neonatal management: Challenges, costs and representative enrollmentc

**Authors:** Rich, Wade; Auten, Kathy; Gantz, Marie; Hale, Ellen; Hensman, Angelita; Newman, Nancy; Finer, Neil

Dear Mr. Rich:

Thank you for your revised manuscript, which has been accepted by Pediatrics. All accepted papers are published online at [www.pediatrics.org](http://www.pediatrics.org), which is the journal of record. The online publication date for your paper is not known at this time. Page proofs will be sent to you shortly before publication. Your paper could also be selected for print publication, but that decision will be made at a later date.

Thank you for submitting your manuscript to Pediatrics and congratulations on its acceptance.

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  
Email: [PediatricsEditorial@aap.org](mailto:PediatricsEditorial@aap.org)

**From:** Cunningham, Meg  
**To:** Archer, Stephanie (NIH/NICHD) [E]  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Submitted\_Abstracts2011.xls  
**Date:** Wednesday, May 26, 2010 11:38:10 AM

---

Will add!

Should LeVan's go under SUPPORT or secondary analyses? What about Sood's?

---

**From:** Archer, Stephanie (NIH/NICHD) [E] [mailto:archerst@mail.nih.gov]  
**Sent:** Wednesday, May 26, 2010 11:19 AM  
**To:** Cunningham, Meg  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** FW: Submitted\_Abstracts2011.xls

Meg,

We have a few more items to add to your list.

First, should the Devaskar paper be under NRN Secondary Analyses? It wasn't a pre-defined secondary protocol.

Here are the additions:

- LeVan, Changes in Therapy and Outcomes Associated with the SUPPORT Trial [GDB and SUPPORT]
- Carlo, Retinopathy of prematurity and actual oxygen saturations: A secondary protocol of the SUPPORT Trial [SUPPORT data only]
- Londhe, Vitamin A supplementation for ELBW infants: Subgroup analysis of SGA infants [Vitamin A and FU]
- Sood, Is There a Difference in the Cytokine Profiles of Preterm Neonates with Bacterial and Fungal Sepsis? [Cytokines only]

Thanks,

Stephanie

---

Stephanie Wilson Archer  
The Eunice Kennedy Shriver  
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6100 Executive Boulevard, Room 4B03  
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Tel. 301-496-0430  
Fax 301-496-3790  
[archerst@mail.nih.gov](mailto:archerst@mail.nih.gov)

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Wednesday, May 26, 2010 10:45 AM  
**To:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** FW: Submitted\_Abstracts2011.xls

Here is meg's list – can you verify that we have all of them?

---

**From:** Cunningham, Meg [mailto:mcunningham@rti.org]  
**Sent:** Monday, May 24, 2010 11:17 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** Submitted\_Abstracts2011.xls

So far...

**From:** Wally Carlo, M.D.  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Duara, Shahnaz; nfiner@ucsd.edu; edward.donovan@cchmc.org; Betty Hastings; Ken Poole; Michele; Wade Rich; Everett, Ruth; adas@rti.org  
**Subject:** RE: SUPPORT time in target range  
**Date:** Wednesday, May 25, 2005 1:49:19 PM

---

Good idea. It will be by days, obviously. Wally

---

**From:** Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]  
**Sent:** Wednesday, May 25, 2005 12:45 PM  
**To:** Duara, Shahnaz; nfiner@ucsd.edu; Wally Carlo, M.D.; edward.donovan@cchmc.org; Betty Hastings; Ken Poole; Michele; Wade Rich; Everett, Ruth; adas@rti.org  
**Subject:** RE: SUPPORT time in target range

Can we separate out the room air babies from those that were actually in oxygen?  
This could give us a better handle on what is going on.

Thanks  
Rose

---

**From:** Duara, Shahnaz [mailto:SDuara@med.miami.edu]  
**Sent:** Tuesday, May 24, 2005 6:08 PM  
**To:** nfiner@ucsd.edu; Wally Carlo, M.D.; edward.donovan@cchmc.org; Betty Hastings; Higgins, Rosemary (NIH/NICHD); Ken Poole; Michele; Wade Rich; Everett, Ruth; adas@rti.org  
**Subject:** RE: SUPPORT time in target range

Hi all,

Sorry to sound like a stuck record, but this was exactly my fear when we decided to continue using the study POX once babies weaned to RA. This way we can't tell whether babies were appropriately handled (nothing to be done if in RA) or not. The other is a concern also, switching back and forth from study to standard POX by RA status, but in trying to reduce work for the RTs we may end up with high-end uninterpretable data.

Shahnaz

-----Original Message-----

**From:** Neil Finer [mailto:nfiner@ucsd.edu]  
**Sent:** Tuesday, May 24, 2005 5:47 PM  
**To:** 'Avroy A. Fanaroff, M.D.'; 'Betty Hastings'; 'Ed Donovan'; higginsr@mail.nih.gov; 'Ken Poole'; 'Michele'; 'Neil Finer'; Duara, Shahnaz; 'Wade Rich'  
**Subject:** FW: SUPPORT time in target range

Hi Everyone

Here is the first data from the oximeters for your reading pleasure Its far too early to say much except that we are getting the data, and the time in the narrow target range is less than we would like. Remember however that some of the time these infants were in room air.

Too my eyes, the biggest difference is the duration above 95%.

Your thoughts??

Be well  
Neil

---

**From:** Gantz, Marie [mailto:mgantz@rti.org]

**Sent:** Tuesday, May 24, 2005 2:03 PM  
**To:** wrich@ucsd.edu; nfiner@ucsd.edu  
**Cc:** Poole, W. Kenneth  
**Subject:** SUPPORT time in target range

Neil and Wade,

Attached is a document showing the percent of time babies in the SUPPORT trial have been kept in the target SpO2 ranges. Separate percentages were calculated for the low and high SpO2 arms and for each center. Please note that these are the oximeter display values, not the actual SpO2 values. Also, note that the numbers are based on a very small number of babies. The tables include the number of babies and total number of hours of SpO2 data that went into calculating the percentages. The percent of time in each range is the overall percent of time babies at the center were kept in the range, as opposed to the average percent of time each baby was kept in the range. In other words, babies for whom more data were collected (over a longer period of time) are more heavily weighted in the percent calculations. If you have any questions regarding how these numbers were calculated, please let me know.

Marie

Marie Gantz, Ph.D.  
Research Statistician  
RTI International  
P.O. Box 12194  
Research Triangle Park, NC 27709-2194  
Telephone (919) 485-7780  
Fax (919) 485-7762  
mgantz@rti.org

**From:** Luc Brion  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; Marie Gantz; Pablo Sanchez  
**Subject:** RE: Concept Proposal - first draft  
**Date:** Monday, May 24, 2010 5:09:17 PM  
**Attachments:** Version 3 before vs after SUPPORT Levan Brion.doc

---

Rose:

Thanks a lot.

I just forwarded you the email I had sent to Marie, Wally, Neil and Barbara yesterday.

Sorry I should have copied you on that email.

I attach the current updated version.

Luc

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>>> "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> 5/24/2010 10:27 AM >>>

Luc

We will have SUPPORT and GDB review the proposal

Thanks

Rose

-----Original Message-----

From: Luc Brion [<mailto:Luc.Brion@UTSouthwestern.edu>]  
Sent: Saturday, May 15, 2010 8:37 PM  
To: Marie Gantz  
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Pablo Sanchez  
Subject: RE: Concept Proposal - first draft

Marie:

Thanks a lot for your response.



I will work at this and get back to you.

Please let me know what time you will be available to talk during the meeting next week.

What time are you coming to the meeting and what time will you leave?

Accordingly, I will try to find a time that would work for hopefully all of us including you, Wally, Neil, Barbara, Rose and Pablo.

Best regards,

Luc

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>>> "Gantz, Marie" <mgantz@rti.org> 5/14/2010 1:53 PM >>>

Luc,

I was the statistician for SUPPORT, so Abhik asked me to review your concept proposal. My comments are attached, both as comments inserted in the text of your proposal and in a separate document that highlights my main concerns. My biggest concern is that there were changes to the GDB before and after SUPPORT that will make comparisons of some of your outcomes difficult. ROP is of particular concern, because not only did the GDB questions change, but any ROP outcome from the GDB will not be comparable to the outcome used in SUPPORT for reasons I describe in the comments.

Please let me know if you have any questions or would like to discuss my comments. I will be available next week.

Marie

Marie Gantz, Ph.D.  
Research Statistician  
RTI International  
mgantz@rti.org  
828-254-6255

-----Original Message-----

From: Das, Abhik

Sent: Thursday, May 13, 2010 12:19 PM  
To: Gantz, Marie  
Subject: FW: Concept Proposal - first draft

Please review.

Thanks

Abhik

-----Original Message-----

From: Luc Brion [<mailto:Luc.Brion@UTSouthwestern.edu>]  
Sent: Thursday, May 13, 2010 12:12 PM  
To: Rosemary (NIH/NICHD) [E] Higgins; Barbara Stoll; Waldemar Carlo; Das, Abhik; Neil Finer  
Cc: JACLYN LEVAN; Pablo Sanchez  
Subject: Concept Proposal - first draft

Hi Rose, Barbara, Abhik, Neil and Wally;

Here is a revised draft of a concept proposal written by one of our fellows, Jaelyn LeVan, which is designed to use GDB data to assess changes after the SUPPORT trial.

Barbara: Thanks a lot for the GDB comments on our first proposal (attached).

As recommended by the GDB,

1. The proposal was modified to analyze intubation/outcome in the years before SUPPORT and compare to the period following completion of SUPPORT and the end of the current Network, and we are listing all SUPPORT authors in the proposal.
2. All your names and all SUPPORT authors are listed in the proposal (please apologize if we missed someone by mistake).
3. I submitted a draft to Abhik on 5/4/10 for his comments.

I wonder whether we might have some time to initiate some preliminary discussion at the upcoming May 20-21 meeting. I know the schedule is busy but I would appreciate it if we could sit for even a few minutes. This could lead to a time frame for comments and editing so I can revise and edit this draft as many times as needed for submission at the next steering committee.

Thank you

Luc

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>>> "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> 2/5/2010

>>> 11:01 AM >>>

Luc

The GDB subcommittee reviewed your proposal on their call this am. Though there was much enthusiasm, a revision is requested prior to presentation at a steering committee meeting. Barbara will send you comments in the next week.

Thanks

Rose

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network Pregnancy and Perinatology Branch Center for Developmental Biology and Perinatal Medicine Eunice Kennedy Shriver National Institute of Child Health and Human Development National Institutes of Health 6100 Executive Blvd., Room 4B03 MSC 7510 Bethesda, MD 20892 For overnight delivery use Rockville, MD 20852  
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## Application to the Full Steering Committee

# Changes in Therapy and Outcomes Associated with The SUPPORT Trial

Jaclyn LeVan, DO, Myra Wyckoff, MD, Pablo Sánchez, MD, Roy Heyne, MD,  
Chul Ahn, PhD, Mambarath Jaleel, MD, Luc P Brion, MD (PI),  
**Finer NN, Carlo WA**, Walsh MC, Rich W, Gantz M, Laptook AR, Yoder BA, Faix RG,  
**Das A**, Poole WK, Ambalavanan N, Schibler K, Donovan E, Newman N, Frantz III ID,  
Sánchez PJ, Buchter S, Morris BH, Laroia N, Poindexter BB, Cotton M, Van Meurs KP,  
Sood B, Duara S, O'Shea TM, Bell EF, Bhandari V, Watterberg KL, **Gantz M, Stoll B,**  
**Higgins RD**

For the NICHD Neonatal Research Network

Version 32

5/2317/2010

## **A. ABSTRACT:**

We propose an observational study (before/after study design) of GDB data and a survey of institutions in the NRN to examine the changes in clinical practices and outcomes following the results of the SUPPORT Trial.

## **B. STATEMENT of the PROBLEM**

The SUPPORT trial (Finer; Carlo, in press) was a multicenter randomized 2 X 2 factorial trial, in which preterm infants of 24 0/7ths weeks to 27 6/7ths weeks were randomized at birth to (1) either continuous positive airway pressure (CPAP) initiated in the delivery room and subsequent use of a protocol-driven limited ventilation strategy, or intubation with surfactant administration (within 1 hour of birth), and (2) oxygen saturation targets of either 85 to 89% or 91 to 95%. The results of the SUPPORT trial were finalized in November 2009 and officially released in May 2010. . The rates of the primary outcome of the CPAP trial (death or bronchopulmonary dysplasia [BPD]) were not significantly different between the CPAP and the surfactant groups. In the CPAP group infants had lower rates of intubation or postnatal steroids for BPD, had fewer days of mechanical ventilation among survivors, and were more likely to be alive and off mechanical ventilation by day 7.

The rates of the primary outcome of the saturation target trial (severe retinopathy of prematurity [ROP] or death) were not significantly different between the two oxygen saturation target groups. However, in the lower oxygen saturation target group, death was significantly more frequent while severe retinopathy of prematurity among survivors occurred significantly less often.

In a retrospective study conducted at Parkland Memorial Hospital we found that the frequency of delivery room intubation among gestational age-matched infants (who did not participate in the SUPPORT trial) decreased significantly after initiation of the SUPPORT trial (Brion 2008).

## **C. HYPOTHESES:**

1. We hypothesize that release of the results of the SUPPORT Trial will be followed by (1) a decrease in frequency of endotracheal intubation in the delivery room in preterm infants with gestational age between 24 0/7 and 27 6/7 weeks, and that the decrease in the frequency of delivery room intubation in each neonatal research network (NRN) center would depend on baseline rate before the trial and (2) institution-specific changes in target oxygen saturation.
2. We hypothesize that the release of the SUPPORT trial results will not affect the rates of death or bronchopulmonary dysplasia at 36 weeks postmenstrual age (BPD, defined by the physiologic definition), death at any time while hospitalized or severe retinopathy of prematurity (ROP), BPD (defined by the physiologic definition), BPD (defined by oxygen requirement at 36 weeks) and ROP among preterm infants, but will reduce the frequency of mechanical ventilation or death at day 7 and the frequency of use of corticosteroids for BPD.
3. We hypothesize that changes in ROP (increase) and mortality rate (decrease) will occur in centers that used low oxygen saturation target (85 to 89% or lower) before the SUPPORT trial and have now increased this target (as reported by the centers to a survey

conducted as part of this concept proposal) to a value similar to the higher range used in the SUPPORT trial, i.e., 91 to 95%.

#### **D. SPECIFIC AIMS:**

1. To determine the impact of the results of the SUPPORT trial on clinical practice, specifically, (1) the incidence of endotracheal intubation in the delivery room in preterm inborn infants and (2) target oxygen saturation in the NRN centers
2. To determine the impact of the results of the SUPPORT trial on outcomes in preterm inborn infants with gestational age between 24 0/7 and 27 6/7 weeks, including: incidence of death or BPD at 36 weeks postmenstrual age (defined by the physiologic definition, death at any time while hospitalized or severe ROP, BPD [defined by the physiologic definition], BPD [defined by oxygen requirement at 36 weeks postmenstrual age], ROP, mechanical ventilation or death at day 7, use of postnatal corticosteroids for BPD, mortality rate in the whole group and mortality rate in each stratum (24 0/7ths weeks to 25 6/7ths weeks and 26 0/7ths weeks to 27 6/7ths weeks).

#### **E. RATIONALE/JUSTIFICATION:**

The SUPPORT trial showed no difference in primary outcome between the two respiratory support strategies but advantages of early CPAP on three secondary outcomes. Therefore, we expect that providers using endotracheal intubation as standard of care in the delivery room before the SUPPORT trial would change their attitudes towards more CPAP and less intubation after the release of the SUPPORT Trial results. The intubation rate among extremely low birth weight infants was high (80%) in NRN centers in 1993-1997 (Shankaran 2002) and was still high at Parkland Memorial Hospital in 2005 (Brion 2008). Since there is substantial heterogeneity in therapy and outcome across NRN centers, we expect that the change in practice after release of the results of the SUPPORT trial would be inversely related with the baseline rate of intubation in each center.

The SUPPORT trial showed no difference in primary outcome between the two oxygen saturation targets, but showed significantly higher mortality and lower rate of ROP with low oxygen saturation target. Specifically the trial showed that targeting lower oxygen saturation resulted in one additional death for approximately every 2 cases of severe ROP prevented. Since the SUPPORT trial is the first trial to show that targeting low oxygen saturation significantly increases mortality in extremely preterm infants, we might expect that some centers or providers using low oxygen saturation target before the SUPPORT trial would consider increasing their target levels after release of the results of the SUPPORT trial.

#### **F. BACKGROUND/PREVIOUS STUDIES:**

##### CPAP vs. intubation and surfactant:

Prophylactic and early natural surfactant administration at less than 2 hours of life significantly decreases mortality, air leak, and death or BPD in intubated preterm infants who are either at risk for respiratory distress syndrome (< 30 weeks of gestational age) or with respiratory distress syndrome (Soll 1997, Soll 1999). Several studies have suggested a benefit for early CPAP for preterm infants with respiratory distress syndrome, including a decrease in the need for mechanical ventilation among very preterm infants without an

increase in morbidity (Avery 1987, Van Marter 2000, VanPee 2007, Jonsson 1997, Gitterman 1997) except for pneumothorax (summary relative risk 2.36; 95% confidence interval 1.25, 5.54) (Ho 2002). In one observational study, 76% of infants with a birth weight  $\leq$  1250 g who were initially treated with CPAP did not require intubation within 72 hours (Ammari 2005).

The NICHD Feasibility Trial (Finer 2004) was designed to determine the feasibility of randomizing ELBW infants of  $<$  28 weeks' gestation to CPAP/positive end expiratory pressure (PEEP) or no CPAP/PEEP during resuscitation immediately after delivery, avoiding routine delivery room intubation for surfactant administration. Forty-five percent (47 of 104) of infants  $<$  28 weeks' gestation required intubation for resuscitation in the delivery room. CPAP/ PEEP in the delivery room did not affect the need for intubation at birth or during the subsequent week. Overall, 20% of infants did not need intubation by 7 days of life.

Three multicenter RCTs have compared early CPAP with intubation in the delivery room. The IFDAS trial (Thomson 2001) showed no significant difference between 4 groups (Elective intubation with surfactant administration and extubation within 2 hrs; early nasal CPAP with selective short intubation for surfactant administration; elective intubation with surfactant administration and artificial ventilation; selective intubation with surfactant administration and artificial ventilation based on clinical criteria) in total respiratory support until estimated date of delivery or discharge home (if earlier) and other neonatal complications. However, this study was not powered for any of the outcomes.

The COIN trial (Morley 2008) randomized 610 infants from 25 0/7 to 28 6/7 weeks gestation, who were able to breathe at 5 minutes of age and had evidence of respiratory distress. Infants were randomized, either to intubation and ventilation, or to CPAP at 8 cm H<sub>2</sub>O with intubation for those who met failure criteria. The primary outcome of death or BPD at 36 weeks was similar in the CPAP and in the intubation arms 33.9% vs. 38.9%, (odds ratio=0.58 to 1.12; P=0.19). Infants randomized to CPAP had a higher frequency of pneumothorax (9.1% vs. 3.0%, p=.001) and a lower frequency of death or need for oxygen at 28 days (odds ratio, 0.63; 95% CI, 0.46 to 0.88; P=0.006).

#### Oxygen administration upon admission to the neonatal intensive care unit:

Trials published in the 1950's comparing restricted ( $\leq$  50%, only for clinical indication or cyanosis) versus unrestricted (routine for 2-4 weeks or until reaching 1500 g) ambient oxygen in very low birth weight infants upon admission or within the first 48 hours showed a significant reduction in ROP and severe ROP (Duc 1992, Askie 2009) without a significant change in mortality (risk difference 4.9%, 95% CI -5.2, + 14.9; risk ratio 1.23, 95% CI 0.80, 1.90). Observational studies have suggested that targeting low oxygen saturation upon admission in very preterm infants may reduce the risk of ROP (Tin 2007) without increasing mortality (Chow 2003, Deulofeut 2007, Wright 2006). No randomized trials until the SUPPORT trial have assessed the effect of targeting different oxygen saturation levels upon admission on morbidity and mortality in very preterm infants.

SUPPORT Trial (extracted from Finer, in press and Carlo, in press):

The SUPPORT trial (Finer, in press; Carlo, in press) was a multicenter randomized 2 X 2 factorial trial, in which preterm infants of 24 0/7ths weeks to 27 6/7ths weeks were randomized at birth to (1) either continuous positive airway pressure (CPAP) initiated in the delivery room and subsequent use of a protocol-driven limited ventilation strategy, or intubation with surfactant administration (within 1 hour of birth), and (2) oxygen saturation targets of either 85 to 89% or 91 to 95%. The primary outcome of the CPAP vs. surfactant trial was the rate of composite primary outcome of death or bronchopulmonary dysplasia (BPD) defined by requirement for oxygen or positive pressure support with CPAP or mechanical ventilation at 36 weeks (with an attempt to remove oxygen in neonates receiving less or equal to 30% oxygen). The primary outcome of the oxygen saturation trial was a composite of severe retinopathy of prematurity (threshold retinopathy, or surgical ophthalmologic intervention, or the use of bevacizumab) and/or death before discharge from the hospital.

The results of the SUPPORT trial were finalized in November 2009 and officially released in May 2010.. The study enrolled 1316 infants. The rates of the primary outcome were not significantly different between the CPAP and surfactant groups (47.8% vs. 51.0%, Relative risk (RR) 0.95 (95% Confidence interval (CI) 0.85, 1.05, adjusting for gestational age, center and familial clustering). In the CPAP group infants had lower rates of intubation or postnatal steroids for BPD, had fewer days of mechanical ventilation among survivors, and were more likely to be alive and off mechanical ventilation by day 7. The rates of other adverse neonatal outcomes were not significantly different in the 2 groups.

The rates of the primary outcome (severe retinopathy of prematurity [ROP] or death) were not significantly different between the two oxygen saturation target groups (28.3 vs. 32.1%, respectively; relative risk (RR) 0.90; 95% confidence interval (CI) 0.76, 1.06; p= 0.21). Death occurred more frequently in the lower oxygen saturation target group (19.9 vs. 16.2%; RR 1.27; CI 1.01, 1.60; p= 0.04) while severe retinopathy among survivors occurred less often in these infants (8.6 vs 17.9%; RR 0.52; CI 0.37, 0.73; p<0.001). However, in the lower oxygen saturation target group, death was significantly more frequent, while severe retinopathy of prematurity among survivors occurred significantly less often. The rates of other adverse neonatal outcomes were not significantly different in the 2 groups.

Retrospective study at Parkland Memorial Hospital:

A retrospective study (Brion 2008) was conducted at Parkland Memorial Hospital to assess the impact of SUPPORT trial initiation in July 2005 on patient management and short-term outcomes in non-participant preterm infants. We analyzed two prospective databases: the resuscitation registry and the neonatal intensive care unit (NICU) database. We included all inborn infants with gestational age < 35 weeks during 3 epochs: 01/03-07/05 (1<sup>st</sup> Epoch), 07/05-12/05 (2<sup>nd</sup> Epoch) and 01/06-11/07 (3<sup>rd</sup> Epoch), corresponding, respectively, to 30 months that preceded enrollment into SUPPORT, the first 6 months of SUPPORT enrollment, and the next 23 months of SUPPORT enrollment. We excluded infants who received comfort care only and those enrolled in the SUPPORT trial. Among neonates < 28 weeks of gestational age, initiation of the SUPPORT trial was associated with significant decreases in the rates of intubation in the delivery room or the



NICU, and surfactant administration, and an increase in the rate of delivery room CPAP.

Infants < 28 wk gestational age (n=267)				
	1st Epoch N=160	2nd Epoch N=17	3rd Epoch N=90	P
Delivery room intubation	87%	77%	52%	<0.001
Delivery room CPAP	30%	47%	50%	0.004
Early NICU intubation	4%	6%	9%	0.28
Intubation in delivery room or NICU	90%	82%	61%	<0.001
Surfactant	78%	71%	52%	<0.001
Pneumothorax	8%	13%	10%	0.58

In the whole population studied (<35 weeks gestational age, n= 2266), multivariate logistic regression analysis taking into account gestational age and umbilical cord base excess, the rate of delivery room intubation significantly decreased after initiation of recruitment into the SUPPORT trial (odds ratio 0.48, 95% CI 0.37, 0.63, p < 0.001).

## G. METHOD/PROCEDURES:

### Study Design:

We propose a retrospective analysis of the GDB using a before/after design with one cohort of patients born before the date of initiation of the SUPPORT trial in each NRN center (1/02-1/05) and a second cohort of patients after release of the SUPPORT trial results to the end of the current cycle of Neonatal Research Network (05/10-4/11)

### Study Population:

#### Cohorts:

We propose to analyze patients in the NRN GDB born between 1/02-4/11, divided into two successive cohorts. The first cohort includes patients born during a 3-year period preceding the SUPPORT trial (from 01/02-1/05). The second cohort includes patients born after the release of the results of the SUPPORT trial to the NRN centers and the end of the neonatal network (05/10-4/11).

#### Eligibility and exclusion criteria:

We will use eligibility and exclusion criteria identical to those in the SUPPORT trial with the exception of intent to provide full resuscitation, which is not available from the GDB forms.

Entry criteria: Eligible infants are 24 0/7ths to 27 6/7th weeks at birth by best obstetrical estimate, born without known malformations at an NRN center participating in the SUPPORT trial, included in the GDB during the entire study period.

#### Gestational age strata:

We will analyze the same strata as in the SUPPORT trial: 24 0/7ths weeks to 25 6/7ths weeks and 26 0/7ths weeks to 27 6/7ths weeks.

**Study Intervention:**

This is a retrospective study with before/after study design comparing preterm infants before the date of initiation of the SUPPORT trial and after the release of the results of the SUPPORT Trial in each participating center.

**Primary/Secondary Outcomes:**

**Primary outcome variables:**

1. Clinical practices:
  - a. The use of intubation vs. CPAP in delivery room
2. Outcomes:
  - a. The incidence of composite of death or BPD at 36 weeks (physiologic definition), i.e., a primary outcome of the SUPPORT trial. The Physiologic Definition of BPD assigns the diagnosis of BPD to any infant who received more than 30% oxygen at 36 weeks or who required positive pressure support, but required demonstration of oxygen dependence by an attempt at oxygen withdrawal for infants who required < 30% oxygen at 36 weeks (Walsh 2003, Walsh 2004).
  - b. The incidence of composite of severe ROP (defined as received surgery for ROP or retinal detachment from ROP or death before discharge from the hospital. This outcome is similar but not identical to a primary outcome of the SUPPORT trial.
  - c. Mortality rate before discharge
  - d. The incidence of severe ROP
  - e. The incidence of BPD at 36 weeks (physiologic definition)

**Secondary outcome variables:**

1. Clinical practices
  - a. Institutional oxygen saturation target during the first and the second epochs (obtained by survey of each institution)
  - b. Institutional intubation rate
  - c. Surfactant administration and number of doses
2. Outcomes:
  - a. Delivery room resuscitation: bag and mask ventilation, cardiac compressions, use of code drugs (intravenous epinephrine, endotracheal epinephrine, bicarbonate), Apgar scores at 1 min and 5 min
  - b. Temperature within 60 min of birth
  - c. Pneumothorax
  - d. Pulmonary hemorrhage
  - e. Use of corticosteroids for BPD
  - f. Duration of ventilation among survivors; duration of CPAP among survivors
  - g. FiO2 at 24 hours for infants on CPAP, NIPPV or mechanical ventilation
  - h. Duration of oxygen supplementation among survivors
  - i. BPD (defined by oxygen requirement at 36 weeks)
  - j. Patent Ductus Arteriosus (PDA), PDA requiring indomethacin (or ibuprofen during the second epoch), PDA requiring surgery

- k. Severe intraventricular hemorrhage (grade III or IV)
- l. Cystic periventricular leukomalacia on cranial ultrasonogram performed closest to 36 weeks postmenstrual age
- m. Early onset sepsis and late onset sepsis
- n. First day full feeds
- o. Weight at 36 weeks
- p. Necrotizing enterocolitis (stage 2 or greater)
- q. Late-onset septicemia/bacteremia
- r. Length of stay
- s. Weight at discharge
- t. Death under 12 hours
- u. Death or mechanical ventilation at day 7
- v. Death or BPD (defined by oxygen requirement at 36 weeks)
- w. Severe ROP, which for this study we propose to define as ROP surgery or retinal detachment, stage 3 or worse in either eye, and plus disease in either eye  
~~ROP stage 3 or worse in either eye; plus disease in either eye~~

Additional variables available in the GDB will be collected, including

1. Maternal variables: diabetes, hypertension, singleton vs. multiple pregnancy, prolonged rupture of membranes, antenatal corticosteroids (betamethasone, any/full course), mode of delivery, antibiotics before delivery
2. Neonatal variables: race/ethnicity, gestational age, birth weight, gender, syndromes and/or major malformations

**Center-specific information requested by survey for both cohorts:**

1. Target oxygen saturation
2. Routine use of prophylactic Indomethacin or Ibuprofen
3. Routine use of caffeine
4. Routine use of I.M. vitamin A if birth weight < 1 kg

**Sample Size/Statistical Analysis:**

Available sample size:

Data in GDB from January 2002 to December 2004 (DATA AND SAFETY MONITORING PLANS for the SUPPORT Trial) included 4055 infants with a gestational age 24 0/7 – 27 6/7. Assuming 10% exclusions, the first 3-year cohort (1/02-1/05) is estimated to yield approximately 3600 infants for analysis.

The GDB data for 2008 included 1738 inborn infants < 29 weeks gestational age. Therefore we estimate that the second cohort (05/10-4/11) would include approximately 1400 infants.

Sample size calculations will be based on available data [which will be updated with more recent data from the GDB]:

1. year 2000 NRN baseline occurrence data among 24 0/7 to 26 6/7 week gestational age infants of death or survival with BPD (by physiologic definition) at 36 weeks of 67%,

2. year 2000 NRN baseline occurrence data among 24 0/7 to 26 6/7 week gestational age infants of death or threshold retinopathy of 50%
3. years 1993-1997 intubation rate of rate of 80% among extremely low birth weight infants (Shankaran 2002).
4. 2002-05 mortality rate of 21% in extremely low birth weight infants (Morris 2008)
5. 2002-05 severe ROP frequency of 20% in extremely low birth weight infants (Morris 2008)

For the primary outcome variables, we calculated power using chi-square analysis, a 1% level of significance (to account for five co-primary outcomes) and two-tailed tests. The available sample size (n = 5000, 3600 before versus 1400 after SUPPORT) gives a power > 99% to find a significant change in delivery room intubation from 80% to 60%, a change in death or BPD (by physiologic definition) from 50% to 40%, a change in death or severe ROP from 67 to 57%, and a change in severe ROP from 20% to 30%. We will have a power of 94% to detect a change in mortality from 21% to 16%. For multivariate analyses, the sample size is much larger than 10 patients per covariate.

#### Bivariate analyses:

We will conduct bivariate analyses comparing the before and after cohorts with respect to variables related to mortality and all the outcomes listed above (antenatal steroids, gender, Apgar scores, etc.). Bivariate analyses will be done using chi-square analysis (Mantel-Haenszel chi-square for analyses by gestational age stratum) for categorical variables and using Student t-test or Mann-Whitney test as appropriate for continuous variables.

To test whether releasing the results of the SUPPORT trial impacted mostly centers using infrequent intubation before the trial we will test whether the change in rate of intubation from the first to the second epoch in each center is inversely correlated with intubation rate during the first epoch. For this purpose we will use Spearman rank correlation coefficient or the Pearson correlation coefficient, depending on distribution of the data.

Assuming some centers decided to change their oxygen saturation targets based on the SUPPORT trial results, we will test whether mortality decreased and the rate of ROP increased in centers changing their oxygen saturation target from low (85 to 89% or lower) during the first epoch to high (91 to 95%) during the second epoch, but not in the other centers.

#### Multivariate analyses:

We will create logistic regression models to predict the primary outcomes based on epoch, center and the prespecified covariates (gestational age, antenatal corticosteroids, gender, singleton vs. multiple, birthweight by 100 g increment) (Tyson 2008).

We will also create models specific for each outcome variable:

- For intubation in the delivery room: Model using as additional variables mode of delivery, and maternal hypertension
- For mortality: Model using as additional covariates Apgar score at 1 minute (Shankaran 2002) and; institution-specific oxygen saturation target during that epoch (Carlo 2010); for mortality after NICU admission, model using, and temperature upon admission (Laptook 2007)
- For death or ROP and for ROP: Model using as additional covariate oxygen saturation target in the institution (Carlo 2010)
- For death or BPD and for BPD: Model using as additional covariates intubation in the delivery room, routine center-specific use of caffeine, indomethacin or vitamin A; number of doses of surfactant (<1 vs > 1), FiO<sub>2</sub> at 24 hours (≥90% vs <90%), PDA ligation, indomethacin for PDA, late-onset septicemia/ bacteremia (Schmidt 2006, Schmidt 2007, Tyson 1999, Ambalavan 2008, Fanaroff 1998, Clyman 2009)

If there are additional variables that differ significantly between the two epochs in bivariate analysis we will also include them as covariates as long as they do or could precede the outcome variable.

We will use survival analysis to compare in-hospital death using a Cox proportional hazards model adjusted for gestational age, antenatal corticosteroids, gender, singleton vs. multiple, birthweight by 100 g increment covariates listed above.

#### Limitations:

Before/after study design is limited by confounding variables that may have occurred in addition to the variable of interest. The two cohorts represent different patient populations separated by several years. For this purpose, we will perform logistic regression analyses as described in the previous section on multivariate analyses.

One exclusion criterion used for the SUPPORT trial, i.e., decision made not to provide full resuscitation, is not listed in the GDB baseline form.

The outcome of ROP as defined in the SUPPORT trial (threshold retinopathy, or surgical ophthalmologic intervention, or the use of bevacizumab) is not available in the GDB. For the SUPPORT trial, infants were followed for as long as it took to reach the final ROP outcome. In SUPPORT, most cases of severe ROP were diagnosed by 55 weeks PMA, however, many infants will have left the hospital before this time. In contrast, the outcome of ROP available in the GDB, which would be used in this study is based on data recorded prior to the infant's discharge, transfer, or 120 days of life. Thus, there will be a lot of variability in the length of time any infant is "followed" for the outcome.

Furthermore, the data collected with regard to ROP changed between 2002 and 2006. The definitions of ROP changed between 2002 and 2006. We are proposing for this concept proposal to assess the frequency of severe ROP (defined as ROP surgery or retinal detachment), stage 3 or worse in either eye, and plus disease in either eye.

Some variables cannot be analyzed because they were collected during only one of the two cohorts (e.g., tocolytics, origin of cord blood gas and base deficit).

**Consenting:**

Patients will be selected from GDB using criteria previously explained. We request a waiver for consent form as this research involves minimal risk to patients and collecting data in the GDB has been pre-approved by the IRB in each institution.

**Available Population/compatibility with other ongoing protocols**

The population available will be those patients in the GDB, corresponding to patients born between 1/01 and 4/11.

We are not aware of any conflict with other ongoing protocols.

**Projected Recruitment Time**

Data collection for the proposed study will start in May 2011.

**H. RISKS/BENEFITS:**

The benefit will be mostly for the society in that there is potential quality improvement of patient care in NICU. The risk is minimal and included accidental disclosure of medical information which is unlikely.

**I. BUDGET:**

Cost for access to GDB and SUPPORT database and statistical analysis

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Carlo WA, Finer NN, Walsh MC, Rich W, Gantz M, Laptook AR, Yoder BA, Faix RG, Das A, Poole WK, Ambalavanan N, Schibler K, Donovan E, Newman N, Frantz III ID, Sánchez PJ, Buchter S, Morris BH, Laroia N, Poindexter BB, Cotton M, Van Meurs KP, Sood B, Duara S, O'Shea TM, Bell EF, Bhandari V, Watterberg KL, Higgins RD; for the NICHD Neonatal Research Network and The SUPPORT Study Group of the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. The SUPPORT Trial: Randomized Trial of Oxygen Saturation Targets in Extremely Premature Infants. *N Engl J Med*, in press

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**From:** [Webb, Robin E.](#)  
**To:** [Webb, Robin E.](#); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Poindexter, Brenda B](#); [richard.ehrenkranz@yale.edu](#); [kwatterberg@salud.unm.edu](#); [ifrantz@tuftsmedicalcenter.org](#); [jon.e.tyson@uth.tmc.edu](#); [kurt.schibler@cchmc.org](#); [Roger.Faix@hsc.utah.edu](#); [Wallace, Dennis](#); [Das, Abhik](#)  
**Cc:** [Archer, Stephanie \(NIH/NICHD\) \[E\]](#); [Zaterka-Baxter, Kristin](#); [Cunningham, Meg](#); [Nancy.M.Smith@uth.tmc.edu](#)  
**Subject:** Protocol Call  
**Date:** Monday, May 24, 2010 4:23:10 PM

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The call to discuss the ROP support genomics protocol and the aEEG prediction protocol has been scheduled for:

**Monday, 6/14**  
**11:00am-1:00pm ET**

Dial:  
**Within the USA**  
866-675-(b)  
or

**Outside the USA**  
1-203-310-(b)

Then, enter Participant Passcode:  
(b) (6)

**From:** Susan Hintz  
**To:** Jean Lowe  
**Cc:** jrlowe@unm.edu; Andrea Duncan; Kristi Watterberg; Betty Vohr; JaneHammond Hammond; Jamie Newman; Higgins, Rosemary (NIH/NICHD) [F]  
**Subject:** Re: Applause and Spanish WISC-IV  
**Date:** Thursday, May 20, 2010 3:54:19 PM  
**Attachments:** FINAL\_Grid\_SUPPORTSchoolAge\_visit.doc  
ATT00001.txt

---

Dear Jean,

Thank you so much for your response. I truly look forward to working with you, and to the substantial benefits I believe this study will gain from your experience and expertise (and energy!)

The cost of the Spanish WISC IV is of course an issue - but we did make the determination early in the course of developing this study (and with your input and the experience of the Extended Hypothermia study) that administering this test particularly in Spanish was critical for primary Spanish speaking subjects. I will need to discuss the cost issue for Spanish versions with Rose and RTI - obviously, that is an "uneven" issue among sites, and could be considered somewhat unfair for some sites to have to pay for the Spanish versions while others do not need to purchase.

I agree it is cumbersome to create certification tapes. I think, if you agree, if a psychologist is going to administer BOTH in English and Spanish, he/she could submit just one tape. However, I think in the cases of psychologists that are contracting with the site for Spanish only, I believe they really need to do certification tape. I realize this could be a challenge, but if we do not have consistent requirements, I think the quality of the data will suffer.

Yes, there are NEPSY II subtests in our visit battery. Attached is the battery grid - you can see the planned NEPSY II subtests there. Is there overlap between the subtests you are using with Robin Ohls' study and these subtests? We had constructed the Spanish version column, which was based on what each of the companies for each of the studies says they have, but I do not know if these versions that are claimed to exist are truly appropriate.

There are definitely opportunities for further neuroimaging studies and analyses for this cohort. Of course it was fiscally prohibitive (and not possible for some sites) to include advanced/quantitative neuroimaging follow-up for these children as a routine within the study. However, at our site we are discussing a number of potential DTI and fMRI proposals (with Heidi Feldman here at Stanford and others) that would study these infants. My dream would be that several sites could work together to propose longitudinal advanced neuroimaging of this cohort -

I look forward to more discussions and to collaborations!

Susan

Extended Follow-up visit battery

August 2009

School age (6 ½ -7 ½ year) SUPPORT Neuroimaging and Neurodevelopmental Outcomes

<b>Test/questionnaire</b>	<b>Estimated time AGE RANGE</b>	<b>Spanish version?</b>
<u>Check in: Wt, Ht, HC</u>	~10 min	
<b><u>WISC-IV</u></b>	~45-60 min <b>6 yr 0 months – 16 yr 11 months</b>	YES <a href="http://pearsonassess.com/HAIWEB/Cultures/en-us/Productdetail.htm?Pid=015-8979-044&amp;Mode=detail&amp;Leaf=avproducts">http://pearsonassess.com/HAIWEB/Cultures/en-us/Productdetail.htm?Pid=015-8979-044&amp;Mode=detail&amp;Leaf=avproducts</a>
<b><u>Movement-ABC –II</u></b>	20-30 min <b>3-12 years</b>	Interpreter if needed <a href="http://pearsonassess.com/haiweb/cultures/en-us/productdetail.htm?pid=015-8541-308">http://pearsonassess.com/haiweb/cultures/en-us/productdetail.htm?pid=015-8541-308</a>
<b><u>Woodcock-Johnson III (ACH)</u></b> <b>Letter-Word Identification Calculation</b>	~15 minutes <b>2 years -90+ years</b>	YES = “Bateria III” <a href="http://www.riverpub.com/products;">http://www.riverpub.com/products;</a> <a href="http://www.riverpub.com/products/wjIIIAchievement/details.html">http://www.riverpub.com/products/wjIIIAchievement/details.html</a>
<b><u>BREAK</u></b>		
<b><u>NEPSY II subtests</u></b> <i>Executive function domain</i> <b>Auditory Attention/Response set Inhibition</b> <i>Visuospatial domain</i> <b>Design Copying Arrows</b> <i>Memory</i> <b>Memory for Names</b>	~25 min <b>Auditory Attention/Response (5-16 yrs); Inhibition (5-12); Design copying (3-16); Arrows (5-16); Memory for names (5-16)</b>	No
<u>Neurologic exam</u>	~15 min	Interpreter if needed
<u>Functional</u> <i>GMFCS</i> <i>Bimanual Fine Motor Function</i>	5 min <b>GMFCS – 6-12 yr BFMF – 4 yrs and older</b>	Interpreter if needed; <a href="http://motorgrowth.canchild.ca/en/GMFCS/resources/GMFCS-ER.pdf">http://motorgrowth.canchild.ca/en/GMFCS/resources/GMFCS-ER.pdf</a>

Extended Follow-up visit battery

August 2009

School age (6 ½ -7 ½ year) SUPPORT Neuroimaging and Neurodevelopmental Outcomes

<b>Test/questionnaire</b>	<b>Estimated time AGE RANGE</b>	<b>Spanish version?</b>
<b>QUESTIONNAIRES</b>		
Medical history/SES/living arrangement	15 min	Interpreter if needed
<b>QUICCC-R</b>	5-10 min <b>2-18 years</b>	YES; <a href="http://www.neserve.org/neserve/pdf/NES%20Publications/QUiCCC_R.PDF">http://www.neserve.org/neserve/pdf/NES%20Publications/QUiCCC_R.PDF</a>
<b>PedsQL (Parent)</b>	5-10 min <b>versions - 2-4 yrs, 5-7, 8-12, 13-18</b>	YES; <a href="http://www.pedsql.org/">http://www.pedsql.org/</a>
<b>Strengths and Difficulties Questionnaire (SDQ) (Parent)</b>	5-10 min <b>version 4-10 yr</b>	YES; <a href="http://www.sdqinfo.com/">http://www.sdqinfo.com/</a>
<b>Conners Rating Scale (Parent) (ADHD or Short only)</b>	10 min <b>6 yr-17 yr 11 months</b>	YES; <a href="http://pearsonassess.com/HAIWEB/Cultures/en-us/Productdetail.htm?Pid=Conners_3&amp;Mode=scoring&amp;Leaf=Conners_3_SF#3">http://pearsonassess.com/HAIWEB/Cultures/en-us/Productdetail.htm?Pid=Conners_3&amp;Mode=scoring&amp;Leaf=Conners_3_SF#3</a>
<b>Social Communication Questionnaire (Parent; Lifetime form)</b>	10 min <b>Over 4 years</b>	YES; <a href="http://portal.wpspublish.com/portal/page?_pageid=53,70432&amp;_dad=portal&amp;_schema=PORTAL">http://portal.wpspublish.com/portal/page?_pageid=53,70432&amp;_dad=portal&amp;_schema=PORTAL</a>
<b>Behavior Rating Inventory of Executive Function (BRIEF-Parent)</b>	15 min <b>5-18 yrs</b>	YES; <a href="http://www3.parinc.com/products/product.aspx?Productid=BRIEF">http://www3.parinc.com/products/product.aspx?Productid=BRIEF</a>

ATT00001.

On May 17, 2010, at 10:02 PM, Jean Lowe wrote:

> Dear Susan  
> Thanks for your email. I would be very interested in working on the  
> 6 1/2 - 7 1/2 SUPPORT study. I have experience with the Spanish WISC-  
> IV which we used in a study at UNMH. As you probably know the  
> Spanish WISC-IV is actually a separate test that needs to be  
> purchased with separate norms and instructions. It is very nicely  
> done and easy for a Spanish speaker to administer as the  
> instructions are already provided in Spanish. Unfortunately the test  
> is expensive and sites will have to purchase both the English and  
> Spanish versions of the test.  
>  
>  
> I think it is important if a person is administering in Spanish to  
> have at least one tape in Spanish to ensure they have the fluency  
> needed to administer in this language. As the administration is  
> similar in both languages, it could be possible that a person can  
> choose to do their tape in Spanish or English for certification  
> purposes. It does seem some sites have many more Spanish speakers  
> than others as expected. The certification tapes can be very time  
> consuming so it may become an issue if you only have a few Spanish  
> speakers at a site. Also if a person is contracting to do one or two  
> tests in Spanish would they be willing and able to do the  
> reliability tape? Some questions that may arise.  
>  
>  
> I also thought there were going to be subtests of the NEPSY in the  
> test battery. The NEPSY is not in Spanish and would have to be  
> translated if that is still going to be used. What we do at our site  
> with questionnaires is have them translated and back translated  
> before use. This could be the strategy to use for instruction on a  
> test that does not have official Spanish instructions - such as the  
> NEPSY.  
>  
>  
> We are currently beginning a new NIH study at UNMH that Robin Ohls  
> was awarded which will involve subtests of the NEPSY, the WIPPSI and  
> BRIEF (parent questionnaire). We have a large number of Spanish  
> speaking children so we can share our experience regarding these  
> tools. We will begin testing in June and will have both a cohort of  
> children born VLBW as well a full term control group.  
>  
>  
> I would be very interested in being involved in any research group  
> you have regarding the neuroimaging and ways that it will be used in  
> the study. I am currently working on two different projects through  
> the MIND institute that involves a variety of MR imaging including  
> ASL, DTI, volume and spectroscopy. The grant Robin got will also  
> involve scanning the children at 3 years and again at 5 years. This  
> technology is a very exciting addition to the studies we are able to  
> do with children born VLBW.  
>  
>  
> Appreciate your email and look forward to working with you on this  
> innovative new study.  
> Jean  
>

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Cunningham, Meg"  
**Subject:** FW: SUPPORT FU  
**Date:** Wednesday, May 19, 2010 3:54:00 PM  
**Attachments:** Network May 2010 meeting.ppt

---

You have this, right??

-----Original Message-----

**From:** Vohr, Betty [mailto:BVohr@WIHRI.org]  
**Sent:** Sunday, May 16, 2010 9:48 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: SUPPORT FU

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]  
**Sent:** Thursday, May 13, 2010 2:52 PM  
**To:** Laptook, Abbot; Vohr, Betty; Hensman, Angelita; Ventura, Suzy  
**Cc:** 'Gantz, Marie'  
**Subject:** SUPPORT FU

Hi,

We are missing the following SUPPORT FOLLOW UP outcomes. Let us know how you are doing.

Thanks for all the effort.

This is terrific given the outstanding recruitment at your site!!

Rose  
CENTER

NETWORK

FU\_message

14

(b)

FU window has closed but NF05 and NF09a have not been completed.

14

(b)

FU window has closed but NF05 and NF09a have not been completed.

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network  
Pregnancy and Perinatology Branch  
Center for Developmental Biology and Perinatal Medicine  
Eunice Kennedy Shriver National Institute of Child Health and Human Development  
National Institutes of Health



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# Network Meeting May 2010

## Follow-up Report

# Updates

- NRN Follow Up PI Meeting
- 2010 PAS Conference – Vancouver
- Sheraton
- Monday May 3, 1:00 pm – 3:00 pm
- Follow-up staff from 19 sites, NICHD and RTI participated

# New NRN Goal For Follow-up Rate

- NRN compliance goal since start of NRN FU has been 85%.
- Most current published studies and trials achieve FU rates of > 90%.
- NRN has demonstrated its ability to achieve rates >90%.
- Current rate for 2009 >90%; Support 98.6%
- New Goal for NRN set at of  $\geq$  90%

# Annual 18 Month Neurological Exam Re-certification

- The plan is to proceed with similar protocol/process as last year – PIs videotape themselves conducting the 18 month neuro exam and send DVD to **RTI** by June 1.
- RTI will make copies and send to Betty Vohr and Anna Dusick who will review the DVDs and identify 6 to include on the annual certification DVD; RTI will make the copies and will distribute them to the PIs at the Centers (RTI maintains a copy).
- PIs score videos using NF05C and site keyers key forms into the data entry system by August 31, 2010.
- October 21-22, 2010 Meeting will focus on scoring discrepancies/inter-rater agreement.
- Plan is to compare protocol results for this year compared to the prior year and write up the NRN protocol.

# Neuro Exam DVDs are to be Sent:

- **RTI :**
- Kimberly Adcock (Tel: 919-541-6865;  
Email: [kba@rti.org](mailto:kba@rti.org))
- RTI International  
3040 Cornwallis Road  
RTP, NC 27709

# Process

- At the May meeting 2 sites had not yet certified examiners at their sites as a result of the October 2009 meeting.
- It was again stressed that this should occur as a soon as possible after the October NRN training.
- Sites are to notify Jamie Newman ([newman@rti.org](mailto:newman@rti.org)) of certifications so that the 18 Month Certification can be listed on the RTI website.

# Bayley III Recertifications

- All Bayley III examiners must be certified annually
- Centers are reminded that at least one examiner per site must submit an annual certification video to the NRN Gold Standard assigned to their Center. This NRN certified Bayley examiner can they certify other Bayley examiners at the site. Following is a listing of Bayley III Gold Standard examiners:
  - Harriet Friedman ([hgf@po.cwru.edu](mailto:hgf@po.cwru.edu)) Houston; Wayne State; Yale, San Diego
  - Terri Leach ([Tleachttesting@aol.com](mailto:Tleachttesting@aol.com)) Dallas, Rochester, Duke
  - Tari Gratton ([Teresa.Gratton@uc.edu](mailto:Teresa.Gratton@uc.edu)) Stanford; Alabama; Emory
  - Heike Minnich ([hminnich@iupui.edu](mailto:hminnich@iupui.edu)) Tufts, New Mexico, Iowa, Utah
- Notify Jamie Newman ([newman@rti.org](mailto:newman@rti.org)) of certifications so that the 18 Month Certification



# Updates of Follow-up Studies were Presented

- Hypothermia 6-7yr Follow-up: Shankaran
- Object Permance: Duncan
- Autism Pilot: Stephens
- Breathing Outcomes: Dr. Vaucher /Dr. D'Angio
- Apo E: Goldstein
- 6-24 Hour Hypothermia Follow-up: Laptook
- New Studies
- Support: Neuroimaging School Age Outcome; Hintz
- Optimizing Cooling: Shankaran
- Nest: Blakley
- Inositol: Phelps

# Additional Discussion

- Use of a “control population” in the Follow Up study; should/would this be an appropriate proposal? School matched or sibling controls (only 40 % of NRN babies have sibs – these are mainly lower SES so data could be skewed. Dr. Vohr will submit a concept proposal and discussion of this topic will continue
- Dr. Tyson should learn the scores regarding the Comprehensive Care Proposal to AHRQ this week;

**From:** Newman, Jamie  
**To:** abodnar@utah.gov; adusick@iupui.edu; Andrea Duncan; Athina Pappas; byohr@wihri.org; adas@rti.org; drfrcmd@aol.com; dmarshal@med.unc.edu; emcgowan@tuftsmedicalcenter.org; Higgins, Rosemary (NIH/NICHD) [E]; iadamsc@emory.edu.; JaFuller@salud.unm.edu; Kimberly.Yolton@cchmc.org; Martha Fuller; michael-acarregui@uiowa.edu; MPeralta@PEDS.UAB.EDU; Patricia.W.Evans@uth.tmc.edu; richard.ehrenkranz@yale.edu; Ricki F Goldstein; Roy.Heyne@utsouthwestern.edu; srhintz@stanford.edu; sshankar@med.wayne.edu; steichij@email.uc.edu; Wallace, Dennis; Yvonne Vaucher  
**Cc:** Cathy.Boatman@childrens.com; scart01@emory.edu; nancy.close@yale.edu; MEDeanda@LPCH.org; cspatter@uab.edu; Charles.Green@uth.tmc.edu; Margaret.Poundstone@uth.tmc.edu; gusta002@mc.duke.edu; mgfuller@ucsd.edu; ckeller@tuftsmedicalcenter.org; diane-eastman@uiowa.edu; Msteffen@utah.gov; jrlowe@unm.edu; hgf@po.cwru.edu; Leach, Theresa; Teresa.Gratton@uc.edu; hminnich@iupui.edu; barbara\_stoll@oz.ped.emory.edu; alaptook@WHRI.org; Bell, Edward; bpoindex@iupui.edu; adas@rti.org; goldb008@mc.duke.edu; Higgins, Rosemary (NIH/NICHD) [E]; ifrantz@tuftsmedicalcenter.org; Kathleen.A.Kennedy@uth.tmc.edu; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; yanmeurs@leland.stanford.edu; Wally Carlo, M.D.  
**Subject:** Primary language at 18-22 month visit for those eligible for SUPPORT School Age  
**Date:** Tuesday, May 18, 2010 6:17:35 PM  
**Attachments:** Primary Language\_by\_Center.docx

---

Dear Follow-up PIs,

As a follow-up from the NRN Follow-up PI meeting at PAS, please see the email below and attachment from Susan Hintz.

Thanks, Jamie

Jamie E. Newman, PhD, MPH  
Statistics and Epidemiology  
RTI International  
Telephone: (919) 485-5719  
Fax: (919) 485-7762  
[newman@rti.org](mailto:newman@rti.org)

\*\*\*\*\*

Dear SUPPORT NEURO School-Age Follow-up team,

It was great seeing many of you at the PAS meeting in Vancouver. Attached, as we discussed at our Follow-up group meeting on May 3rd, is a breakdown of primary language spoken at the 18-22 month follow-up visit among those eligible for follow-up at 6½ - 7½ years of age (i.e., the SUPPORT NEURO cohort). These numbers are for patients seen and data keyed through March 2010. The RTI team will run these analyses for us every 3-4 months, and we will distribute the tables.

As we talked about at our meeting, these data from 18-22 month visits may not reflect the primary language spoken by the time of the 6½ - 7½ year visit. However, this may allow your team to plan for your site needs for Spanish-speaking WISC-IV examiners. Hopefully, the tracking checks throughout the period between follow-up visits may provide additional, evolving language information.

Thank you again for your dedication to this project,  
Susan

*Susan R. Hintz, M.D., M.S. Epi*  
*Associate Professor of Pediatrics*  
*Division of Neonatal and Developmental Medicine*  
*Stanford University School of Medicine*  
*750 Welch Road, Suite 315*

This document is provided for reference purposes only. Persons with disabilities having difficulty accessing information in this document should e-mail NICHD FOIA Office at NICHDFOIARequest@mail.nih.gov for assistance.

*Palo Alto, CA 94304*

*phone: 650-723-5711*

*email: [srhintz@stanford.edu](mailto:srhintz@stanford.edu)*

**Primary Language Spoken by Child: SUPPORT NEURO Cohort 18-22 month follow-up  
Data through March 2010**

SRH\_May 14 2010

**Primary Language @ 18-22 month - to March 2010: OVERALL NEURO COHORT**

Language	Frequency	Percent
English	269	78.2%
Spanish	57	16.6%
Other	18	5.2%

**By Center**

	Center number															
	3	4	5	9	12	14	15	16	18	19	21	22	23	24	25	26
<b>Engl</b>	42 (93%)	14 (42%)	5	2	7	38 (84%)	14 (56%)	69 (99%)	24 (83%)	4 (50%)	1	8 (57%)	13 (46%)	9	18 (86%)	1
<b>Span</b>	2 (4%)	17 (52%)	0	0	0	5 (11%)	9 (36%)	1 (1%)	5 (17%)	0	0	6 (43%)	8 (29%)	0	3 (14%)	1
<b>Other</b>	1 (2%)	2 (6%)	0	0	0	2 (4%)	2 (8%)	0	0	4 (50%)	0	0	7 (25%)	0	0	0

**From:** Luc Brion  
**To:** Higgins, Rosemary (NIH/NICHD) [F]; Barbara Stoll; WCarlo@peds.uab.edu; Abhik Das; das@rti.org; Marie Gantz; Finer Neil; Pablo Sanchez  
**Subject:** RE: Concept Proposal - first draft  
**Date:** Tuesday, May 18, 2010 1:13:38 AM

---

Neil, Rose, Abhik, Barbara, Wally, Abhik, Pablo:

Please let me know how best to proceed. I would hope we could have a preliminary meeting/conference call to discuss this concept proposal at the meeting in Washington.  
I just emailed you a second draft in response to Marie's comments.

Best regards,

Luc

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  
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Office: (214) 648-2835  
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luc.brion@utsouthwestern.edu

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>>> "Gantz, Marie" <mgantz@rti.org> 5/17/2010 10:12 AM >>>

Luc,

I won't be at the meeting, but I'm available Thursday between 11 and 5 if you want to gather the others someplace where I can call in or be called. Neil likely won't be at the meeting in person either.

Marie

Marie Gantz, Ph.D.  
Research Statistician  
RTI International  
mgantz@rti.org  
828-254-6255

-----Original Message-----

From: Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]  
Sent: Saturday, May 15, 2010 8:37 PM  
To: Gantz, Marie  
Cc: higginsr@mail.nih.gov; Pablo Sanchez  
Subject: RE: Concept Proposal - first draft

Marie:

Thanks a lot for your response.  
I will work at this and get back to you.  
Please let me know what time you will be available to talk during the meeting next week.  
What time are you coming to the meeting and what time will you leave?  
Accordingly, I will try to find a time that would work for hopefully all of us including you, Wally, Neil, Barbara, Rose and Pablo.  
Best regards,  
Luc

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  
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luc.brion@utsouthwestern.edu

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>>> "Gantz, Marie" <mgantz@rti.org> 5/14/2010 1:53 PM >>>

Luc,

I was the statistician for SUPPORT, so Abhik asked me to review your concept proposal. My comments are attached, both as comments inserted in the text of your proposal and in a separate document that highlights my main concerns. My biggest concern is that there were changes to the GDB before and after SUPPORT that will make comparisons of some of your outcomes difficult. ROP is of particular concern, because not only did the GDB questions change, but any ROP outcome from the GDB will not be comparable to the outcome used in SUPPORT for reasons I describe in the comments.

Please let me know if you have any questions or would like to discuss my comments. I will be available next week.

Marie

Marie Gantz, Ph.D.  
Research Statistician  
RTI International  
mgantz@rti.org  
828-254-6255

-----Original Message-----

From: Das, Abhik  
Sent: Thursday, May 13, 2010 12:19 PM  
To: Gantz, Marie  
Subject: FW: Concept Proposal - first draft

Please review.

Thanks

Abhik

-----Original Message-----

From: Luc Brion [mailto:[Luc.Brion@UTSouthwestern.edu](mailto:Luc.Brion@UTSouthwestern.edu)]  
Sent: Thursday, May 13, 2010 12:12 PM  
To: Rosemary (NIH/NICHD) [E] Higgins; Barbara Stoll; Waldemar Carlo;  
Das, Abhik; Neil Finer  
Cc: JACLYN LEVAN; Pablo Sanchez  
Subject: Concept Proposal - first draft

Hi Rose, Barbara, Abhik, Neil and Wally;

Here is a revised draft of a concept proposal written by one of our fellows, Jaclyn LeVan, which is designed to use GDB data to assess changes after the SUPPORT trial.

Barbara: Thanks a lot for the GDB comments on our first proposal (attached).

As recommended by the GDB,

1. The proposal was modified to analyze intubation/outcome in the years before SUPPORT and compare to the period following completion of SUPPORT and the end of the current Network, and we are listing all SUPPORT authors in the proposal.
2. All your names and all SUPPORT authors are listed in the proposal (please apologize if we missed someone by mistake).
3. I submitted a draft to Abhik on 5/4/10 for his comments.

I wonder whether we might have some time to initiate some preliminary discussion at the upcoming May 20-21 meeting. I know the schedule is busy but I would appreciate it if we could sit for even a few minutes. This could lead to a time frame for comments and editing so I can revise and edit this draft as many times as needed for submission at the next steering committee.



Thank you

Luc

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  
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>>> "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> 2/5/2010

>>> 11:01 AM >>>

Luc

The GDB subcommittee reviewed your proposal on their call this am. Though there was much enthusiasm, a revision is requested prior to presentation at a steering committee meeting. Barbara will send you comments in the next week.

Thanks

Rose

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network Pregnancy and Perinatology Branch Center for Developmental Biology and Perinatal Medicine Eunice Kennedy Shriver National Institute of Child Health and Human Development National Institutes of Health 6100 Executive Blvd., Room 4B03 MSC 7510 Bethesda, MD 20892 For overnight delivery use Rockville, MD 20852  
301-496-5575  
301-496-3790 (FAX)  
higginsr@mail.nih.gov

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Nancy Newman"; "Zaterka-Baxter, Kristin"  
**Cc:** "Beau Batton"; "Michelle Walsh"  
**Subject:** RE: HFNC  
**Date:** Tuesday, May 18, 2010 12:15:00 PM

---

Sounds ok as long as Michele agrees  
Rose

---

**From:** Nancy Newman [mailto:nxs5@case.edu]  
**Sent:** Monday, May 17, 2010 2:58 PM  
**To:** Zaterka-Baxter, Kristin  
**Cc:** Beau Batton; Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** Re: HFNC

I reviewed the SUPPORT as well. some of the SUPPORT info was related to when to stop the study oximeter in the first 14 days. I have revised the EBP Observational to define high flow >.5 lpm- is that what everyone wants? .....Nancy

On Mon, May 17, 2010 at 2:13 PM, Zaterka-Baxter, Kristin <kzaterka@rti.org> wrote:  
I did not see the answer to this spelled out in the MOP but is in the FAQ's and Tech Memo #4 as:

**FAQ:**

2. If NC's are used please clarify liter flow e.g. can 2L flow be used?  
Again, in the first 14 days the use of high flow nasal cannula (*1 liter or greater*) is discouraged in the Early CPAP arm for the same reasons.

**TM4: I presume Technical memo number 4 overrides the FAQ:**

- 1) High Flow Nasal Cannula, for purposes of this trial, is > *500cc/min*.  
a) An infant on >500cc/min of room air is considered to be on respiratory support.  
b) An infant on >500cc/min of room air should not have his oximeter d/c'd.

Thanks,  
Kris

*Kris Zaterka-Baxter  
RTI International  
3040 Cornwallis Road  
P.O. Box 12194  
RTP, NC 27709-2194 USA  
(tel) 919-485-7750  
(fax) 919.485.7762  
kzaterka@rti.org  
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*Federal Express/UPS/DHL Shipping Address:  
Kris Zaterka-Baxter  
RTI International  
3040 Cornwallis Road  
RTP, NC 27709 USA*

## Higgins, Rosemary (NIH/NICHD) [E]

---

**From:** Finer, Neil <nfiner@ucsd.edu>  
**Sent:** Monday, May 17, 2010 6:09 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; 'wcarlo@peds.uab.edu'  
**Cc:** 'adas@rti.org'  
**Subject:** RE: Support secondaries

Hi Rose

We need to look at saturations and Outcomes- but the most important look will be to look at NDI and saturations The look at death and saturations is essential for understanding the SpO2 paper and study We will also look at the population enrolled vs the eligible's as per my previous call to you. We will look at the short and later long term outcomes of infants enrolled compared with those who were not approached/consented - ie enrolled in the GDB in the same gestational ages as the study during the period of study enrollment.

This will allow us to determine if the difference in ANS was real, and the subsequent outcomes - ie death, severe IVH and NDI which one would postulate would be higher in the non-enrolled simultaneous cohort.

This information is essential to look at the way we do trials and enroll patients.

Thanks for your support

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

-----Original Message-----

**From:** Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]  
**Sent:** Monday, May 17, 2010 5:01 AM  
**To:** 'wcarlo@peds.uab.edu'; Finer, Neil  
**Cc:** 'adas@rti.org'  
**Subject:** Re: Support secondaries

This is the one on the list, correct??

Also - this study has been an immense amount of effort and - am very grateful to have both you and Neil to lead this study - i agree, the impact on the field will be profound!

Thanks  
Rose

----- Original Message -----

**From:** Wally Carlo, M.D. <[WCarlo@peds.uab.edu](mailto:WCarlo@peds.uab.edu)>

To: Higgins, Rosemary (NIH/NICHD) [E]; [nfiner@ucsd.edu](mailto:nfiner@ucsd.edu) <[nfiner@ucsd.edu](mailto:nfiner@ucsd.edu)>; [wcarlo@peds.uab.edu](mailto:wcarlo@peds.uab.edu) <[wcarlo@peds.uab.edu](mailto:wcarlo@peds.uab.edu)>  
Cc: [adas@rti.org](mailto:adas@rti.org) <[adas@rti.org](mailto:adas@rti.org)>  
Sent: Mon May 17 07:59:01 2010  
Subject: RE: Support secondaries

Rose and Neil:

In March I sent a protocol on saturations and ROP. It is the one we had input from RTI on the methods.

We should add it to the list. I will look for it and send it.

I thought the three presentations went very well. Too bad the room was so way out. Anyway, the timing with NEJM was also so good.

It has been great to work with both of you. These will be seminal papers.

Wally

-----Original Message-----

From: Higgins, Rosemary (NIH/NICHD) [E] <[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)>  
Sent: Monday, May 17, 2010 6:39 AM  
To: 'nfiner@ucsd.edu' <[nfiner@ucsd.edu](mailto:nfiner@ucsd.edu)>; 'wcarlo@peds.uab.edu' <[wcarlo@peds.uab.edu](mailto:wcarlo@peds.uab.edu)>  
Cc: 'adas@rti.org' <[adas@rti.org](mailto:adas@rti.org)>  
Subject: Support secondaries

Neil and Wally -

For the SUPPORT secondaries, please add to this list:

- 1 growth- Miami
- 2 neuroimaging-Hintz
- 3 breathing outcomes-stevens
- 4 antenatal consent (support enrolled vs non-consented and non-approached population-Finer
- 5 saturation and rop-Martin, Difiore, walsh
- 6 saturation and death- Carlo
- 7 BPD - phys + other- walsh + laptook
- 8 Center diffs - Cotten

Please add others so we can have a list for RTI for PAS 2011 Hope you got home safely!

Thanks

Rose

## Higgins, Rosemary (NIH/NICHD) [E]

---

**From:** Finer, Neil <nfiner@ucsd.edu>  
**Sent:** Monday, May 17, 2010 1:38 PM  
**To:** Das, Abhik; Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Support secondaries

You guys were great  
Lots more to come!!  
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

-----Original Message-----

**From:** Das, Abhik [<mailto:adas@rti.org>]  
**Sent:** Monday, May 17, 2010 6:09 AM  
**To:** Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil  
**Subject:** RE: Support secondaries

Thanks to all. This was a great experience for both Marie and me, and we also learned a lot from it.

Abhik

-----Original Message-----

**From:** Wally Carlo, M.D. [<mailto:WCarlo@peds.uab.edu>]  
**Sent:** Monday, May 17, 2010 8:04 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; [nfiner@ucsd.edu](mailto:nfiner@ucsd.edu)  
**Cc:** Das, Abhik  
**Subject:** RE: Support secondaries

It probably is. I had also a protocol on O2 saturation monitoring approved about 3 years ago that I have to go back and see what should be done with it.

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: 205 266 (b)

-----Original Message-----

From: Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]  
Sent: Monday, May 17, 2010 7:01 AM  
To: Wally Carlo, M.D.; 'nfiner@ucsd.edu'  
Cc: 'adas@rti.org'  
Subject: Re: Support secondaries

This is the one on the list, correct??

Also - this study has been an immense amount of effort and - am very grateful to have both you and Neil to lead this study - i agree, the impact on the field will be profound!

Thanks  
Rose

----- Original Message -----

From: Wally Carlo, M.D. <[WCarlo@peds.uab.edu](mailto:WCarlo@peds.uab.edu)>  
To: Higgins, Rosemary (NIH/NICHD) [E]; [nfiner@ucsd.edu](mailto:nfiner@ucsd.edu) <[nfiner@ucsd.edu](mailto:nfiner@ucsd.edu)>; [wcarlo@peds.uab.edu](mailto:wcarlo@peds.uab.edu) <[wcarlo@peds.uab.edu](mailto:wcarlo@peds.uab.edu)>  
Cc: [adas@rti.org](mailto:adas@rti.org) <[adas@rti.org](mailto:adas@rti.org)>  
Sent: Mon May 17 07:59:01 2010  
Subject: RE: Support secondaries

Rose and Neil:

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I thought the three presentations went very well. Too bad the room was so way out. Anyway, the timing with NEJM was also so good.

It has been great to work with both of you. These will be seminal papers.

Wally

-----Original Message-----

From: Higgins, Rosemary (NIH/NICHD) [E] <[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)>  
Sent: Monday, May 17, 2010 6:39 AM  
To: 'nfiner@ucsd.edu' <[nfiner@ucsd.edu](mailto:nfiner@ucsd.edu)>; 'wcarlo@peds.uab.edu' <[wcarlo@peds.uab.edu](mailto:wcarlo@peds.uab.edu)>  
Cc: 'adas@rti.org' <[adas@rti.org](mailto:adas@rti.org)>  
Subject: Support secondaries

Neil and Wally -

For the SUPPORT secondaries, please add to this list:

- 1 growth- Miami
- 2 neuroimaging-Hintz

3 breathing outcomes-stevens

4 antenatal consent (support enrolled vs non-consented and non-approached population-Finer

5 saturation and rop-Martin, Difiore, walsh

6 saturation and death- Carlo

7 BPD - phys + other- walsh + laptook

8 Center diffs - Cotten

Please add others so we can have a list for RTI for PAS 2011 Hope you got home safely!

Thanks

Rose

**From:** Das, Abhik  
**To:** Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu  
**Subject:** RE: Support secondaries  
**Date:** Monday, May 17, 2010 9:08:50 AM

---

Thanks to all. This was a great experience for both Marie and me, and we also learned a lot from it.

Abhik

-----Original Message-----

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]  
Sent: Monday, May 17, 2010 8:04 AM  
To: Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu  
Cc: Das, Abhik  
Subject: RE: Support secondaries

It probably is. I had also a protocol on O2 saturation monitoring approved about 3 years ago that I have to go back and see what should be done with it.

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: 205 266 (b)

-----Original Message-----

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
Sent: Monday, May 17, 2010 7:01 AM  
To: Wally Carlo, M.D.; 'nfiner@ucsd.edu'  
Cc: 'adas@rti.org'  
Subject: Re: Support secondaries

This is the one on the list, correct??

Also - this study has been an immense amount of effort and - am very grateful to have both you and Neil to lead this study - i agree, the impact on the field will be profound!

Thanks  
Rose

----- Original Message -----

From: Wally Carlo, M.D. <WCarlo@peds.uab.edu>  
To: Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu <nfiner@ucsd.edu>; wcarlo@peds.uab.edu <wcarlo@peds.uab.edu>  
Cc: adas@rti.org <adas@rti.org>  
Sent: Mon May 17 07:59:01 2010  
Subject: RE: Support secondaries

Rose and Neil:



In March I sent a protocol on saturations and ROP. It is the one we had input from RTI on the methods.

We should add it to the list. I will look for it and send it.

I thought the three presentations went very well. Too bad the room was so way out. Anyway, the timing with NEJM was also so good.

It has been great to work with both of you. These will be seminal papers.

Wally

-----Original Message-----

From: Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov>

Sent: Monday, May 17, 2010 6:39 AM

To: 'nfiner@ucsd.edu' <nfiner@ucsd.edu>; 'wcarlo@peds.uab.edu' <wcarlo@peds.uab.edu>

Cc: 'adas@rti.org' <adas@rti.org>

Subject: Support secondaries

Neil and Wally -

For the SUPPORT secondaries, please add to this list:

1 growth- Miami

2 neuroimaging-Hintz

3 breathing outcomes-stevens

4 antenatal consent (support enrolled vs non-consented and non-approached population-Finer

5 saturation and rop-Martin, Difiore, walsh

6 saturation and death- Carlo

7 BPD - phys + other- walsh + laptook

8 Center diffs - Cotten

Please add others so we can have a list for RTI for PAS 2011

Hope you got home safely!

Thanks

Rose

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Bara, Rebecca"; "Shankaran, Seetha"; "Sood, Beena"; "Pappas, Athina"  
**Cc:** "Gantz, Marie"  
**Subject:** RE: SUPPORT FU infants  
**Date:** Friday, May 14, 2010 4:54:00 PM

---

Thanks  
Rose

---

**From:** Bara, Rebecca [mailto:rbara@med.wayne.edu]  
**Sent:** Friday, May 14, 2010 4:53 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Shankaran, Seetha; Sood, Beena; Pappas, Athina  
**Cc:** 'Gantz, Marie'  
**Subject:** RE: SUPPORT FU infants

Hi Rose,

Still trying, here's the latest...

Thanks,  
Becky

*This message and any files transmitted with it may contain information that is privileged, confidential and exempt from disclosure. It is intended for use only by the person to whom it is addressed. If you have received this in error, please (1) do not forward or use this information in any way, (2) delete or destroy this message and its attachments and (3) please contact me immediately.*

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]  
**Sent:** Thursday, May 13, 2010 2:50 PM  
**To:** Bara, Rebecca; Shankaran, Seetha; Sood, Beena; Pappas, Athina  
**Cc:** 'Gantz, Marie'  
**Subject:** SUPPORT FU infants

Hi,  
We are missing the following SUPPORT FOLLOW UP outcomes. Let us know how you are doing.

Thanks for all the effort.

Rose

CENTER	NETWORK	FU_message
5	(b)	FU window has closed but NF05 and NF09a have not been completed.
5	(b)	FU window has closed but NF09a has not been completed.
5	(b)	FU window has closed but NF05 and NF09a have not been completed.
5	(b)	FU window has closed but NF05 and NF09a have not been completed.
5	(b)	FU window has closed but NF05 and NF09a have not been completed.

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network  
Pregnancy and Perinatology Branch  
Center for Developmental Biology and Perinatal Medicine  
 Eunice Kennedy Shriver National Institute of Child Health and Human Development  
National Institutes of Health  
6100 Executive Blvd., Room 4B03  
MSC 7510

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301-496-5575  
301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

**From:** [Bara, Rebecca](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Shankaran, Seetha](#); [Sood, Beena](#); [Pappas, Athina](#)  
**Cc:** "Gantz, Marie"  
**Subject:** RE: SUPPORT FU infants  
**Date:** Friday, May 14, 2010 4:53:30 PM  
**Attachments:** [SUPPORT Follow Up as of 5-14-10\[1\]\[1\].doc](#)

---

Hi Rose,

Still trying, here's the latest...

Thanks,  
Becky

*This message and any files transmitted with it may contain information that is privileged, confidential and exempt from disclosure. It is intended for use only by the person to whom it is addressed. If you have received this in error, please (1) do not forward or use this information in any way, (2) delete or destroy this message and its attachments and (3) please contact me immediately.*

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)]  
**Sent:** Thursday, May 13, 2010 2:50 PM  
**To:** Bara, Rebecca; Shankaran, Seetha; Sood, Beena; Pappas, Athina  
**Cc:** 'Gantz, Marie'  
**Subject:** SUPPORT FU infants

Hi,

We are missing the following SUPPORT FOLLOW UP outcomes. Let us know how you are doing.

Thanks for all the effort.

Rose

CENTER	NETWORK	FU_message
5	(b)	FU window has closed but NF05 and NF09a have not been completed.
5	(b)	FU window has closed but NF09a has not been completed.
5	(b)	FU window has closed but NF05 and NF09a have not been completed.
5	(b)	FU window has closed but NF05 and NF09a have not been completed.
5	(b)	FU window has closed but NF05 and NF09a have not been completed.

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network  
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301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

**As of May 14, 2010**

**Center 05 18 – 22 month SUPPORT Follow-Up outcomes outstanding:**

(b) (6) We have scheduled multiple visits with this mother which she has never kept. Still trying.

(b) (6) The BSID remains outstanding. It has been difficult for the family to schedule an appointment. Mom has completed (b) (6) Scheduled for May 28<sup>th</sup>!!

(b) (6) This child was transferred to U of M during the NICU stay and now receives all Follow-Up care there. The child was D/C home vent-dependent. A home visit has been offered, parents are considering.

(b) (6) We have scheduled multiple visits with this father (mother speaks very little English), none kept. Father does not see the need for this visit, but is still considering.

(b) (6) This child has moved to Georgia just outside of Atlanta—all recent contact information has been forwarded to Emory. They've so far been unable to contact the mother.

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Fuller, Martha"; "Finer, Neil"; "Rich, Wade"; "Vaucher, Yvonne"  
**Cc:** "Gantz, Marie"  
**Subject:** RE: SUPPORT follow up  
**Date:** Friday, May 14, 2010 10:33:00 AM

---

OK  
Thanks for getting back to us!  
Rose

---

**From:** Fuller, Martha [mailto:mgfuller@ucsd.edu]  
**Sent:** Friday, May 14, 2010 10:33 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; Rich, Wade; Vaucher, Yvonne  
**Cc:** 'Gantz, Marie'  
**Subject:** RE: SUPPORT follow up

Family refused follow-up. (including offers of home visit).  
I will check on the status of the paperwork.  
Martha

Martha G. Fuller, RN, MSN  
Pediatric Nurse Practitioner  
UCSD Infant Special Care Follow-up Program  
(619) 543-3771 (office)  
(619) 543-3822 (direct line/voice mail)

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---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Thursday, May 13, 2010 11:56 AM  
**To:** Finer, Neil; Rich, Wade; Vaucher, Yvonne; Fuller, Martha  
**Cc:** 'Gantz, Marie'  
**Subject:** SUPPORT follow up

Hi,  
We are missing the following SUPPORT FOLLOW UP outcomes. Let us know how you are doing.

Thanks for all the effort.

Rose

CENTER	NETWORK	FU_message
22	(b)	FU window has closed but NF05 and NF09a have not been completed.

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network  
Pregnancy and Perinatology Branch  
Center for Developmental Biology and Perinatal Medicine  
Eunice Kennedy Shriver National Institute of Child Health and Human Development  
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301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)**

**From:** [Auman, Jeanette O.](#)  
**To:** [Gantz, Marie](#); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Poundstone, Margaret](#); [Kennedy, Kathleen A](#); [Evans, Patricia W](#); [Tyson, Jon E](#); [Mcdavid, Georgia E](#)  
**Cc:** [Auman, Jeanette O.](#)  
**Subject:** RE: SUPPORT follow up  
**Date:** Thursday, May 13, 2010 6:32:12 PM

---

Layne,

You'll be able to key missing codes for either the entire date of death or just the portion of the date field that is unknown (so for example, if you know the month and year, you can key 03\*\*2010 to denote the missing day portion of the date or if you only know the year, you can key \*\*\*\*2010). To further explain the missing date, go ahead and F5 it and provide a short explanation.

Thanks,

*Jenny*

---

**From:** Gantz, Marie  
**Sent:** Thursday, May 13, 2010 3:42 PM  
**To:** 'Higgins, Rosemary (NIH/NICHD) [E]'; 'Poundstone, Margaret'; Kennedy, Kathleen A; Evans, Patricia W; Tyson, Jon E; Mcdavid, Georgia E  
**Cc:** Auman, Jeanette O.  
**Subject:** RE: SUPPORT follow up

I believe that the death can be recorded without an actual death date (Jenny, please correct me if I'm wrong). I would suggest F5ing the missing date to explain.

Thanks,

Marie

Marie Gantz, Ph.D.  
Research Statistician  
RTI International  
[mgantz@rti.org](mailto:mgantz@rti.org)  
828-254-6255

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]  
**Sent:** Thursday, May 13, 2010 3:32 PM  
**To:** 'Poundstone, Margaret'; Kennedy, Kathleen A; Evans, Patricia W; Tyson, Jon E; Mcdavid, Georgia E  
**Cc:** Gantz, Marie  
**Subject:** RE: SUPPORT follow up

Marie

Can the death be inputted without the date of death known??

Also, sometimes the dates can appear in a published obituary – it may be worth doing a Google search for the child's name.

Thanks for getting back to me so quickly!!

Rose

---

**From:** Poundstone, Margaret [<mailto:Margaret.Poundstone@uth.tmc.edu>]  
**Sent:** Thursday, May 13, 2010 2:59 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Kennedy, Kathleen A; Evans, Patricia W; Tyson, Jon E; Mcdavid, Georgia E



**Cc:** 'Gantz, Marie'  
**Subject:** RE: SUPPORT follow up

Rose

(b) has proven to be very difficult to get a hold of. The family will not return phone calls, emails, or letters even when offered double incentive and a home visit. Still working on it.

(b) expired; however, grandma was unable to give me an exact date of her death, so I'm hoping it will eventually show up on the "death database". If it does not, I may be able to mark that part of the data as "unknown".

Thanks,  
Layne

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Thursday, May 13, 2010 1:55 PM  
**To:** Kennedy, Kathleen A; Evans, Patricia W; Tyson, Jon E; Mcdavid, Georgia E; Poundstone, Margaret  
**Cc:** 'Gantz, Marie'  
**Subject:** SUPPORT follow up

Hi,  
We are missing the following SUPPORT FOLLOW UP outcomes. Let us know how you are doing.

Thanks for all the effort.

Rose

CENTER	NETWORK	FU_message
18	(b)	FU window has closed but NF05 and NF09a have not been completed.
18	(b)	FU window has closed but NF05 and NF09a have not been completed.

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network  
Pregnancy and Perinatology Branch  
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For overnight delivery use Rockville, MD 20852  
301-496-5575  
301-496-3790 (FAX)  
higginsr@mail.nih.gov

**From:** [Cunningham, Meg](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Subject:** RE: PAS 2011  
**Date:** Thursday, May 13, 2010 5:10:11 PM

---

What is SUPPORT Neuroimaging secondary? Didn't Susan present already?

-----Original Message-----

From: Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]  
Sent: Thursday, May 13, 2010 3:30 PM  
To: Cunningham, Meg; Archer, Stephanie (NIH/NICHD) [E]  
Cc: Das, Abhik  
Subject: PAS 2011

This is the approved Vitamin A protocol.

Also,

For the main studies, we need to list:

term and near term hypotension (Fernandez)

INS-2 (potentially late breaker)

Hypothermia extended FU

SUPPORT Neuroimaging secondary

SUPPORT Growth study

Breathing outcomes and SUPPORT 18-22 month FU likely won't be completed in time for PAS 2011 SUPPORT Secondaries from the primary data set(I

need a list from Neil and Wally) Premie aEEG Apo e

EOS(?)

Genomics repository studies

Am I missing any??

Rose

**From:** Bell, Edward  
**To:** Eastman, Diane; Higgins, Rosemary (NIH/NICHD) [E]; Johnson, Karen; Acarregui, Michael  
**Cc:** Gantz, Marie  
**Subject:** RE: SUPPORT FU  
**Date:** Thursday, May 13, 2010 4:10:31 PM

---

Fantastic! Well done.

---

**From:** Eastman, Diane  
**Sent:** Thursday, May 13, 2010 3:01 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Johnson, Karen; Bell, Edward; Acarregui, Michael  
**Cc:** 'Gantz, Marie'  
**Subject:** RE: SUPPORT FU

Rose,

This is the one who moved to Maryland. She was seen last Friday the 7<sup>th</sup>. I'm waiting to receive the forms back from there and I have already done the other questionnaire information by phone. Once I receive the neuro exam form and Bayley test form, we'll be able to get her entered. Hopefully that will be soon. Diane

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Thursday, May 13, 2010 1:57 PM  
**To:** Johnson, Karen; Bell, Edward; Acarregui, Michael; Eastman, Diane  
**Cc:** 'Gantz, Marie'  
**Subject:** SUPPORT FU

Hi,

We are missing the following SUPPORT FOLLOW UP outcomes. Let us know how you are doing.

This may be the infant who moved to the East Coast for whom there is a plan to see in the next month.

Thanks for all the effort.

Rose

CENTER	NETWORK	FU_message
24	(b)	FU window has closed but NF05 and NF09a have not been completed.

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network  
Pregnancy and Perinatology Branch  
Center for Developmental Biology and Perinatal Medicine  
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301-496-3790 (FAX)  
higginsr@mail.nih.gov

**From:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**To:** ["Poundstone, Margaret"](#)  
**Subject:** RE: SUPPORT follow up  
**Date:** Thursday, May 13, 2010 3:34:00 PM

---

OK, thanks – just a thought!!!

We have a primary outcome for this unfortunate infant  
Rose

---

**From:** Poundstone, Margaret [mailto:[Margaret.Poundstone@uth.tmc.edu](mailto:Margaret.Poundstone@uth.tmc.edu)]  
**Sent:** Thursday, May 13, 2010 3:33 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: SUPPORT follow up

I've googled several times, and found nothing. It's a very strange situation.

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)]  
**Sent:** Thursday, May 13, 2010 2:32 PM  
**To:** Poundstone, Margaret; Kennedy, Kathleen A; Evans, Patricia W; Tyson, Jon E; Mcdavid, Georgia E  
**Cc:** 'Gantz, Marie'  
**Subject:** RE: SUPPORT follow up

Marie

Can the death be inputted without the date of death known??

Also, sometimes the dates can appear in a published obituary – it may be worth doing a Google search for the child's name.

Thanks for getting back to me so quickly!!  
Rose

---

**From:** Poundstone, Margaret [mailto:[Margaret.Poundstone@uth.tmc.edu](mailto:Margaret.Poundstone@uth.tmc.edu)]  
**Sent:** Thursday, May 13, 2010 2:59 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Kennedy, Kathleen A; Evans, Patricia W; Tyson, Jon E; Mcdavid, Georgia E  
**Cc:** 'Gantz, Marie'  
**Subject:** RE: SUPPORT follow up

Rose

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(b) (6) expired; however, grandma was unable to give me an exact date of her death, so I'm hoping it will eventually show up on the "death database". If it does not, I may be able to mark that part of the data as "unknown".

Thanks,  
Layne

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Thursday, May 13, 2010 1:55 PM  
**To:** Kennedy, Kathleen A; Evans, Patricia W; Tyson, Jon E; Mcdavid, Georgia E; Poundstone, Margaret  
**Cc:** 'Gantz, Marie'  
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Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network  
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For overnight delivery use Rockville, MD 20852  
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301-496-3790 (FAX)  
higginsr@mail.nih.gov

**From:** Das, Abhik  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: \*\*\*\*CONFIDENTIAL UPDATE ON SUPPORT PAPERS AND EMBARGO\*\*\*\*\*  
**Date:** Thursday, May 13, 2010 3:00:27 PM  
**Attachments:** Neonatal studies rev2.doc

---

Here is the fixed version. I did not use 'saturation targets' to make it more accessible. Let me know if you see any other errors.

Thanks

Abhik

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Thursday, May 13, 2010 12:59 PM  
**To:** Das, Abhik  
**Subject:** RE: \*\*\*\*CONFIDENTIAL UPDATE ON SUPPORT PAPERS AND EMBARGO\*\*\*\*\*

Abhik

We do not approve or disapprove individual releases for the grantees.  
I would offer the following factual suggestions:

The study was performed on infants from 24-27 weeks (not 23-26 weeks). We really didn't test higher oxygen flows, we tested a higher and lower oxygen saturation targets.

Thanks  
Rose

---

**From:** Das, Abhik [mailto:adas@rti.org]  
**Sent:** Thursday, May 13, 2010 11:28 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** FW: \*\*\*\*CONFIDENTIAL UPDATE ON SUPPORT PAPERS AND EMBARGO\*\*\*\*\*

Rose:

We have prepared the attached news item for posting on the RTI external website ([www.rti.org](http://www.rti.org)) once the embargo is lifted. Please let me know if you approve, or have any other comments.

Thanks

Abhik

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Wednesday, May 12, 2010 2:33 PM  
**To:** 'Finer, Neil'; 'Rich, Wade'; Gantz, Marie; 'Nancy Newman'; 'Anthony Piazza (Anthony.Piazza@oz.ped.emory.edu)'; ' (susie.buchter@oz.ped.emory.edu)'; 'Brenda Morris'; 'Laroia,

Nirupama'; 'Phelps, Dale'; 'Duara, Shahnaz'; 'Vivek Narendran'; 'vineet.bhandari@yale.edu'; 'Sood, Beena'; 'Michael O` Shea'; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Das, Abhik; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); 'Brenda Poindexter'; 'Carlo Waldemar (E-mail)'; cotte010@mc.duke.edu; Wallace, Dennis; 'Ed Bell'; 'Ed Donovan'; 'Ehrenkranz Richard (E-mail)'; Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; 'Kristi Watterberg'; Kurt Schibler [kurt.schibler@cchmc.org]; 'Matthew Bizzarro'; 'Michelle Walsh'; 'Mickey Caplan'; 'Oh William (E-mail)'; 'Pablo Sanchez'; Poole, W. Kenneth; 'Roger Faix'; 'Ronald Goldberg'; 'Seetha Shankaran'; 'Stevenson David (E-mail)'; [SCRN] Stoll, Barbara; 'Tyson Jon (E-mail)'; VanMeurs, Krisa

**Cc:** Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Cunningham, Meg; Huitema, Carolyn Petrie

**Subject:** \*\*\*\*CONFIDENTIAL UPDATE ON SUPPORT PAPERS AND EMBARGO\*\*\*\*\*

**Hello again everyone:**

**I have several items regarding SUPPORT.**

**Both manuscripts are attached along with the appendices.**

**The authors appear at the end of the paper as formal “authors” due to space limits from NEJM. I have also attached the NIH press release for the papers. Finally, there is an editorial which will appear on-line and in the May 27 issue of NEJM.**

**ALL OF THIS INFORMATION IS SUBJECT TO EMBARGO RULES AND NOT TO BE RELEASED UNTIL SUNDAY MAY 16 at 1 PM ET. This information can be *confidentially shared with your institutional press/public affairs office* as long as the embargo is respected.**

**Thanks to everyone at each and every site for all of the hard work and effort on this study. A special appreciation of gratitude goes to the coordinators who really went above and beyond to get the patients enrolled in this difficult study.**

**A very, very special and heart felt thanks to Neil and Wally for all of their hard work, commitment, effort and patience to bring this to completion!!!!**

**Both SUPPORT Papers will be *accelerated Online First release* scheduled to coincide with the presentations of the results at the American Thoracic Society's annual meeting on Sunday May 16, 2010. The on-line release will occur at 1 PM EDT on 5/16/2010. The print publication is slated to appear in the May 27, 2010 issue of NEJM.**

If you have any questions, please contact me

Rose

Rosemary D. Higgins, MD

Program Scientist for the Neonatal Research Network

Pregnancy and Perinatology Branch

Center for Developmental Biology and Perinatal Medicine

Eunice Kennedy Shriver National Institute of Child Health and Human Development

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## New Study Sheds Light on Benefits, Methods of Using Oxygen to Improve Preterm Infants' Survival

RESEARCH TRIANGLE PARK, N.C. -- A new study provides valuable insights on the use of oxygen by medical professionals seeking to increase the chances for healthy survival in very preterm infants.

The study, published in the *New England Journal of Medicine*, was conducted by researchers from the Neonatal Research Network, a multi-center clinical research network funded by the National Institutes of Health's *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, for which RTI International serves as the data coordinating center. This study also received funding from the National Heart, Lung, and Blood Institute

The study tested two different treatment strategies simultaneously on the same group of infants (born at 24<sup>3</sup>-27<sup>6</sup> weeks gestation). In the first test, researchers assessed the potential benefit of increasing the ~~flow~~amount of oxygen to very preterm infants.

For the second test, researchers compared the potential benefit of using a device known as a continuous positive airway pressure (CPAP) machine that is typically used for adults with sleep apnea, with a more traditional ventilator. The CPAP machine can blow air through a preterm infant's nostrils, to gently inflate the lungs.

The results:

- Higher oxygen levels were found to improve preterm infants' survival, but also increase the risk for eye disease.
- Using a CPAP device is as safe and effective as a ventilator in managing breathing problems in premature babies, with fewer complications.

"This study provides much needed data on health outcomes in severely premature babies given different levels of oxygen," said Abhik Das, Ph.D., senior research statistician at RTI and a co-author of the paper. "In addition, it shows that CPAP is a safe, effective and less invasive alternative to the ventilator in helping these babies breathe, and may result in fewer complications."

Researchers plan to evaluate the children again when they are 18 to 22 months old, to learn whether any developmental differences arise among the children who took part in the different treatments arms of the study.

The study results will be presented on May 16 at the American Thoracic Society 2010 International Conference in New Orleans and also appear in two articles published online by The New England Journal of Medicine.

-end-

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "kwatterberg@salud.unm.edu"; "Conra Lacy"; "JaFuller@salud.unm.edu (JaFuller@salud.unm.edu)"; "Rebecca Montman"  
**Cc:** "Gantz, Marie"  
**Subject:** SUPPORT Follow Up  
**Date:** Thursday, May 13, 2010 2:57:00 PM

---

Hi,  
We are missing the following SUPPORT FOLLOW UP outcomes. Let us know how you are doing.

Thanks for all the effort.

Rose

CENTER	NETWORK	FU_message
26	(b)	FU window has closed but NF05 and NF09a have not been completed.

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network  
Pregnancy and Perinatology Branch  
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higginsr@mail.nih.gov

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**To:** "kwatterberg@salud.unm.edu"; "Conra Lacy"; "JaFuller@salud.unm.edu (JaFuller@salud.unm.edu)"; "Rebecca Montman"  
**Cc:** "Gantz, Marie"  
**Subject:** SUPPORT Follow Up  
**Date:** Thursday, May 13, 2010 2:57:00 PM

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Rose

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301-496-3790 (FAX)  
higginsr@mail.nih.gov

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Johnson, Karen"; "Bell, Edward"; "Acarregui, Michael"; "Eastman, Diane"  
**Cc:** "Gantz, Marie"  
**Subject:** SUPPORT FU  
**Date:** Thursday, May 13, 2010 2:56:00 PM

---

Hi,

We are missing the following SUPPORT FOLLOW UP outcomes. Let us know how you are doing.

This may be the infant who moved to the East Coast for whom there is a plan to see in the next month.

Thanks for all the effort.

Rose

CENTER	NETWORK	FU_message
24	(b)	FU window has closed but NF05 and NF09a have not been completed.

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network  
Pregnancy and Perinatology Branch  
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higginsr@mail.nih.gov

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Finer, Neil"; "Rich, Wade"; "Yvonne Vaucher"; "Fuller, Martha"  
**Cc:** "Gantz, Marie"  
**Subject:** SUPPORT follow up  
**Date:** Thursday, May 13, 2010 2:55:00 PM

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Hi,

We are missing the following SUPPORT FOLLOW UP outcomes. Let us know how you are doing.

Thanks for all the effort.

Rose

<b>CENTER</b>	<b>NETWORK</b>	<b>FU_message</b>
22	(b)	FU window has closed but NF05 and NF09a have not been completed.

Rosemary D. Higgins, MD  
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higginsr@mail.nih.gov

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Kathleen.A.Kennedy@uth.tmc.edu"; "Evans, Patricia W."; "Tyson Jon (E-mail)"; "Georgia.E.McDavid@uth.tmc.edu"; "Poundstone, Margaret"  
**Cc:** "Gantz, Marie"  
**Subject:** SUPPORT follow up  
**Date:** Thursday, May 13, 2010 2:54:00 PM

---

Hi,  
We are missing the following SUPPORT FOLLOW UP outcomes. Let us know how you are doing.

Thanks for all the effort.

Rose

<b>CENTER</b>	<b>NETWORK</b>	<b>FU_message</b>
18	(b)	FU window has closed but NF05 and NF09a have not been completed.
18	(b)	FU window has closed but NF05 and NF09a have not been completed.

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:** vanmeurs@leland.stanford.edu; srhintz@stanford.edu; Bethany Ball  
**Cc:** "Gantz, Marie"  
**Subject:** SUPPORT FU  
**Date:** Thursday, May 13, 2010 2:53:00 PM

---

Hi,  
We are missing the following SUPPORT FOLLOW UP outcomes. Let us know how you are doing.

Thanks for all the effort.

Rose

<b>CENTER</b>	<b>NETWORK</b>	<b>FU_message</b>
15	(b)	FU window has closed but NF05 and NF09a have not been completed.

Rosemary D. Higgins, MD  
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 Eunice Kennedy Shriver National Institute of Child Health and Human Development  
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301-496-3790 (FAX)  
higginsr@mail.nih.gov

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** [alantook@WIHRI.org](mailto:alantook@WIHRI.org); [Yohr, Betty](mailto:Yohr, Betty); [ahensman@wihri.org](mailto:ahensman@wihri.org); "[sventura@wihri.org](mailto:sventura@wihri.org)"  
**Cc:** "[Gantz, Marie](mailto:Gantz, Marie)"  
**Subject:** SUPPORT FU  
**Date:** Thursday, May 13, 2010 2:52:00 PM

---

Hi,

We are missing the following SUPPORT FOLLOW UP outcomes. Let us know how you are doing.

Thanks for all the effort.

This is terrific given the outstanding recruitment at your site!!

Rose

CENTER	NETWORK	FU_message
14	(b)	FU window has closed but NF05 and NF09a have not been completed.
14	(b)	FU window has closed but NF05 and NF09a have not been completed.

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network  
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**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "hpoindex@iupui.edu"; "Dusick, Anna M."; "ldw@iupui.edu"; "Faithe Hammer"  
**Cc:** "Fuller, Martha"  
**Subject:** SUPPORT OUTCOMES  
**Date:** Thursday, May 13, 2010 2:51:00 PM

---

Hi,  
We are missing the following SUPPORT FOLLOW UP outcomes. Let us know how you are doing.

Thanks for all the effort.

Rose

CENTER	NETWORK	FU_message
12	(b)	FU window has closed but NF09a has not been completed.
12	(b)	FU window has closed but NF05 and NF09a have not been completed.

Rosemary D. Higgins, MD  
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higginsr@mail.nih.gov

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "rbara@med.wayne.edu"; "sshankar@med.wayne.edu"; "Sood, Beena"; "Pappas, Athina"  
**Cc:** "Gantz, Marie"  
**Subject:** SUPPORT FU infants  
**Date:** Thursday, May 13, 2010 2:50:00 PM

---

Hi,  
We are missing the following SUPPORT FOLLOW UP outcomes. Let us know how you are doing.

Thanks for all the effort.

Rose

<b>CENTER</b>	<b>NETWORK</b>	<b>FU_message</b>
5	(b)	FU window has closed but NF05 and NF09a have not been completed.
5	(b)	FU window has closed but NF09a has not been completed.
5	(b)	FU window has closed but NF05 and NF09a have not been completed.
5	(b)	FU window has closed but NF05 and NF09a have not been completed.
5	(b)	FU window has closed but NF05 and NF09a have not been completed.

Rosemary D. Higgins, MD  
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higginsr@mail.nih.gov

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** [SCRN] Stoll, Barbara; Ira Adams-Chapman; ellen\_hale@oz.ped.emory.edu  
**Cc:** "Gantz, Marie"  
**Subject:** SUPPORT FU  
**Date:** Thursday, May 13, 2010 2:50:00 PM

---

Hi,  
We are missing the following SUPPORT FOLLOW UP outcomes. Let us know how you are doing.

Thanks for all the effort.

Rose

CENTER	NETWORK	FU_message
9	(b)	FU window has closed but NF05 and NF09a have not been completed.
9	(b)	FU marked as complete (per NF10/SF10) but NF05 has not been completed.

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network  
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higginsr@mail.nih.gov

**From:** [Gantz, Marie](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\)](#) [E]  
**Cc:** [Das, Abhik](#)  
**Subject:** SUPPORT missing FU outcomes  
**Date:** Thursday, May 13, 2010 2:03:35 PM  
**Attachments:** [Infants with missing FU outcomes 13MAY10.xls](#)

---

Rose,

Attached is the list of SUPPORT infants who are missing FU outcomes this month.

Marie

Marie Gantz, Ph.D.  
Research Statistician  
RTI International  
[mgantz@rti.org](mailto:mgantz@rti.org)  
828-254-6255

Missing\_FU

CENTER	NETWORK	FU_message
5	(b) (6)	FU window has closed but NF05 and NF09a have not been completed.
5		FU window has closed but NF09a has not been completed.
5		FU window has closed but NF05 and NF09a have not been completed.
5		FU window has closed but NF05 and NF09a have not been completed.
5		FU window has closed but NF05 and NF09a have not been completed.
9		FU window has closed but NF05 and NF09a have not been completed.
9		FU marked as complete (per NF10/SF10) but NF05 has not been completed.
12		FU window has closed but NF09a has not been completed.
12		FU window has closed but NF05 and NF09a have not been completed.
14		FU window has closed but NF05 and NF09a have not been completed.
14		FU window has closed but NF05 and NF09a have not been completed.
15		FU window has closed but NF05 and NF09a have not been completed.
18		FU window has closed but NF05 and NF09a have not been completed.
18		FU window has closed but NF05 and NF09a have not been completed.
22		FU window has closed but NF05 and NF09a have not been completed.
24		FU window has closed but NF05 and NF09a have not been completed.
26		FU window has closed but NF05 and NF09a have not been completed.

**From:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**To:** ["Cunningham, Meg"](#)  
**Subject:** FW: SUPPORT data queries  
**Date:** Thursday, May 13, 2010 1:13:00 PM  
**Attachments:** [cpap\\_center\\_and\\_learning\\_effects\\_4-21-10final.docx](#)  
[oxygen-SUPPORT\\_secondary\\_4-21-10final.docx](#)

---

---

**From:** Michael Cotten [mailto:cotte010@mc.duke.edu]  
**Sent:** Saturday, May 01, 2010 8:19 PM  
**To:** Neil Finer; Wally Carlo, M.D.  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]; Ronald N Goldberg  
**Subject:** SUPPORT data queries

Hi Neil and Wally, Rose and Ron...

first..congratulations on the first presentation of results and publication of the manuscripts!!!!

here are two secondary data analysis proposals for SUPPORT,,,,one looking at the DR CPAP portion of the study, the other at the oxygen sat target portion.

thanks

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: 919-681-6024  
fax: 919-681-6065  
email: cotte010@mc.duke.edu

## **Center Effects within the SUPPORT Trial**

Lenfestey, Cotten, Smith, Tanaka, Laughon, Goldberg, RTI, SUPPORT subcommittee (Finer)

### **Abstract**

The NICHD Neonatal Research Network's SUPPORT trial tested initiation of delivery room NCPAP followed by a mechanical ventilation algorithm intended to accelerate extubation if intubation was needed against use of delivery room intubation and administration of surfactant, followed by a mechanical ventilation algorithm that was less permissive of extubation. Variations in center expertise in interventions tested in clinical trials can impact overall trial outcome, as noted in the Neonatal HIFI trial.<sup>1</sup> When clinicians in the hundreds of centers caring for extremely low gestational age infants consider the results of the SUPPORT trial, they are likely to ask two questions: 1) If my centers' rate of survival free of chronic lung disease among infants of a similar demographic as the study is high, and the standard at my center is early intubation and surfactant, should I change practice and do as well and maybe better with a delivery room CPAP strategy? and 2) If I adopt NCPAP, will the first infants I try it on have as good a chance at success as the 40<sup>th</sup> or 50<sup>th</sup>? Data collected during the SUPPORT trial will be useful to address these questions. Prior to and throughout the period of enrollment in the SUPPORT trial, centers which had a standard approach of intubation and administering surfactant early in the delivery room or the first postnatal hour prior to study participation continued to have among the highest survival and lowest rates of chronic lung disease in the Network. It is unknown whether effects related to delivery room and respiratory support approach noted in the overall trial were consistently noted among the infants enrolled in the high performing centers, or if the centers with prior adoption of delivery room NCPAP saw a consistent outcome in the infants randomized to NCPAP compared to sites adopting this practice for the first time in the clinical trial. Because study randomization was stratified by site, and the 4 centers with high performance (Brown, UAB, Duke, and Miami) enrolled over 300 infants, a carefully done subgroup analysis to assess whether the effect noted in these 4 benchmark centers was consistent with overall trial results is feasible. Assessment of whether or not outcome of infants in the NCPAP arm is associated with center experience with delivery room NCPAP can be addressed with analysis of clusters of infants enrolled throughout the study at each center, i.e., did infants enrolled in the NCPAP arm early in the study fare the same as infants enrolled later in the study at that center?

**Purpose:** The overall purpose of this proposal is to assess how adopting a new delivery room approach influenced survival and pulmonary outcomes, and whether adopting the new approach was equally successful early and late during the clinical trial.

**Aim 1:** Assess whether SUPPORT trial overall results were consistent with results in the 300+ subjects enrolled and randomized at centers with consistently good survival and low rates of chronic lung disease (Brown, UAB, Duke, Miami)

**Aim 2.** Assess whether there was a center-specific NCPAP training effect among infants enrolled in the NCPAP arm of the SUPPORT trial at sites which had not used delivery room NCPAP as usual care prior to the trial .

**Statement of the Problem:** Clinicians caring for extremely low gestational age newborn (ELGAN) infants have adopted strategies for initial respiratory support (use of surfactant after endotracheal intubation or initial use of continuous positive airway pressure and later rescue intubation and surfactant treatment) and ventilator management based on available evidence from high quality clinical trials, and the less validated but compelling single center reports and

“experience and reason.” Using this combination, there is extreme site variation in the rate of survival free of BPD at Network centers.<sup>2</sup> The NICHD neonatal Research network SUPPORT trial tested the hypothesis of whether or not initial NCPAP and subsequent stringent ventilator management parameters would improve survival free of bronchopulmonary dysplasia (BPD) compared with initial intubation with surfactant administration and more conservative ventilator management. Before initiation of the study, and throughout the study period, several centers, all of whom primarily used initial intubation and surfactant administration prior to the study, consistently had the highest survival free of BPD. It is not known whether the trend in the primary outcome noted in the overall trial was noted in the cohort of subjects enrolled and randomized at the benchmark centers that used initial intubation and surfactant for ELGANs. This query will inform potential adopters of NCPAP regarding the potential clinical and economic impact of adopting NCPAP in the delivery room in sites with high rates of survival free of BPD. It is also not known whether infants enrolled at sites which had not made initial NCPAP standard practice prior to the study start-up were as successful maintaining infants randomized to NCPAP on NCPAP throughout the first 14 postnatal days at the start of study enrollment as at the end of enrollment. This query would be important to inform new adopters of the likelihood of a learning curve for adopting NCPAP in the delivery room.

***Aims 1 and 2:***

Study Design: Retrospective post hoc subgroup analysis (Aim 1) and retrospective cohort study (Aim 2).

Study population:

*Inclusion criteria*

1. Infants in enrolled in the SUPPORT trial

*Exclusion criteria*

1. None

Study intervention:

There is no specific study intervention. This will be analysis of existing data.

Primary and Secondary Outcomes:

Aim 1:

Primary outcome: death or BPD

Secondary outcomes: death or BPD separately.

Aim 2:

Primary Outcome: death or intubated during the first 14 postnatal days.

Secondary Outcome: death or BPD

Statistical Plans:

*Outcome variables*

1. Death or BPD



2. Death
3. BPD
4. Completion of 14 days of NCPAP

*Predictor variables for multivariable analyses*

1. gestational age
2. gender
3. race
4. antenatal steroids
5. multiple birth
6. small for gestational age (SGA)

**Targeted Analyses**

**Aim 1. Testing results in 4 benchmark centers**

Consistent with recently published subgroup analysis guidelines<sup>3</sup>, We will perform two post-hoc subgroup analyses with 2 levels comparing heterogeneity of odd ratios for the primary outcomes between group 1 defined as the 4 Low BPD and High survival sites vs. Group 2, the 11 remaining centers (Cincinnati is excluded as it was a training site for NCPAP in the delivery room). We also will assess whether or not the primary outcome measured among infants enrolled at the 4 Low BPD and high survival sites before the study is homogenous with the overall outcome of the clinical trial using methodologies testing for homogeneity of study results for subgroup analysis. These analyses will involve statistical tests for interaction between the center level variable and the outcome. We plan to calculate point estimates and confidence intervals for effect size of the center level variable using the Breslow-Day test for heterogeneity of odds ratios. We will use multivariable logistic regression to determine if group has an effect on outcome. Finally we will correct p-values for multiple comparisons using the equation  $1-(1-p)^K$  where p is our accepted alpha error and K is the number of comparisons<sup>3</sup>.

**Aim 2. Testing for consistency of successful NCPAP maintenance throughout enrollment.**

We will perform two exploratory visual analyses and more traditional exploratory multivariable logistic regression models

**Visual Analysis #1.** Each center would have enrollment in the CPAP arm (X axis) and primary outcome (Y axis) plotted in two dimensions. The Y axis score of 0 for the outcome, survival without intubation in the first 14 postnatal days and a score of 1 for death or intubation within the first 14 postnatal days. The X axis would be the order of enrollment at each site. The first baby enrolled at a site would be plotted at the X axis point of '1', the second baby at '2', and so on. This would be the equivalent of a multivariable logistic regression predicting the primary outcome for NCPAP arm infants testing whether order enrolled was associated with outcome.

**Visual Analysis #2,** using each center's cohort randomized to NCPAP, would plot by month of study enrollment, to assess whether the course of the study use of NCPAP (and familiarity with the procedure overall) was associated with outcome among the NCPAP enrolled infants. Again, the score "0" would be assigned if the infant survived the first 14 postnatal days and was not intubated, and "1" would be assigned if the baby was intubated or died in the first 14 postnatal days. For example, the X axis would have a block for September 2008, 0's and 1's would be plotted, within each month of enrollment block.

These 2 visual models would be the equivalent of a logistic regression predicting the primary outcome for NCPAP arm infants testing whether order enrolled or time during the study was associated with outcome.

We will perform two exploratory analyses using multivariable logistic regression using infants assigned to the NCPAP arm to determine if centers became more successful at maintaining subjects on NCPAP as they gained experience. The outcome for these two analyses is the composite of intubation during the first 14 postnatal days or death. Analysis 1#: Each infant would be assigned a variable based on the order of enrollment at their respective site. We will then perform a multivariable logistic regression to determine magnitude of enrollment order effect, with the additional predictor variables as listed (GA, gender, race, antenatal steroids, multiple birth, and SGA)

Analysis 2: Each infant would be assigned a variable based on the study month of enrollment at their respective site. We will then perform a multivariable logistic regression to determine magnitude of enrollment order effect on the composite outcome of intubation during the first 14 postnatal days or death, with the additional predictor variables as listed (GA, gender, race, antenatal steroids, multiple birth, and SGA).

## References

1. Bryan AC, Froese AB. Reflections on the HIFI trial. *Pediatrics*. 1991;87:565-567.
2. Fanaroff, A.A., et al., Trends in neonatal morbidity and mortality for very low birthweight infants. *Am J Obstet Gynecol*. 2007;196:e1-8.
3. Lagakos SW. The challenge of subgroup analyses--reporting without distorting. *N Engl J Med*. 2006;354:1667-1669.

## **NICHD Neonatal Research Network Protocol Outline**

Title: Oxygen saturations and risk of mortality and morbidity in the SUPPORT trial.

### **Authors:**

P. Brian Smith MD MPH MHS

C. Michael Cotten MD MHS

Ronald N. Goldberg MD

RTI and SUPPORT Subcommittee (Carlo)

for the Eunice Kennedy Shriver NICHD Neonatal Research Network

### **A. Statement of the Problem**

Previous studies demonstrated increased rates of mortality, ROP, BPD, PVL and CP among infants with higher exposures to oxygen.<sup>1-6</sup> The SUPPORT study demonstrated lower rates of severe ROP in the lower saturation group but higher rates of mortality. No difference in severe ROP/death was observed between the two groups. Because many infants in the low saturation group spent time with saturations >89% and many infants in the high saturation group spent time with saturations <91%, there was a great deal of overlap in oxygen saturations between the two groups.

The SUPPORT study's finding that higher oxygen saturation limits are associated with lower mortality but higher rates of severe ROP leaves uncertainty for clinicians. The rationale for this proposal is that evidence for determining the safest range for oxygen saturation for premature infants is conflicting.<sup>5,6</sup> In the protocol described below, we will be able to examine the association between the actual recorded oxygen saturation with the clinical outcomes of the infants. *We propose to examine the incidence of mortality and morbidities using actual oxygen saturations as a predictor for infants enrolled in the SUPPORT trial.*

### **B. Hypothesis**

*Hypothesis:* Higher oxygen saturations are associated with an increased risk of death, ROP, BPD, death/ROP, or death/BPD for infants receiving supplemental oxygen.

### **C. Specific Aim**

*Specific Aim:* Determine whether oxygen saturations for infants receiving supplemental oxygen are related to death, ROP, BPD, death/ROP, or death/BPD.

### **D. Method/ Procedures**

1. Study Design: Retrospective cohort study.

2. Study population:

#### *Inclusion criteria*

1. 1316 infants in enrolled in the SUPPORT trial

*Exclusion criteria*

1. None
3. Study intervention:  
There is no specific study intervention. This will be analysis of existing data.
4. Primary and Secondary Outcomes:  
Primary outcome: Death  
Secondary outcomes: ROP, BPD, death/ROP, death/BPD
5. Statistical Plans:  
*Outcome variables*
  1. death
  2. ROP
  3. BPD
  4. death/ROP
  5. death/BPD

*Predictor variables*

Oxygen saturation for each infant while receiving supplemental oxygen

*Confounding variables*

1. saturation group (low vs. high)
2. gestational age
3. birth weight
4. sex
5. singleton vs. multiple birth

*Observations for analysis*

Observations recorded when the infant's SaO<sub>2</sub> could not be altered will not be used in the analysis.

1. Infant receiving 21% FiO<sub>2</sub> with SaO<sub>2</sub> > than upper target limit range
2. Infant receiving 100% FiO<sub>2</sub> with SaO<sub>2</sub> < than lower target limit range

*Weighting of observations*

Although the number of observations varied by subject in the dataset, each infant will contribute equally to the overall statistical calculations.

*Bivariable analysis*

We will compare mean oxygen saturations for infants that died vs. those that lived using the Student's t-test. The comparison will be repeated for each of the secondary outcomes: ROP, BPD, death/ROP, and death/BPD.

*Multivariable analysis*

We will build a multivariable logistic regression model to determine the relationship between outcome variables and mean oxygen saturation for each infant (continuous variable) controlling for saturation group (low vs. high), mean FiO<sub>2</sub> (continuous variable), gestational age, birth weight, sex, and singleton birth.

## E. References

1. Jobe, A.H. and Bancalari, E., Bronchopulmonary dysplasia. *Am J Respir Crit Care Med.* 163, 1723-9(2001).
2. Flynn, J.T., Bancalari, E., Snyder, E.S., Goldberg, R.N., Feuer, W., Cassady, J., Schiffman, J., Feldman, H.I., Bachynski, B., Buckley, E., and et al., A cohort study of transcutaneous oxygen tension and the incidence and severity of retinopathy of prematurity. *N Engl J Med.* 326, 1050-4(1992).
3. Saugstad, O.D., Bronchopulmonary dysplasia-oxidative stress and antioxidants. *Semin Neonatol.* 8, 39-49(2003).
4. Haynes, R.L., Baud, O., Li, J., Kinney, H.C., Volpe, J.J., and Folkerth, D.R., Oxidative and nitrative injury in periventricular leukomalacia: a review. *Brain Pathol.* 15, 225-33(2005).
5. Anderson, C.G., Benitz, W.E., and Madan, A., Retinopathy of prematurity and pulse oximetry: a national survey of recent practices. *J Perinatol.* 24, 164-8(2004).
6. Tin, W., Milligan, D.W., Pennefather, P., and Hey, E., Pulse oximetry, severe retinopathy, and outcome at one year in babies of less than 28 weeks gestation. *Arch Dis Child Fetal Neonatal Ed.* 84, F106-10(2001).

**From:** Miller, Marianne Glass (NIH/NICHD) [E]  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; McGrath, John (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]  
**Subject:** RE: \*\*\*\*CONFIDENTIAL UPDATE ON SUPPORT PAPERS AND EMBARGO\*\*\*\*\*  
**Date:** Thursday, May 13, 2010 12:31:50 PM

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Yes, absolutely.

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Thursday, May 13, 2010 11:34 AM  
**To:** McGrath, John (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]; Miller, Marianne Glass (NIH/NICHD) [E]  
**Subject:** FW: \*\*\*\*CONFIDENTIAL UPDATE ON SUPPORT PAPERS AND EMBARGO\*\*\*\*\*  
**Importance:** High

Here is the RTI press release. I would like to send the following:

I would suggest you consider the following??

The study was performed on infants from 24-27 weeks (not 23-26 weeks). We really didn't test higher oxygen flows, we tested a higher and lower oxygen saturation targets.

Is this ok??

---

**From:** Das, Abhik [mailto:adas@rti.org]  
**Sent:** Thursday, May 13, 2010 11:28 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** FW: \*\*\*\*CONFIDENTIAL UPDATE ON SUPPORT PAPERS AND EMBARGO\*\*\*\*\*

Rose:

We have prepared the attached news item for posting on the RTI external website ([www.rti.org](http://www.rti.org)) once the embargo is lifted. Please let me know if you approve, or have any other comments.

Thanks

Abhik

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Wednesday, May 12, 2010 2:33 PM  
**To:** 'Finer, Neil'; 'Rich, Wade'; Gantz, Marie; 'Nancy Newman'; 'Anthony Piazza (Anthony.Piazza@oz.ped.emory.edu)'; ' (susie.buchter@oz.ped.emory.edu)'; 'Brenda Morris'; 'Laroia, Nirupama'; 'Phelps, Dale'; 'Duara, Shahnaz'; 'Vivek Narendran'; 'vineet.bhandari@yale.edu'; 'Sood, Beena'; 'Michael O` Shea'; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Das, Abhik; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); 'Brenda Poindexter'; 'Carlo Waldemar (E-mail)'; cotte010@mc.duke.edu; Wallace, Dennis; 'Ed Bell'; 'Ed Donovan'; 'Ehrenkranz Richard (E-mail)'; Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; 'Kristi Watterberg'; Kurt Schibler [kurt.schibler@cchmc.org]; 'Matthew Bizzarro'; 'Michelle Walsh'; 'Mickey Caplan'; 'Oh William (E-mail)'; 'Pablo Sanchez'; Poole, W. Kenneth; 'Roger Faix'; 'Ronald Goldberg'; 'Seetha Shankaran'; 'Stevenson David (E-mail)'; [SCRN] Stoll, Barbara; 'Tyson Jon (E-mail)'; VanMeurs, Krisa

**Cc:** Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Cunningham, Meg; Huitema, Carolyn Petrie

**Subject:** \*\*\*\*CONFIDENTIAL UPDATE ON SUPPORT PAPERS AND EMBARGO\*\*\*\*\*

**Hello again everyone:**

**I have several items regarding SUPPORT.**

**Both manuscripts are attached along with the appendices.**

**The authors appear at the end of the paper as formal “authors” due to space limits from NEJM. I have also attached the NIH press release for the papers. Finally, there is an editorial which will appear on-line and in the May 27 issue of NEJM.**

**ALL OF THIS INFORMATION IS SUBJECT TO EMBARGO RULES AND NOT TO BE RELEASED UNTIL SUNDAY MAY 16 at 1 PM ET. This information can be *confidentially shared with your institutional press/public affairs office* as long as the embargo is respected.**

**Thanks to everyone at each and every site for all of the hard work and effort on this study. A special appreciation of gratitude goes to the coordinators who really went above and beyond to get the patients enrolled in this difficult study.**

**A very, very special and heart felt thanks to Neil and Wally for all of their hard work, commitment, effort and patience to bring this**

**to completion!!!!**

**Both SUPPORT Papers will be *accelerated Online First release* scheduled to coincide with the presentations of the results at the American Thoracic Society's annual meeting on Sunday May 16, 2010. The on-line release will occur at 1 PM EDT on 5/16/2010. The print publication is slated to appear in the May 27, 2010 issue of NEJM.**

If you have any questions, please contact me

**Rose**

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network  
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**From:** Luc Brion  
**To:** Higgins, Rosemary (NIH/NICHD) [F]; Barbara Stoll; Waldemar Carlo; Abhik Das; Neil Finer  
**Cc:** JACLYN LEVAN; Pablo Sanchez  
**Subject:** Concept Proposal - first draft  
**Date:** Thursday, May 13, 2010 12:12:23 PM  
**Attachments:** Proposal.rtf  
Newest\_concept\_proposal\_050410\_rev.doc

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Hi Rose, Barbara, Abhik, Neil and Wally;

Here is a revised draft of a concept proposal written by one of our fellows, Jaclyn LeVan, which is designed to use GDB data to assess changes after the SUPPORT trial.

Barbara: Thanks a lot for the GDB comments on our first proposal (attached).

As recommended by the GDB,

1. The proposal was modified to analyze intubation/outcome in the years before SUPPORT and compare to the period following completion of SUPPORT and the end of the current Network, and we are listing all SUPPORT authors in the proposal.
2. All your names and all SUPPORT authors are listed in the proposal (please apologize if we missed someone by mistake).
3. I submitted a draft to Abhik on 5/4/10 for his comments.

I wonder whether we might have some time to initiate some preliminary discussion at the upcoming May 20-21 meeting. I know the schedule is busy but I would appreciate it if we could sit for even a few minutes. This could lead to a time frame for comments and editing so I can revise and edit this draft as many times as needed for submission at the next steering committee.

Thank you

Luc

Luc P. Brion, MD  
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+++++CONFIDENTIALITY NOTICE+++++

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>>> "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> 2/5/2010 11:01 AM >>>

Luc

The GDB subcommittee reviewed your proposal on their call this am. Though there was much enthusiasm, a revision is requested prior to presentation at a steering committee meeting. Barbara will send you comments in the next week.

Thanks

Rose

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network  
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**From:** "Barbara Stoll" <Barbara.Stoll@oz.ped.emory.edu>  
**To:** "Lbrion" (b) (6)  
**CC:** "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>, <" <Luc.Bri...>  
**Date:** 2/5/2010 2:08 PM  
**Subject:** Proposal

Luc

Your proposal was reviewed on the GDB Subcommittee call this morning. There was general enthusiasm for doing a study to look at clinical practices and outcomes pre and post SUPPORT. However, the subcommittee thought the proposal needed revisions before it would be ready for presentation at a Steering Committee Meeting. The Subcommittee suggested that you consider putting off this study so that you could do an analysis of the pre/post SUPPORT eras-- ie look at intubation/outcome in the years before SUPPORT and compare to the period following completion of SUPPORT and the end of the current Network (April 2011).

Specific comments:

Subcommittee thought it likely that the those infants who were eligible but not randomized into SUPPORT would likely be different-- need analysis to understand these differences not simply whether there was a change in DR interventions vs pre SUPPORT

RTI statisticians thought that this would be a more complicated analysis than presented and wanted to work with you to better think through the analysis and write up. Please contact Dr Das re analysis.

Need to evaluate uniform time periods, rather than based on when a center started or stopped SUPPORT

Might have substantial missing data in the non SUPPORT group who don't have as intense tracking after discharge

Suggest adding PDA and Late onset sepsis to the secondary outcomes-- because of their impact on outcome of preterm infants

In addition to intubation in the DR suggest looking at chest compressions and code drugs

This would be a paper from the full steering committee-- with all PIs (or designees) included as authors because of the enormous amount of work that went into completing SUPPORT and GDB

No need for additional IRB approval-- have approval for both GDB and SUPPORT

Best regards

BJS

Barbara J. Stoll, MD  
George W. Brumley, Jr., Professor and Chair, Department of Pediatrics

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## Application to the Full Steering Committee

# Changes in Therapy and Outcomes Associated with The SUPPORT Trial

Jaclyn LeVan, DO, Myra Wyckoff, MD, Pablo Sánchez, MD, Roy Heyne, MD,  
Chul Ahn, PhD, Mambarath Jaleel, MD, Luc P Brion, MD (PI),  
**Finer NN, Carlo WA**, Walsh MC, Rich W, Gantz M, Laptook AR, Yoder BA, Faix RG,  
**Das A**, Poole WK, Ambalavanan N, Schibler K, Donovan E, Newman N, Frantz III ID,  
Sánchez PJ, Buchter S, Morris BH, Laroia N, Poindexter BB, Cotton M, Van Meurs KP,  
Sood B, Duara S, O'Shea TM, Bell EF, Bhandari V, Watterberg KL, **Stoll B, Higgins RD**

**For the NICHD Neonatal Research Network**

**Version: 12/2/2015**

### **A. ABSTRACT:**

We propose an observational study (before/after study design) of GDB data and a survey of institutions in the NRN to examine the changes in clinical practices and outcomes following the results of the SUPPORT Trial.

### **B. STATEMENT of the PROBLEM**

The SUPPORT trial (Finer; Carlo, in press) was a multicenter randomized 2 X 2 factorial trial, in which preterm infants of 24 0/7ths weeks to 27 6/7ths weeks were randomized at birth to (1) either continuous positive airway pressure (CPAP) initiated in the delivery room and subsequent use of a protocol-driven limited ventilation strategy, or intubation with surfactant administration (within 1 hour of birth), and (2) oxygen saturation targets of either 85 to 89% or 91 to 95%. The results of the SUPPORT trial have been released to the participating network centers in October 2009. The rates of the primary outcome of the CPAP trial (death or bronchopulmonary dysplasia [BPD]) were not significantly different between the CPAP and the surfactant groups. In the CPAP group infants had lower rates of intubation or postnatal steroids for BPD, had fewer days of mechanical ventilation, and were more likely to be alive and off mechanical ventilation by day 7. The rates of the primary outcome of the saturation target trial (severe retinopathy of prematurity [ROP] or death) were not significantly different between the two oxygen saturation target groups. However, in the lower oxygen saturation target group, death was significantly more frequent while severe retinopathy of prematurity among survivors occurred significantly less often.

In a retrospective study conducted at Parkland Memorial Hospital we found that the frequency of delivery room intubation among gestational age-matched infants decreased significantly after initiation of the SUPPORT trial (Brion 2008).

### **C. HYPOTHESES:**

1. We hypothesize that release of the results of the SUPPORT Trial will be followed by (1) a decrease in frequency of endotracheal intubation in the delivery room in preterm infants, and that the decrease in the frequency of delivery room intubation in each neonatal research network (NRN) center would depend on baseline rate before the trial and (2) institution-specific changes in target oxygen saturation.
2. We hypothesize that the release of the SUPPORT trial results will not affect the rates of death or bronchopulmonary dysplasia (BPD, defined by the physiologic definition), death or retinopathy of prematurity (ROP), BPD (defined by the physiologic definition), BPD (defined by oxygen requirement at 36 weeks) and ROP among preterm infants, but will reduce the frequency of artificial ventilation or death at day 7 and the frequency of use of corticosteroids for BPD.
3. We hypothesize that changes in ROP and mortality rate will occur in centers that used low oxygen saturation target (85 to 89% or lower) before the SUPPORT trial and have now increased this target to a value similar to the higher range used in the SUPPORT trial, i.e., 91 to 95%.

#### **D. SPECIFIC AIMS:**

1. To determine the impact of the results of the SUPPORT trial on clinical practice, specifically, (1) the incidence of endotracheal intubation in the delivery room in preterm inborn infants and (2) target oxygen saturation in the NRN centers
2. To determine the impact of the results of the SUPPORT trial on outcomes in preterm inborn infants, including: incidence of death or BPD (defined by the physiologic definition, death or ROP, BPD [defined by the physiologic definition], BPD [defined by oxygen requirement at 36 weeks postmenstrual age], ROP, artificial ventilation or death at day 7, use of postnatal corticosteroids for BPD, mortality rate in the whole group and mortality rate in each stratum (24 0/7ths weeks to 25 6/7ths weeks and 26 0/7ths weeks to 27 6/7ths weeks).

#### **E. RATIONALE/JUSTIFICATION:**

The SUPPORT trial showed no difference in primary outcome between the two respiratory support strategies but advantages of early CPAP on three secondary outcomes. Therefore, we expect that providers using endotracheal intubation as standard of care in the delivery room before the SUPPORT trial would change their attitudes towards more CPAP and less intubation after the release of the SUPPORT Trial results. The intubation rate among extremely low birth weight infants was high (80%) in NRN centers in 1993-1997 (Shankaran 2002) and was still high at Parkland Memorial Hospital in 2005 (Brion 2008). Since there is substantial heterogeneity in therapy and outcome across NRN centers, we expect that the change in practice after initiating the SUPPORT trial would be inversely related with the baseline rate of intubation in each center.

The SUPPORT trial showed no difference in primary outcome between the two oxygen saturation targets, but showed significantly higher mortality and lower rate of ROP with low oxygen saturation target. Specifically the trial showed that targeting lower oxygen saturation resulted in one additional death for approximately every 2 cases of severe ROP prevented. Since the SUPPORT trial is the first trial to show that targeting low oxygen saturation significantly increases mortality in extremely preterm infants, we might expect that some centers or providers using low oxygen saturation target before the SUPPORT trial would consider increasing their target levels after release of the results of the SUPPORT trial.

#### **F. BACKGROUND/PREVIOUS STUDIES:**

##### CPAP vs. intubation and surfactant:

Prophylactic and early natural surfactant administration at less than 2 hours of life significantly decreases mortality, air leak, and death or BPD in intubated preterm infants who are either at risk for respiratory distress syndrome (< 30 weeks of gestational age) or with respiratory distress syndrome (Soll 1997, Soll 1999). Several studies have suggested a benefit for early CPAP for preterm infants with respiratory distress syndrome, including a decrease in the need for mechanical ventilation among very preterm infants without an increase in morbidity (Avery 1987, Van Marter 2000, VanPee 2007, Jonsson 1997, Gitterman 1997) except for pneumothorax (summary relative risk 2.36; 95% confidence interval 1.25, 5.54) (Ho 2002). In one observational study, 76% of infants with a birth weight  $\leq$  1250 g who were initially treated with CPAP did not require intubation within

72 hours (Ammari 2005).

The NICHD Feasibility Trial (Finer 2004) was designed to determine the feasibility of randomizing ELBW infants of < 28 weeks' gestation to CPAP/positive end expiratory pressure (PEEP) or no CPAP/PEEP during resuscitation immediately after delivery, avoiding routine delivery room intubation for surfactant administration. Forty-five percent (47 of 104) of infants < 28 weeks' gestation required intubation for resuscitation in the delivery room. CPAP/ PEEP in the delivery room did not affect the need for intubation at birth or during the subsequent week. Overall, 20% of infants did not need intubation by 7 days of life.

Three multicenter RCTs have compared early CPAP with intubation in the delivery room. The IFDAS trial (Thomson 2001) showed no significant difference between 4 groups (Elective intubation with surfactant administration and extubation within 2 hrs; early nasal CPAP with selective short intubation for surfactant administration; elective intubation with surfactant administration and artificial ventilation; selective intubation with surfactant administration and artificial ventilation based on clinical criteria) in total respiratory support until estimated date of delivery or discharge home (if earlier) and other neonatal complications. However, this study was not powered for any of the outcomes.

The COIN trial (Morley 2008) randomized 610 infants from 25 0/7 to 28 6/7 weeks gestation, who were able to breathe at 5 minutes of age and had evidence of respiratory distress. Infants were randomized, either to intubation and ventilation, or to CPAP at 8 cm H<sub>2</sub>O with intubation for those who met failure criteria. The primary outcome of death or BPD at 36 weeks was similar in the CPAP and in the intubation arms 33.9% vs. 38.9%, (odds ratio=0.58 to 1.12; P=0.19). Infants randomized to CPAP had a higher frequency of pneumothorax (9.1% vs. 3.0%, p=.001) and a lower frequency of death or need for oxygen at 28 days (odds ratio, 0.63; 95% CI, 0.46 to 0.88; P=0.006).

Oxygen administration upon admission to the neonatal intensive care unit:

Trials published in the 1950's comparing restricted ( $\leq 50\%$ , only for clinical indication or cyanosis) versus unrestricted (routine for 2-4 weeks or until reaching 1500 g) ambient oxygen in very low birth weight infants upon admission or within the first 48 hours showed a significant reduction in ROP and severe ROP (Duc 1992, Askie 2009) without a significant change in mortality (risk difference 4.9%, 95% CI -5.2, + 14.9; risk ratio 1.23, 95% CI 0.80, 1.90). Observational studies have suggested that targeting low oxygen saturation upon admission in very preterm infants may reduce the risk of ROP (Tin 2007) without increasing mortality (Chow 2003, Deulofeut 2007, Wright 2006). No randomized trials until the SUPPORT trial have assessed the effect of targeting different oxygen saturation levels upon admission on morbidity and mortality in very preterm infants.

SUPPORT Trial (extracted from Finer, in press and Carlo, in press):

The SUPPORT trial (Finer, in press; Carlo, in press) was a multicenter randomized 2 X 2 factorial trial, in which preterm infants of 24 0/7ths weeks to 27 6/7ths weeks were randomized at birth to (1) either continuous positive airway pressure (CPAP) initiated in the delivery room and subsequent use of a protocol-driven limited ventilation strategy, or



intubation with surfactant administration (within 1 hour of birth), and (2) oxygen saturation targets of either 85 to 89% or 91 to 95%. The primary outcome of the CPAP vs. surfactant trial was the rate of composite primary outcome of death or bronchopulmonary dysplasia (BPD) defined by requirement for oxygen at 36 weeks (with an attempt to remove oxygen in neonates receiving less than 30% oxygen). The primary outcome of the oxygen saturation trial was a composite of severe retinopathy of prematurity (threshold retinopathy, or surgical ophthalmologic intervention, or the use of bevacizumab) and/or death before discharge from the hospital.

The results of the SUPPORT trial have been released to the participating network centers in October 2009. The study enrolled 1316 infants. The rates of the primary outcome were not significantly different between the CPAP and surfactant groups (47.8% vs. 51.0%, Relative risk (RR) 0.95 (95% Confidence interval (CI) 0.85, 1.05, adjusting for gestational age, center and familial clustering). In the CPAP group infants had lower rates of intubation or postnatal steroids for BPD, had fewer days of mechanical ventilation, and were more likely to be alive and off mechanical ventilation by day 7. The rates of other adverse neonatal outcomes were not significantly different in the 2 groups.

The rates of the primary outcome (severe retinopathy of prematurity [ROP] or death) were not significantly different between the two oxygen saturation target groups (28.3 vs. 32.1%, respectively; relative risk (RR) 0.90; 95% confidence interval (CI) 0.76, 1.06;  $p=0.21$ ). Death occurred more frequently in the lower oxygen saturation target group (19.9 vs. 16.2%; RR 1.27; CI 1.01, 1.60;  $p=0.04$ ) while severe retinopathy among survivors occurred less often in these infants (8.6 vs 17.9%; RR 0.52; CI 0.37, 0.73;  $p<0.001$ ).

However, in the lower oxygen saturation target group, death was significantly more frequent, while severe retinopathy of prematurity among survivors occurred significantly less often. The rates of other adverse neonatal outcomes were not significantly different in the 2 groups.

#### Retrospective study at Parkland Memorial Hospital:

A retrospective study (Brion 2008) was conducted at Parkland Memorial Hospital to assess the impact of SUPPORT trial initiation in July 2005 on patient management and short-term outcomes in non-participant preterm infants. We analyzed two prospective databases: the resuscitation registry and the neonatal intensive care unit (NICU) database. We included all inborn infants with gestational age < 35 weeks during 3 epochs: 01/03-07/05 (1<sup>st</sup> Epoch), 07/05-12/05 (2<sup>nd</sup> Epoch) and 01/06-11/07 (3<sup>rd</sup> Epoch), corresponding, respectively, to 30 months that preceded enrollment into SUPPORT, the first 6 months of SUPPORT enrollment, and the next 23 months of SUPPORT enrollment. We excluded infants who received comfort care only and those enrolled in the SUPPORT trial.

Among neonates < 28 weeks of gestational age, initiation of the SUPPORT trial was associated with significant decreases in the rates of intubation in the delivery room or the NICU, and surfactant administration, and an increase in the rate of delivery room CPAP.

Infants < 28 wk gestational age (n=267)				
	1st Epoch N=160	2nd Epoch N=17	3rd Epoch N=90	P
Delivery room intubation	87%	77%	52%	<0.001
Delivery room CPAP	30%	47%	50%	0.004
Early NICU intubation	4%	6%	9%	0.28
Intubation in delivery room or NICU	90%	82%	61%	<0.001
Surfactant	78%	71%	52%	<0.001
Pneumothorax	8%	13%	10%	0.58

In the whole population studied (<35 weeks gestational age, n= 2266), multivariate logistic regression analysis taking into account gestational age and umbilical cord base excess, the rate of delivery room intubation significantly decreased after initiation of recruitment into the SUPPORT trial (odds ratio 0.48, 95% CI 0.37, 0.63, p < 0.001).

## G. METHOD/PROCEDURES:

### Study Design:

We propose a retrospective analysis of the GDB using a before/after design with one cohort of patients born before the date of initiation of the SUPPORT trial in each NRN center (1/02-2/05) and a second cohort of patients after release of the SUPPORT trial results to the end of the current cycle of Neonatal Research Network (10/09-4/11)

### Study Population:

#### Cohorts:

We propose to analyze patients in the NRN GDB born between 1/02-4/11, divided into two successive cohorts. The first cohort includes patients born during a 3-year period preceding the SUPPORT trial (from 01/02-2/05). The second cohort includes patients born after the release of the results of the SUPPORT trial to the NRN centers and the end of the neonatal network (10/09-4/11).

#### Eligibility and exclusion criteria:

We will use eligibility and exclusion criteria identical to those in the SUPPORT trial.

Entry criteria: Eligible infants are 24 0/7ths to 27 6/7th weeks at birth by best obstetrical estimate, born without known malformations at an NRN center participating in the SUPPORT trial, included in the GDB during the entire study period.

#### Gestational age strata:

We will analyze the same strata as in the SUPPORT trial: 24 0/7ths weeks to 25 6/7ths weeks and 26 0/7ths weeks to 27 6/7ths weeks.

### **Study Intervention:**

This is a retrospective study with before/after study design comparing preterm infants before the date of initiation of the SUPPORT trial and after the release of the results of the SUPPORT Trial in each participating center.

### **Primary/Secondary Outcomes:**

#### **Primary outcome variables:**

1. Clinical practices:
  - a. The use of intubation vs. CPAP in delivery room
2. Outcomes:
  - a. The incidence of composite of death or BPD (physiologic definition), i.e., a primary outcome of the SUPPORT trial. The Physiologic Definition of BPD assigns the diagnosis of BPD to any infant who received more than 30% oxygen at 36 weeks or who required positive pressure support, but required demonstration of oxygen dependence by an attempt at oxygen withdrawal for infants who required < 30% oxygen at 36 weeks (Walsh 2003, Walsh 2004).
  - b. The incidence of composite of severe ROP (threshold retinopathy, surgical ophthalmologic intervention, or bevacizumab) or death before discharge from the hospital, i.e., a primary outcome of the SUPPORT trial.
  - c. Mortality rate before discharge
  - d. The incidence of severe ROP

#### **Secondary outcome variables:**

1. Clinical practices
  - a. Institutional oxygen saturation target (obtained by survey of each institution)
  - b. Institutional intubation rate
  - c. Surfactant administration
2. Outcomes:
  - a. Delivery room resuscitation: bag and mask ventilation, cardiac compressions, use of code drugs (intravenous epinephrine, endotracheal epinephrine, bicarbonate), Apgar scores at 1 min and 5 min
  - b. Temperature within 60 min of birth
  - c. Pneumothorax
  - d. Pulmonary hemorrhage
  - e. Use of corticosteroids for BPD
  - f. Duration of ventilation; duration of CPAP
  - g. Duration of oxygen supplementation
  - h. BPD (physiologic definition)
  - i. BPD (defined by oxygen requirement at 36 weeks)
  - j. Patent Ductus Arteriosus (PDA), PDA requiring indomethacin or ibuprofen, PDA requiring surgery
  - k. Severe intraventricular hemorrhage (grade III or IV)
  - l. Cystic periventricular leukomalacia
  - m. Early onset sepsis and late onset sepsis

- n. First day full feeds
- o. Weight at 36 weeks
- p. Necrotizing enterocolitis (stage 2 or greater)
- q. Length of stay
- r. Weight at discharge
- s. Death under 12 hours
- t. Death or artificial ventilation at day 7
- u. Death or BPD (defined by oxygen requirement at 36 weeks)
- v. Death or severe ROP (threshold retinopathy, surgical ophthalmologic intervention, or bevacizumab)

Additional variables available in the GDB will be collected, including

- 1. Maternal variables: race/ethnicity, diabetes, hypertension, singleton vs. multiple pregnancy, chorioamnionitis, prolonged rupture of membranes, antenatal corticosteroids (betamethasone, any/full course), mode of delivery, antibiotics before delivery
- 2. Neonatal variables: birth weight, gender, cord gas and base deficit, syndromes and/or major malformations

#### **Sample Size/Statistical Analysis:**

##### Available sample size:

Data in GDB from January 2002 to December 2004 (DATA AND SAFETY MONITORING PLANS for the SUPPORT Trial) included 4055 infants with a gestational age 24 0/7 – 27 6/7. Assuming 10% exclusions, the first 3-year cohort (1/02-2/05) is estimated to yield approximately 3600 infants for analysis.

The GDB data for 2008 included 1738 inborn infants < 29 weeks gestational age. Therefore we estimate that the second cohort (10/09-4/11) would include approximately 2000 infants.

Sample size calculations will be based on available data [which will be updated with more recent data from the GDB]:

- 1. year 2000 NRN baseline occurrence data among 24 0/7 to 26 6/7 week gestational age infants of death or survival with BPD (by physiologic definition) at 36 weeks of 67%,
- 2. year 2000 NRN baseline occurrence data among 24 0/7 to 26 6/7 week gestational age infants of death or threshold retinopathy of 50%
- 3. years 1993-1997 intubation rate of rate of 80% among extremely low birth weight infants (Shankaran 2002).
- 4. 2002-05 mortality rate of 21% in extremely low birth weight infants (Morris 2008)
- 5. 2002-05 severe ROP frequency of 20% in extremely low birth weight infants (Morris 2008)

For the primary outcome variables, we calculated power using chi-square analysis, a

1% level of significance (to account for five co-primary outcomes) and two-tailed tests. The available sample size ( $n = 5600$ , 3600 before versus 2000 after SUPPORT) gives a power  $> 99\%$  to find a significant change in delivery room intubation from 80% to 60%, a change in death or BPD (by physiologic definition) from 50% to 40%, a change in death or severe ROP from 67 to 57%, and a change in severe ROP from 20% to 30%, and a power of 86% to find a change in mortality from 21% to 17%.

#### Uni- or bivariate analyses:

Univariate analyses will be done using chi-square analysis (Mantel-Haenszel chi-square for analyses by gestational age stratum) for categorical variables and using Student t-test for continuous variables. We will also use survival analysis.

For the primary outcome variables, we will calculate power using chi-square analysis, and a conservative 1% level of significance (to account for three co-primary outcomes), based on the most recent GDB data.

The change in rate of intubation from the first to the second epoch in each center will be correlated with baseline intubation rate.

Assuming some centers decide to change their oxygen saturation targets based on the SUPPORT trial results, we will test whether mortality decreased and the rate of ROP increased in centers changing their oxygen saturation target from low during the first epoch to high during the second epoch, but not in the other centers.

#### Multivariate analyses:

Multivariate analyses of death or BPD (by physiologic definition), death and ROP and death, BPD, and severe ROP will be done using adjusted odds ratios calculated using logistic regression analysis, taking into account institution and the variables reported in Tyson's analysis in extremely low birth weight infants (Tyson 2008): exposure to antenatal corticosteroids, female sex, singleton birth, and higher birth weight (per each 100-g increment). In addition, we will assess whether oxygen saturation target in each institution affects the rates of death and of severe ROP.

#### Limitations:

Before/after study design is limited by confounding variables that may have occurred in addition to the variable of interest. The two cohorts represent different patient populations separated by several years.

One exclusion criterion used for the SUPPORT trial, i.e., decision made not to provide full resuscitation, is not listed in the GDB baseline form.

We will perform logistic regression analyses including, in addition to variables reported in Tyson's analysis in extremely low birth weight infants (Tyson 2008), other variables known to affect mortality in extremely low birth weight infants (Shankaran 2002), i.e., also including Apgar score at 1 minute and use of tocolytic.

**Consenting:**

Patients will be selected from GDB using criteria previously explained. We request a waiver for consent form as this research involves minimal risk to patients and collecting data in the GDB has been pre-approved by the IRB in each institution.

**Available Population/compatibility with other ongoing protocols**

The population available will be those patients in the GDB, corresponding to patients born between 1/01 and 4/11.

We are not aware of any conflict with other ongoing protocols.

**Projected Recruitment Time**

Data collection for the proposed study will start in May 2011.

**H. RISKS/BENEFITS:**

The benefit will be mostly for the society in that there is potential quality improvement of patient care in NICU. The risk is minimal and included accidental disclosure of medical information which is unlikely.

**I. BUDGET:**

Cost for access to GDB and SUPPORT database and statistical analysis

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Carlo WA, Finer NN, Walsh MC, Rich W, Gantz M, Laptook AR, Yoder BA, Faix RG, Das A, Poole WK, Ambalavanan N, Schibler K, Donovan E, Newman N, Frantz III ID, Sánchez PJ, Buchter S, Morris BH, Laroia N, Poindexter BB, Cotton M, Van Meurs KP, Sood B, Duara S, O'Shea TM, Bell EF, Bhandari V, Watterberg KL, Higgins RD; for the NICHD Neonatal Research Network and The SUPPORT Study Group of the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. The SUPPORT Trial: Randomized Trial of Oxygen Saturation Targets in Extremely Premature Infants. *N Engl J Med*, in press

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**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** McGrath, John (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]; Miller, Marianne Glass (NIH/NICHD) [E]  
**Subject:** FW: \*\*\*\*CONFIDENTIAL UPDATE ON SUPPORT PAPERS AND EMBARGO\*\*\*\*\*  
**Date:** Thursday, May 13, 2010 11:34:00 AM  
**Attachments:** Neonatal studies.doc  
**Importance:** High

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Here is the RTI press release. I would like to send the following:

I would suggest you consider the following??

The study was performed on infants from 24-27 weeks (not 23-26 weeks). We really didn't test higher oxygen flows, we tested a higher and lower oxygen saturation targets.

Is this ok??

---

**From:** Das, Abhik [mailto:adas@rti.org]  
**Sent:** Thursday, May 13, 2010 11:28 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** FW: \*\*\*\*CONFIDENTIAL UPDATE ON SUPPORT PAPERS AND EMBARGO\*\*\*\*\*

Rose:

We have prepared the attached news item for posting on the RTI external website ([www.rti.org](http://www.rti.org)) once the embargo is lifted. Please let me know if you approve, or have any other comments.

Thanks

Abhik

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**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Wednesday, May 12, 2010 2:33 PM  
**To:** 'Finer, Neil'; 'Rich, Wade'; Gantz, Marie; 'Nancy Newman'; 'Anthony Piazza (Anthony.Piazza@oz.ped.emory.edu)'; ' (susie.buchter@oz.ped.emory.edu)'; 'Brenda Morris'; 'Laroia, Nirupama'; 'Phelps, Dale'; 'Duara, Shahnaz'; 'Vivek Narendran'; 'vineet.bhandari@yale.edu'; 'Sood, Beena'; 'Michael O`Shea'; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Das, Abhik; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); 'Brenda Poindexter'; 'Carlo Waldemar (E-mail)'; cotte010@mc.duke.edu; Wallace, Dennis; 'Ed Bell'; 'Ed Donovan'; 'Ehrenkranz Richard (E-mail)'; Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; 'Kristi Watterberg'; Kurt Schibler [kurt.schibler@cchmc.org]; 'Matthew Bizzarro'; 'Michelle Walsh'; 'Mickey Caplan'; 'Oh William (E-mail)'; 'Pablo Sanchez'; Poole, W. Kenneth; 'Roger Faix'; 'Ronald Goldberg'; 'Seetha Shankaran'; 'Stevenson David (E-mail)'; [SCRN] Stoll, Barbara; 'Tyson Jon (E-mail)'; VanMeurs, Krisa  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Cunningham, Meg; Huitema, Carolyn Petrie  
**Subject:** \*\*\*\*CONFIDENTIAL UPDATE ON SUPPORT PAPERS AND EMBARGO\*\*\*\*\*

**Hello again everyone:**

**I have several items regarding SUPPORT.**

**Both manuscripts are attached along with the appendices. The authors appear at the end of the paper as formal “authors” due to space limits from NEJM. I have also attached the NIH press release for the papers. Finally, there is an editorial which will appear on-line and in the May 27 issue of NEJM.**

**ALL OF THIS INFORMATION IS SUBJECT TO EMBARGO RULES AND NOT TO BE RELEASED UNTIL SUNDAY MAY 16 at 1 PM ET. This information can be *confidentially shared with your institutional press/public affairs office* as long as the embargo is respected.**

**Thanks to everyone at each and every site for all of the hard work and effort on this study. A special appreciation of gratitude goes to the coordinators who really went above and beyond to get the patients enrolled in this difficult study.**

**A very, very special and heart felt thanks to Neil and Wally for all of their hard work, commitment, effort and patience to bring this to completion!!!!**

**Both SUPPORT Papers will be *accelerated Online First release* scheduled to coincide with the presentations of the results at the**

**American Thoracic Society's annual meeting on Sunday May 16, 2010. The on-line release will occur at 1 PM EDT on 5/16/2010. The print publication is slated to appear in the May 27, 2010 issue of NEJM.**

If you have any questions, please contact me

**Rose**

Rosemary D. Higgins, MD

Program Scientist for the Neonatal Research Network

Pregnancy and Perinatology Branch

Center for Developmental Biology and Perinatal Medicine

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## New Study Sheds Light on Benefits, Methods of Using Oxygen to Improve Preterm Infants' Survival

RESEARCH TRIANGLE PARK, N.C. -- A new study provides valuable insights on the use of oxygen by medical professionals seeking to increase the chances for healthy survival in very preterm infants.

The study, published in the *New England Journal of Medicine*, was conducted by researchers from the Neonatal Research Network, a multi-center clinical research network funded by the National Institutes of Health's *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, for which RTI International serves as the data coordinating center. This study also received funding from the National Heart, Lung, and Blood Institute

The study tested two different treatment strategies simultaneously on the same group of infants (born at 23-26 weeks gestation). In the first test, researchers assessed the potential benefit of increasing the flow of oxygen to very preterm infants.

For the second test, researchers compared the potential benefit of using a device known as a continuous positive airway pressure (CPAP) machine that is typically used for adults with sleep apnea, with a more traditional ventilator. The CPAP machine can blow air through a preterm infant's nostrils, to gently inflate the lungs.

The results:

- Higher oxygen levels were found to improve preterm infants' survival, but also increase the risk for eye disease.
- Using a CPAP device is as safe and effective as a ventilator in managing breathing problems in premature babies, with fewer complications.

"This study provides much needed data on health outcomes in severely premature babies given different levels of oxygen," said Abhik Das, Ph.D., senior research statistician at RTI and a co-author of the paper. "In addition, it shows that CPAP is a safe, effective and less invasive alternative to the ventilator in helping these babies breathe, and may result in fewer complications."

Researchers plan to evaluate the children again when they are 18 to 22 months old, to learn whether any developmental differences arise among the children who took part in the different treatments arms of the study.

The study results will be presented on May 16 at the American Thoracic Society 2010 International Conference in New Orleans and also appear in two articles published online by *The New England Journal of Medicine*.

-end-

**From:** Das, Abhik  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** FW: \*\*\*\*CONFIDENTIAL UPDATE ON SUPPORT PAPERS AND EMBARGO\*\*\*\*\*  
**Date:** Thursday, May 13, 2010 11:29:50 AM  
**Attachments:** Neonatal studies.doc

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**Sent:** Wednesday, May 12, 2010 2:33 PM  
**To:** 'Finer, Neil'; 'Rich, Wade'; Gantz, Marie; 'Nancy Newman'; 'Anthony Piazza (Anthony.Piazza@oz.ped.emory.edu)'; ' (susie.buchter@oz.ped.emory.edu)'; 'Brenda Morris'; 'Laroia, Nirupama'; 'Phelps, Dale'; 'Duara, Shahnaz'; 'Vivek Narendran'; 'vineet.bhandari@yale.edu'; 'Sood, Beena'; 'Michael O` Shea'; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Das, Abhik; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); 'Brenda Poindexter'; 'Carlo Waldemar (E-mail)'; cotte010@mc.duke.edu; Wallace, Dennis; 'Ed Bell'; 'Ed Donovan'; 'Ehrenkranz Richard (E-mail)'; Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; 'Kristi Watterberg'; Kurt Schibler [kurt.schibler@cchmc.org]; 'Matthew Bizzarro'; 'Michelle Walsh'; 'Mickey Caplan'; 'Oh William (E-mail)'; 'Pablo Sanchez'; Poole, W. Kenneth; 'Roger Faix'; 'Ronald Goldberg'; 'Seetha Shankaran'; 'Stevenson David (E-mail)'; [SCRN] Stoll, Barbara; 'Tyson Jon (E-mail)'; VanMeurs, Krisa  
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National Institutes of Health

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-end-

**From:** Blaisdell, Carol (NIH/NHLBI) [E]  
**To:** Archer, Stephanie (NIH/NICHD) [E]  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: NRN SUPPORT Pulmonary Outcomes protocol, manual, and forms  
**Date:** Thursday, May 13, 2010 10:08:37 AM

---

Thank you so much.

This may serve as a base for the PROP (Prematurity and Respiratory Outcomes Program) at NHLBI where we are trying to developing more detailed respiratory phenotyping of NICU grads.

Carol

Carol J. Blaisdell, M.D.  
Medical Officer  
Lung Developmental Biology and  
Pediatric Pulmonary Diseases  
Division of Lung Diseases, NHLBI/NIH  
(301) 435-0222 phone

---

**From:** Archer, Stephanie (NIH/NICHD) [E]  
**Sent:** Wednesday, May 12, 2010 1:25 PM  
**To:** Blaisdell, Carol (NIH/NHLBI) [E]  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** NRN SUPPORT Pulmonary Outcomes protocol, manual, and forms

Hi Carol,

The NICHD Neonatal Research Network Steering Committee approved the request from the Prematurity and Respiratory Outcomes Program (PROP) investigators for copies of the NRN's SUPPORT Pulmonary Outcomes materials. Attached is a pdf that includes the protocol, manual, and forms (in English and in Spanish). Please let me know if you have any difficulty receiving or viewing the attachment.

In exchange, we request that the PROP investigators acknowledge the "NICHD Neonatal Research Network" when using the attached materials in all relevant applications, presentations, and publications.

Thank you,

Stephanie Archer

---

Stephanie Wilson Archer  
The Eunice Kennedy Shriver  
National Institute of Child Health and Human Development  
Pregnancy & Perinatology Branch  
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Rockville, MD 20852

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[archerst@mail.nih.gov](mailto:archerst@mail.nih.gov)

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Wednesday, May 12, 2010 1:16 PM

**To:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** FW: Prop investigators

Can you send Carol the breathing outcomes forms and manual with the usual caveats?

---

**From:** Blaisdell, Carol (NIH/NHLBI) [E]  
**Sent:** Tuesday, May 11, 2010 9:17 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** Re: Prop investigators

Wonderful thanks  
Cb

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Blaisdell, Carol (NIH/NHLBI) [E]  
**Sent:** Tue May 11 09:14:51 2010  
**Subject:** RE: Prop investigators

No need -

John Kinsella had planned on being at PAS but couldn't come as someone was ill and he had to cover the clinical service. He had planned on attending the SUPPORT Presentations. He contacted Neil and wanted to see the slides. I asked our public information folks and they told me it was ok as long as he kept them confidential, so we have shared them. I did see Rose Viscardi at the meeting so she had an opportunity to see the information.

Also, we are likely to have enough votes today or tomorrow to share all of the breathing outcomes forms and manual with the PROP folks

Rose

---

**From:** Blaisdell, Carol (NIH/NHLBI) [E]  
**Sent:** Monday, May 10, 2010 6:14 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Prop investigators

Try my cell 410-900-(b) and I will try to pop out of an all day network meeting on asthma if tomorrow works for you (I have a break around 10-10:15 or 12 to 12:45).

Carol

Carol J. Blaisdell, M.D.  
Medical Officer  
Lung Developmental Biology and  
Pediatric Pulmonary Diseases  
Division of Lung Diseases, NHLBI/NIH  
(301) 435-0222 phone

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Monday, May 10, 2010 4:47 PM  
**To:** Blaisdell, Carol (NIH/NHLBI) [E]  
**Subject:** RE: Prop investigators

I am on the phone for awhile – can I call you tomorrow?

---

**From:** Blaisdell, Carol (NIH/NHLBI) [E]  
**Sent:** Monday, May 10, 2010 4:35 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Prop investigators

Hi rose,

Yes, this is the list of PIs (Hamvas is at Wash U) for PROP.

I am now at my home number (after (b) (6) 410-560 (b) (6))

Carol

Carol J. Blaisdell, M.D.  
Medical Officer  
Lung Developmental Biology and  
Pediatric Pulmonary Diseases  
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---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Monday, May 10, 2010 4:30 PM  
**To:** Blaisdell, Carol (NIH/NHLBI) [E]  
**Subject:** Prop investigators

Carol

For the steering committee request for the Breathing outcomes forms and manual – do I have the complete list of the PROP Investigators??

The PROP Network includes:

Alan Jobe (Cincinnati)  
Judy Aschner (Vanderbilt)  
Aaron Hamvas (Mercy/Kansas)  
Roberta Kellar (UCSF)  
Gloria Pryhuber (Rochester)  
Barbara Schmidt (Penn) – Coordinating center

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network  
Pregnancy and Perinatology Branch  
Center for Developmental Biology and Perinatal Medicine  
 Eunice Kennedy Shriver National Institute of Child Health and Human Development  
National Institutes of Health  
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**From:** [Webb, Robin E.](mailto:Webb,Robin.E)  
**To:** [alaptook@WIHRI.org](mailto:alaptook@WIHRI.org); [Bradley Yoder](mailto:Bradley.Yoder); [adas@rti.org](mailto:adas@rti.org); [mgantz@rti.org](mailto:mgantz@rti.org); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](mailto:Higgins,Rosemary(NIH/NICHD)[E]); [kurt.schibler@cchmc.org](mailto:kurt.schibler@cchmc.org); [mcw3@cwru.edu](mailto:mcw3@cwru.edu); [nancy.newman](mailto:nancy.newman); [nfiner@ucsd.edu](mailto:nfiner@ucsd.edu); [Roger.Faix@hsc.utah.edu](mailto:Roger.Faix@hsc.utah.edu); [Wallace, Dennis](mailto:Wallace,Dennis); [Wally Carlo, M.D.](mailto:WallyCarlo.M.D.); [wrich@ucsd.edu](mailto:wrich@ucsd.edu)  
**Cc:** [sharon.gough@hsc.utah.edu](mailto:sharon.gough@hsc.utah.edu); [Archer, Stephanie \(NIH/NICHD\) \[E\]](mailto:Archer,Stephanie(NIH/NICHD)[E]); [Brenda Vecchio](mailto:Brenda.Vecchio); [Cunningham, Meg](mailto:Cunningham,Meg); [fmartinez@ucsd.edu](mailto:fmartinez@ucsd.edu); [Huitema, Carolyn Petrie](mailto:Huitema,Carolyn.Petrie); [Zaterka-Baxter, Kristin](mailto:Zaterka-Baxter,Kristin); [Starlett Williams](mailto:Starlett.Williams); [Webb, Robin E.](mailto:Webb,Robin.E)  
**Subject:** SUPPORT data queries  
**Date:** Wednesday, May 12, 2010 7:25:53 PM  
**Attachments:** [cpap\\_center\\_and\\_learning\\_effects\\_4-21-10final.docx](#)  
[oxygen-SUPPORT\\_secondary\\_4-21-10final.docx](#)

---

We need to schedule a call to discuss the attached. Please send your availability for the days below, indicating time zone if other than ET.

Thanks,  
Robin Webb  
RTI, International  
6110 Executive Blvd, Suite 902  
Rockville, MD 20852

Mon 5/24  
Wed 5/26  
Thurs 5/27

Tues 6/1  
Wed 6/2

Wed 6/9  
Thurs 6/10  
Fri 6/11

Mon 6/14  
Tues 6/15  
Wed 6/16  
Thurs 6/17  
Fri 6/18

Mon 6/21  
Tues 6/22  
Wed 6/23  
Thurs 6/24  
Fri 6/25

Mon 6/28  
Tues 6/29  
Wed 6/30  
Thurs 7/1  
Fri 7/2

## **Center Effects within the SUPPORT Trial**

Lenfestey, Cotten, Smith, Tanaka, Laughon, Goldberg, RTI, SUPPORT subcommittee (Finer)

### **Abstract**

The NICHD Neonatal Research Network's SUPPORT trial tested initiation of delivery room NCPAP followed by a mechanical ventilation algorithm intended to accelerate extubation if intubation was needed against use of delivery room intubation and administration of surfactant, followed by a mechanical ventilation algorithm that was less permissive of extubation.

Variations in center expertise in interventions tested in clinical trials can impact overall trial outcome, as noted in the Neonatal HIFI trial.<sup>1</sup> When clinicians in the hundreds of centers caring for extremely low gestational age infants consider the results of the SUPPORT trial, they are likely to ask two questions: 1) If my centers' rate of survival free of chronic lung disease among infants of a similar demographic as the study is high, and the standard at my center is early intubation and surfactant, should I change practice and do as well and maybe better with a delivery room CPAP strategy? and 2) If I adopt NCPAP, will the first infants I try it on have as good a chance at success as the 40<sup>th</sup> or 50<sup>th</sup>? Data collected during the SUPPORT trial will be useful to address these questions. Prior to and throughout the period of enrollment in the SUPPORT trial, centers which had a standard approach of intubation and administering surfactant early in the delivery room or the first postnatal hour prior to study participation continued to have among the highest survival and lowest rates of chronic lung disease in the Network. It is unknown whether effects related to delivery room and respiratory support approach noted in the overall trial were consistently noted among the infants enrolled in the high performing centers, or if the centers with prior adoption of delivery room NCPAP saw a consistent outcome in the infants randomized to NCPAP compared to sites adopting this practice for the first time in the clinical trial. Because study randomization was stratified by site, and the 4 centers with high performance (Brown, UAB, Duke, and Miami) enrolled over 300 infants, a carefully done subgroup analysis to assess whether the effect noted in these 4 benchmark centers was consistent with overall trial results is feasible. Assessment of whether or not outcome of infants in the NCPAP arm is associated with center experience with delivery room NCPAP can be addressed with analysis of clusters of infants enrolled throughout the study at each center, i.e., did infants enrolled in the NCPAP arm early in the study fare the same as infants enrolled later in the study at that center?

**Purpose:** The overall purpose of this proposal is to assess how adopting a new delivery room approach influenced survival and pulmonary outcomes, and whether adopting the new approach was equally successful early and late during the clinical trial.

**Aim 1:** Assess whether SUPPORT trial overall results were consistent with results in the 300+ subjects enrolled and randomized at centers with consistently good survival and low rates of chronic lung disease (Brown, UAB, Duke, Miami)

**Aim 2:** Assess whether there was a center-specific NCPAP training effect among infants enrolled in the NCPAP arm of the SUPPORT trial at sites which had not used delivery room NCPAP as usual care prior to the trial .

**Statement of the Problem:** Clinicians caring for extremely low gestational age newborn (ELGAN) infants have adopted strategies for initial respiratory support (use of surfactant after endotracheal intubation or initial use of continuous positive airway pressure and later rescue intubation and surfactant treatment) and ventilator management based on available evidence from high quality clinical trials, and the less validated but compelling single center reports and

“experience and reason.” Using this combination, there is extreme site variation in the rate of survival free of BPD at Network centers.<sup>2</sup> The NICHD neonatal Research network SUPPORT trial tested the hypothesis of whether or not initial NCPAP and subsequent stringent ventilator management parameters would improve survival free of bronchopulmonary dysplasia (BPD) compared with initial intubation with surfactant administration and more conservative ventilator management. Before initiation of the study, and throughout the study period, several centers, all of whom primarily used initial intubation and surfactant administration prior to the study, consistently had the highest survival free of BPD. It is not known whether the trend in the primary outcome noted in the overall trial was noted in the cohort of subjects enrolled and randomized at the benchmark centers that used initial intubation and surfactant for ELGANs. This query will inform potential adopters of NCPAP regarding the potential clinical and economic impact of adopting NCPAP in the delivery room in sites with high rates of survival free of BPD. It is also not known whether infants enrolled at sites which had not made initial NCPAP standard practice prior to the study start-up were as successful maintaining infants randomized to NCPAP on NCPAP throughout the first 14 postnatal days at the start of study enrollment as at the end of enrollment. This query would be important to inform new adopters of the likelihood of a learning curve for adopting NCPAP in the delivery room.

***Aims 1 and 2:***

Study Design: Retrospective post hoc subgroup analysis (Aim 1) and retrospective cohort study (Aim 2).

Study population:

*Inclusion criteria*

1. Infants in enrolled in the SUPPORT trial

*Exclusion criteria*

1. None

Study intervention:

There is no specific study intervention. This will be analysis of existing data.

Primary and Secondary Outcomes:

Aim 1:

Primary outcome: death or BPD

Secondary outcomes: death or BPD separately.

Aim 2:

Primary Outcome: death or intubated during the first 14 postnatal days.

Secondary Outcome: death or BPD

Statistical Plans:

*Outcome variables*

1. Death or BPD



2. Death
3. BPD
4. Completion of 14 days of NCPAP

*Predictor variables for multivariable analyses*

1. gestational age
2. gender
3. race
4. antenatal steroids
5. multiple birth
6. small for gestational age (SGA)

Targeted Analyses

Aim 1. Testing results in 4 benchmark centers

Consistent with recently published subgroup analysis guidelines<sup>3</sup>, We will perform two post-hoc subgroup analyses with 2 levels comparing heterogeneity of odd ratios for the primary outcomes between group 1 defined as the 4 Low BPD and High survival sites vs. Group 2, the 11 remaining centers (Cincinnati is excluded as it was a training site for NCPAP in the delivery room). We also will assess whether or not the primary outcome measured among infants enrolled at the 4 Low BPD and high survival sites before the study is homogenous with the overall outcome of the clinical trial using methodologies testing for homogeneity of study results for subgroup analysis. These analyses will involve statistical tests for interaction between the center level variable and the outcome. We plan to calculate point estimates and confidence intervals for effect size of the center level variable using the Breslow-Day test for heterogeneity of odds ratios. We will use multivariable logistic regression to determine if group has an effect on outcome. Finally we will correct p-values for multiple comparisons using the equation  $1-(1-p)^K$  where p is our accepted alpha error and K is the number of comparisons<sup>3</sup>.

Aim 2. Testing for consistency of successful NCPAP maintenance throughout enrollment.

We will perform two exploratory visual analyses and more traditional exploratory multivariable logistic regression models

Visual Analysis #1. Each center would have enrollment in the CPAP arm (X axis) and primary outcome (Y axis) plotted in two dimensions. The Y axis score of 0 for the outcome, survival without intubation in the first 14 postnatal days and a score of 1 for death or intubation within the first 14 postnatal days. The X axis would be the order of enrollment at each site. The first baby enrolled at a site would be plotted at the X axis point of '1', the second baby at '2', and so on. This would be the equivalent of a multivariable logistic regression predicting the primary outcome for NCPAP arm infants testing whether order enrolled was associated with outcome.

Visual Analysis #2, using each center's cohort randomized to NCPAP, would plot by month of study enrollment, to assess whether the course of the study use of NCPAP (and familiarity with the procedure overall) was associated with outcome among the NCPAP enrolled infants. Again, the score "0" would be assigned if the infant survived the first 14 postnatal days and was not intubated, and "1" would be assigned if the baby was intubated or died in the first 14 postnatal days. For example, the X axis would have a block for September 2008, 0's and 1's would be plotted, within each month of enrollment block.

These 2 visual models would be the equivalent of a logistic regression predicting the primary outcome for NCPAP arm infants testing whether order enrolled or time during the study was associated with outcome.

We will perform two exploratory analyses using multivariable logistic regression using infants assigned to the NCPAP arm to determine if centers became more successful at maintaining subjects on NCPAP as they gained experience. The outcome for these two analyses is the composite of intubation during the first 14 postnatal days or death. Analysis 1#: Each infant would be assigned a variable based on the order of enrollment at their respective site. We will then perform a multivariable logistic regression to determine magnitude of enrollment order effect, with the additional predictor variables as listed (GA, gender, race, antenatal steroids, multiple birth, and SGA)

Analysis 2: Each infant would be assigned a variable based on the study month of enrollment at their respective site. We will then perform a multivariable logistic regression to determine magnitude of enrollment order effect on the composite outcome of intubation during the first 14 postnatal days or death, with the additional predictor variables as listed (GA, gender, race, antenatal steroids, multiple birth, and SGA).

## References

1. Bryan AC, Froese AB. Reflections on the HIFI trial. *Pediatrics*. 1991;87:565-567.
2. Fanaroff, A.A., et al., Trends in neonatal morbidity and mortality for very low birthweight infants. *Am J Obstet Gynecol*. 2007;196:e1-8.
3. Lagakos SW. The challenge of subgroup analyses--reporting without distorting. *N Engl J Med*. 2006;354:1667-1669.

## **NICHD Neonatal Research Network Protocol Outline**

Title: Oxygen saturations and risk of mortality and morbidity in the SUPPORT trial.

### **Authors:**

P. Brian Smith MD MPH MHS

C. Michael Cotten MD MHS

Ronald N. Goldberg MD

RTI and SUPPORT Subcommittee (Carlo)

for the Eunice Kennedy Shriver NICHD Neonatal Research Network

### **A. Statement of the Problem**

Previous studies demonstrated increased rates of mortality, ROP, BPD, PVL and CP among infants with higher exposures to oxygen.<sup>1-6</sup> The SUPPORT study demonstrated lower rates of severe ROP in the lower saturation group but higher rates of mortality. No difference in severe ROP/death was observed between the two groups. Because many infants in the low saturation group spent time with saturations >89% and many infants in the high saturation group spent time with saturations <91%, there was a great deal of overlap in oxygen saturations between the two groups.

The SUPPORT study's finding that higher oxygen saturation limits are associated with lower mortality but higher rates of severe ROP leaves uncertainty for clinicians. The rationale for this proposal is that evidence for determining the safest range for oxygen saturation for premature infants is conflicting.<sup>5,6</sup> In the protocol described below, we will be able to examine the association between the actual recorded oxygen saturation with the clinical outcomes of the infants. *We propose to examine the incidence of mortality and morbidities using actual oxygen saturations as a predictor for infants enrolled in the SUPPORT trial.*

### **B. Hypothesis**

*Hypothesis:* Higher oxygen saturations are associated with an increased risk of death, ROP, BPD, death/ROP, or death/BPD for infants receiving supplemental oxygen.

### **C. Specific Aim**

*Specific Aim:* Determine whether oxygen saturations for infants receiving supplemental oxygen are related to death, ROP, BPD, death/ROP, or death/BPD.

### **D. Method/ Procedures**

1. Study Design: Retrospective cohort study.
2. Study population:
  - Inclusion criteria*
    1. 1316 infants in enrolled in the SUPPORT trial

*Exclusion criteria*

1. None
3. Study intervention:  
There is no specific study intervention. This will be analysis of existing data.
4. Primary and Secondary Outcomes:  
Primary outcome:           Death  
Secondary outcomes:      ROP, BPD, death/ROP, death/BPD
5. Statistical Plans:  
*Outcome variables*
  1. death
  2. ROP
  3. BPD
  4. death/ROP
  5. death/BPD

*Predictor variables*

Oxygen saturation for each infant while receiving supplemental oxygen

*Confounding variables*

1. saturation group (low vs. high)
2. gestational age
3. birth weight
4. sex
5. singleton vs. multiple birth

*Observations for analysis*

Observations recorded when the infant's SaO<sub>2</sub> could not be altered will not be used in the analysis.

1. Infant receiving 21% FiO<sub>2</sub> with SaO<sub>2</sub> > than upper target limit range
2. Infant receiving 100% FiO<sub>2</sub> with SaO<sub>2</sub> < than lower target limit range

*Weighting of observations*

Although the number of observations varied by subject in the dataset, each infant will contribute equally to the overall statistical calculations.

*Bivariable analysis*

We will compare mean oxygen saturations for infants that died vs. those that lived using the Student's t-test. The comparison will be repeated for each of the secondary outcomes: ROP, BPD, death/ROP, and death/BPD.

*Multivariable analysis*

We will build a multivariable logistic regression model to determine the relationship between outcome variables and mean oxygen saturation for each infant (continuous variable) controlling for saturation group (low vs. high), mean FiO<sub>2</sub> (continuous variable), gestational age, birth weight, sex, and singleton birth.

## E. References

1. Jobe, A.H. and Bancalari, E., Bronchopulmonary dysplasia. *Am J Respir Crit Care Med.* 163, 1723-9(2001).
2. Flynn, J.T., Bancalari, E., Snyder, E.S., Goldberg, R.N., Feuer, W., Cassady, J., Schiffman, J., Feldman, H.I., Bachynski, B., Buckley, E., and et al., A cohort study of transcutaneous oxygen tension and the incidence and severity of retinopathy of prematurity. *N Engl J Med.* 326, 1050-4(1992).
3. Saugstad, O.D., Bronchopulmonary dysplasia-oxidative stress and antioxidants. *Semin Neonatol.* 8, 39-49(2003).
4. Haynes, R.L., Baud, O., Li, J., Kinney, H.C., Volpe, J.J., and Folkerth, D.R., Oxidative and nitrative injury in periventricular leukomalacia: a review. *Brain Pathol.* 15, 225-33(2005).
5. Anderson, C.G., Benitz, W.E., and Madan, A., Retinopathy of prematurity and pulse oximetry: a national survey of recent practices. *J Perinatol.* 24, 164-8(2004).
6. Tin, W., Milligan, D.W., Pennefather, P., and Hey, E., Pulse oximetry, severe retinopathy, and outcome at one year in babies of less than 28 weeks gestation. *Arch Dis Child Fetal Neonatal Ed.* 84, F106-10(2001).

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Michael Cotten"  
**Subject:** RE: \*\*\*\*CONFIDENTIAL UPDATE ON SUPPORT PAPERS AND EMBARGO\*\*\*\*\*  
**Date:** Wednesday, May 12, 2010 3:09:00 PM

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We do not have anything formally scheduled.

Rose

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**From:** Michael Cotten [mailto:cotte010@mc.duke.edu]  
**Sent:** Wednesday, May 12, 2010 2:47 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** Re: \*\*\*\*CONFIDENTIAL UPDATE ON SUPPORT PAPERS AND EMBARGO\*\*\*\*\*

will there be a briefing/discussion w/ NICHD people/co-authors about potential questions and answers?

mc

C. Michael Cotten MD MHS  
Associate Professor of Pediatrics  
Medical Director Neonatology Clinical Research  
Duke University Medical Center  
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"Higgins, Rosemary (NIH/NICHD) [E]"  
<higginsr@mail.nih.gov>

05/12/2010 02:35 PM

To "Finer, Neil" <nfiner@ucsd.edu>, "Rich, Wade" <wrich@ucsd.edu>, "Gantz, Marie" <mgantz@rti.org>, "Nancy Newman" <nxs5@case.edu>, "Anthony Piazza (Anthony.Piazza@oz.ped.emory.edu)" <Anthony.Piazza@oz.ped.emory.edu>, " (susie.buchter@oz.ped.emory.edu)" <susie.buchter@oz.ped.emory.edu>, "Brenda Morris" <brenda (b) (6) Laroya@URMC.Rochester.edu>, "Nirupama\_Laroya@URMC.Rochester.edu", "Phelps, Dale" <Dale\_Phelps@URMC.Rochester.edu>, "Duara, Shahnaz" <SDuara@med.miami.edu>, "Vivek Narendran" <Vivek.Narendran@cchmc.org>, "vineet.bhandari@yale.edu" <vineet.bhandari@yale.edu>, "Sood, Beena" <bsood@med.wayne.edu>, "Michael O'Shea" <moshea@wfubmc.edu>, " (Luc.Brion@UTSouthwestern.edu)" <Luc.Brion@UTSouthwestern.edu>, " (rohls@unm.edu)" <rohls@unm.edu>, "aaf2@po.cwr.edu" <aaf2@po.cwr.edu>, "Abhik Das" <adas@rti.org>, "alaptook@WHRI.org" <alaptook@WHRI.org>, "Ambal (ambal@uab.edu)" <ambal@uab.edu>, "Brad Yoder (Bradley.yoder@hsc.utah.edu)" <Bradley.yoder@hsc.utah.edu>, "Brenda Poindexter" <bpoindex@iupui.edu>, "Carlo Waldemar (E-mail)" <wcarlo@peds.uab.edu>, "cotte010@mc.duke.edu" <cotte010@mc.duke.edu>, "Dennis Wallace" <dwallace@rti.org>, "Ed Bell" <Edward-bell@uiowa.edu>, "Ed Donovan" <edward.donovan@cchmc.org>, "Ehrenkranz Richard (E-mail)" <richard.ehrenkranz@yale.edu>, "Ivan Frantz (ifrantz@tuftsmedicalcenter.org)" <ifrantz@tuftsmedicalcenter.org>, "Kennedy, Kathleen A" <Kathleen.A.Kennedy@uth.tmc.edu>, "Kristi Watterberg" <kwatterberg@salud.unm.edu>, "Kurt Schibler" <kurt.schibler@cchmc.org>, "Matthew

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cc "Archer, Stephanie (NIH/NICHD) [E]" <archerst@mail.nih.gov>, "Zaterka-Baxter, Kristin" <kzaterka@rti.org>, "Cunningham, Meg" <mcunningham@rti.org>, "Huitema, Carolyn Petrie" <petrie@rti.org>

Subject \*\*\*\*CONFIDENTIAL UPDATE ON SUPPORT PAPERS AND EMBARGO\*\*\*\*\*

**Hello again everyone:**

**I have several items regarding SUPPORT.**

**Both manuscripts are attached along with the appendices. The authors appear at the end of the paper as formal "authors" due to space limits from NEJM. I have also attached the NIH press release for the papers. Finally, there is an editorial which will appear on-line and in the May 27 issue of NEJM.**

**ALL OF THIS INFORMATION IS SUBJECT TO EMBARGO RULES AND NOT TO BE RELEASED UNTIL SUNDAY MAY 16 at 1 PM ET. This information can be *confidentially shared with your institutional press/public affairs office* as long as the embargo is respected.**

**Thanks to everyone at each and every site for all of the hard work and effort on this study. A special appreciation of gratitude goes to the coordinators who really went above and beyond to get the patients enrolled in this difficult study.**

**A very, very special and heart felt thanks to Neil and Wally for all of their hard work, commitment, effort and patience to bring this to completion!!!!**

**Both SUPPORT Papers will be *accelerated Online First release* scheduled to coincide with the presentations of the results at the American Thoracic Society's annual meeting on Sunday May 16, 2010. The on-line release will occur at 1 PM EDT on 5/16/2010. The print publication is slated to appear in the May 27, 2010 issue of NEJM.**

If you have any questions, please contact me

Rose

Rosemary D. Higgins, MD

Program Scientist for the Neonatal Research Network

Pregnancy and Perinatology Branch

Center for Developmental Biology and Perinatal Medicine

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[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

[attachment "SUPPORT Press release.docx" deleted by Michael Cotten/Pediatrics/mc/Duke]

[attachment "Carlo.pdf" deleted by Michael Cotten/Pediatrics/mc/Duke] [attachment

"Carlo\_supapp.pdf" deleted by Michael Cotten/Pediatrics/mc/Duke] [attachment "Finer.pdf"

deleted by Michael Cotten/Pediatrics/mc/Duke] [attachment "Finer\_supapp.pdf" deleted by

Michael Cotten/Pediatrics/mc/Duke] [attachment "Morley.pdf" deleted by Michael

Cotten/Pediatrics/mc/Duke]



**From:** Avroy Fanaroff  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** Re: \*\*\*\*CONFIDENTIAL UPDATE ON SUPPORT PAPERS AND EMBARGO\*\*\*\*\*  
**Date:** Wednesday, May 12, 2010 2:48:51 PM

---

I thought that the editorial is fairly balanced and appropriate  
well done team captain  
Av

On Wed, May 12, 2010 at 2:33 PM, Higgins, Rosemary (NIH/NICHD) [E]  
<higginsr@mail.nih.gov> wrote:

> Hello again everyone:

>

>

>

> I have several items regarding SUPPORT.

>

>

>

> Both manuscripts are attached along with the appendices. The authors appear  
> at the end of the paper as formal "authors" due to space limits from NEJM.  
> I have also attached the NIH press release for the papers. Finally, there  
> is an editorial which will appear on-line and in the May 27 issue of NEJM.

>

>

>

> ALL OF THIS INFORMATION IS SUBJECT TO EMBARGO RULES AND NOT TO BE RELEASED  
> UNTIL SUNDAY MAY 16 at 1 PM ET. This information can be confidentially  
> shared with your institutional press/public affairs office as long as the  
> embargo is respected.

>

>

>

> Thanks to everyone at each and every site for all of the hard work and  
> effort on this study. A special appreciation of gratitude goes to the  
> coordinators who really went above and beyond to get the patients enrolled  
> in this difficult study.

>

>

>

> A very, very special and heart felt thanks to Neil and Wally for all of  
> their hard work, commitment, effort and patience to bring this to  
> completion!!!!

>

>

>

>

>

> Both SUPPORT Papers will be accelerated Online First release scheduled to  
> coincide with the presentations of the results at the American Thoracic  
> Society's annual meeting on Sunday May 16, 2010. The on-line release will  
> occur at 1 PM EDT on 5/16/2010. The print publication is slated to appear  
> in the May 27, 2010 issue of NEJM.

>

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- > If you have any questions, please contact me
- >
- >
- >
- > Rose
- >
- > Rosemary D. Higgins, MD
- >
- > Program Scientist for the Neonatal Research Network
- >
- > Pregnancy and Perinatology Branch
- >
- > Center for Developmental Biology and Perinatal Medicine
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- > Eunice Kennedy Shriver National Institute of Child Health and Human
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--  
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Eliza Henry Barnes Professor of Neonatology  
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Professor of Pediatrics  
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(216) 844-3387  
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**From:** Walsh, Michele  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Request for breathing outcomes forms and manual  
**Date:** Tuesday, May 11, 2010 4:29:05 PM

---

yes

Michele Walsh  
beeper (b) (6)  
Ph 216 844 3759

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**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Monday, May 10, 2010 4:36 PM  
**To:** (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Matthew Bizzarro; Michelle Walsh; Mickey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOLDBERG; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; 'Stevens, Timothy'  
**Subject:** Request for breathing outcomes forms and manual

Hi

The prematurity and respiratory outcomes program (PROP) which is sponsored by NHLBI has asked for the breathing outcomes forms and manual. Please send me a yes/no vote by May 17 to share these items with this newly formed group of investigators.

The PROP Network includes:

Alan Jobe (Cincinnati)  
Judy Aschner (Vanderbilt)  
Aaron Hamvas (Washington Univ)  
Roberta Kellar (UCSF)  
Gloria Pryhuber (Rochester)  
Barbara Schmidt (Penn) – Coordinating center

Rose

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network  
Pregnancy and Perinatology Branch  
Center for Developmental Biology and Perinatal Medicine  
 Eunice Kennedy Shriver National Institute of Child Health and Human Development  
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**From:** Archer, Stephanie (NIH/NICHD) [E]  
**To:** Blaisdell, Carol (NIH/NHLBI) [E]  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** NRN SUPPORT Pulmonary Outcomes protocol, manual, and forms  
**Date:** Wednesday, May 12, 2010 1:24:39 PM  
**Attachments:** NRNSUPPORTPulmonaryOutcome.pdf

---

Hi Carol,

The NICHD Neonatal Research Network Steering Committee approved the request from the Prematurity and Respiratory Outcomes Program (PROP) investigators for copies of the NRN's SUPPORT Pulmonary Outcomes materials. Attached is a pdf that includes the protocol, manual, and forms (in English and in Spanish). Please let me know if you have any difficulty receiving or viewing the attachment.

In exchange, we request that the PROP investigators acknowledge the "NICHD Neonatal Research Network" when using the attached materials in all relevant applications, presentations, and publications.

Thank you,

Stephanie Archer

---

Stephanie Wilson Archer  
The Eunice Kennedy Shriver  
National Institute of Child Health and Human Development  
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Tel. 301-496-0430  
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**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Wednesday, May 12, 2010 1:16 PM  
**To:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** FW: Prop investigators

Can you send Carol the breathing outcomes forms and manual with the usual caveats?

---

**From:** Blaisdell, Carol (NIH/NHLBI) [E]  
**Sent:** Tuesday, May 11, 2010 9:17 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** Re: Prop investigators

Wonderful thanks  
Cb

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Blaisdell, Carol (NIH/NHLBI) [E]  
**Sent:** Tue May 11 09:14:51 2010

**Subject:** RE: Prop investigators

No need -

John Kinsella had planned on being at PAS but couldn't come as someone was ill and he had to cover the clinical service. He had planned on attending the SUPPORT Presentations. He contacted Neil and wanted to see the slides. I asked our public information folks and they told me it was ok as long as he kept them confidential, so we have shared them. I did see Rose Viscardi at the meeting so she had an opportunity to see the information.

Also, we are likely to have enough votes today or tomorrow to share all of the breathing outcomes forms and manual with the PROP folks

Rose

---

**From:** Blaisdell, Carol (NIH/NHLBI) [E]  
**Sent:** Monday, May 10, 2010 6:14 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Prop investigators

Try my cell 410-900-(b) and I will try to pop out of an all day network meeting on asthma if tomorrow works for you (I have a break around 10-10:15 or 12 to 12:45).

Carol

Carol J. Blaisdell, M.D.  
Medical Officer  
Lung Developmental Biology and  
Pediatric Pulmonary Diseases  
Division of Lung Diseases, NHLBI/NIH  
(301) 435-0222 phone

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Monday, May 10, 2010 4:47 PM  
**To:** Blaisdell, Carol (NIH/NHLBI) [E]  
**Subject:** RE: Prop investigators

I am on the phone for awhile – can I call you tomorrow?

---

**From:** Blaisdell, Carol (NIH/NHLBI) [E]  
**Sent:** Monday, May 10, 2010 4:35 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Prop investigators

Hi rose,

Yes, this is the list of PIs (Hamvas is at Wash U) for PROP.

I am now at my home number (after (b) (6) 410-560-(b)

Carol

Carol J. Blaisdell, M.D.  
Medical Officer  
Lung Developmental Biology and  
Pediatric Pulmonary Diseases  
Division of Lung Diseases, NHLBI/NIH  
(301) 435-0222 phone

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Monday, May 10, 2010 4:30 PM  
**To:** Blaisdell, Carol (NIH/NHLBI) [E]  
**Subject:** Prop investigators

Carol  
For the steering committee request for the Breathing outcomes forms and manual –  
do I have the complete list of the PROP Investigators??

The PROP Network includes:  
Alan Jobe (Cincinnati)  
Judy Aschner (Vanderbilt)  
Aaron Hamvas (Mercy/Kansas)  
Roberta Kellar (UCSF)  
Gloria Pryhuber (Rochester)  
Barbara Schmidt (Penn) – Coordinating center

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network  
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# **NICHD SUPPORT Trial**

## **Breathing Outcomes Study Protocol**

**University of Rochester  
Golisano Children's Hospital at Strong**

**Timothy P. Stevens, MD, MPH  
Peter Szilagyi, MD, MPH  
Dale Phelps, MD**

Proposal Updated: December 6, 2005

Contact Information:

Timothy P. Stevens, MD  
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## **ABSTRACT**

**Statement of Problem** Premature infants have a greater risk of recurrent wheezing and chronic cough and greater need for pulmonary care in early childhood than term infants (1-11). Although Chronic Lung Disease (CLD) is a risk factor, the etiology of symptomatic airway dysfunction, defined hereafter as recurrent wheezing and/or chronic cough, in formerly premature infants is not known.

**Hypotheses** The goal of this clinical project is to understand better the antecedents of symptomatic airway dysfunction among preterm infants during early childhood by evaluating the effect of treatment with different levels of targeted oxygen saturation in the immediate neonatal period. **The overarching hypothesis is that premature infants exposed to supplemental oxygen suffer oxidant stress in the lung in the immediate newborn period that results in impaired airway growth and development. These airway changes predispose premature infants to greater airway dysfunction and respiratory symptoms when challenged with subsequent environmental or infectious exposures.**

*Hypothesis #1-* Relative to infants managed with a higher SpO<sub>2</sub> range, infants who are managed with a lower targeted SpO<sub>2</sub> range will have less symptomatic airway dysfunction and reduced need for outpatient pulmonary care in the first 18-22 months' corrected age (CA), whether they develop CLD or not.

*Hypothesis #2-* Relative to infants managed with prophylactic surfactant and conventional ventilation, infants who are managed with the early use of CPAP and a permissive ventilator strategy will have less symptomatic airway dysfunction and reduced need for outpatient pulmonary care in the first 18-22 months' CA, whether they develop CLD or not.

## **Design**

This study is a longitudinal follow-up of infants enrolled in the SUPPORT Trial to determine the effect of lower targeted oxygen saturation ranges and more aggressive use of CPAP on the incidence of symptomatic airway dysfunction and volume of outpatient pulmonary care in the first 18-22 months' CA.

### *Definition of outcomes:*

- A) Parental Report Symptomatic Airway Dysfunction Defined as Recurrent Wheezing or Chronic Cough
- B) Parental Report of Physician Diagnosed Wheezing
- C) Volume of Outpatient Pulmonary Care including number of pulmonary medications, office and emergency room visits and re-hospitalizations for respiratory illnesses.

### *Ascertainment of outcomes:*

Outcomes will be measured at 4 time points in the first 18-22 months' CA as follows:

1. NICU discharge -baseline interview at to obtain family and environmental history
2. Six months' CA - telephone or face to face interview to ascertain incidence of symptomatic airway dysfunction and obtain interval history of need for pulmonary care.
3. Twelve months' CA - telephone or face to face interview as at 6 months'
4. 18-22 months' CA- Prior to or as part of the NICHD follow-up clinic visit, a telephone or face to face interview will be conducted to ascertain incidence of symptomatic airway dysfunction and obtain history of need for pulmonary care.

## **Anticipated Results**

We anticipate that, for infants who develop CLD and those who do not, treatment with a lower vs. higher targeted oxygen saturation range will have less symptomatic airway dysfunction and less need for outpatient pulmonary care in the first 18-22 months' CA. We also anticipate that greater use of CPAP compared with conventional management will be associated with less symptomatic airway dysfunction.

## **Benefits and Risks**

The proposed SUPPORT Breathing Outcomes Study will directly measure symptomatic airway dysfunction and outpatient pulmonary morbidity in infants treated with either a higher vs. lower targeted oxygen saturation. These data will provide important insight into the effect of different levels of supplemental oxygen exposure on airway growth and development in formerly premature infants. In addition to creating a potential model for outpatient pulmonary follow up, the proposed follow on study may improve follow up at the 18-22 month NICHD visit by maintaining contact with families during the interval between NICU discharge and the neurodevelopmental follow up visit. We anticipate no risk to patients enrolled in this observational follow-up study.

## **B. STATEMENT OF THE PROBLEM**

Premature infants have a greater risk for recurrent wheezing, chronic cough and more need for pulmonary care in early childhood than term infants(1-11). Although Chronic Lung Disease (CLD) is a risk factor, the etiology of symptomatic airway dysfunction, defined hereafter as recurrent wheezing and/or chronic cough, in formerly premature infants is not known.

## **C. HYPOTHESES**

The overarching hypothesis is that premature infants exposed to supplemental oxygen and, to a lesser extent, mechanical ventilation, in the immediate neonatal period suffer oxidant stress in the lung that results in impaired airway growth and development. These airway changes predispose premature infants to greater airway dysfunction, respiratory symptoms and need for pulmonary care when challenged with subsequent environmental or infectious exposures.

### Specific Hypotheses:

*Hypothesis #1-* We hypothesize that relative to infants managed with a higher SpO<sub>2</sub> range, infants managed with a lower SpO<sub>2</sub> range will have less frequent episodes of symptomatic airway dysfunction and reduced need for outpatient pulmonary care at 18-22 months' CA.

*Hypothesis #2-* We hypothesize that relative to infants managed with prophylactic surfactant and conventional ventilation, infants managed with early CPAP and permissive ventilator strategy will have less frequent episodes of symptomatic airway dysfunction and reduced need for outpatient pulmonary care in the first 18-22 months' CA.

*Hypothesis #3-* We hypothesize that **among infants with CLD**, infants managed with a lower SpO<sub>2</sub> range relative to those managed with a higher SpO<sub>2</sub> target range and infants managed with early CPAP and permissive ventilator strategy compared with those managed with prophylactic surfactant and conventional ventilation will have less frequent episodes of symptomatic airway dysfunction and reduced need for outpatient pulmonary care during the first 18-22 months' CA.

*Hypothesis #4-* We hypothesize that **among infants without CLD**, infants managed with a lower SpO<sub>2</sub> range relative to those managed with a higher SpO<sub>2</sub> target range and infants managed with early CPAP and permissive ventilator strategy compared with those managed with prophylactic surfactant and conventional ventilation will have less frequent episodes of symptomatic airway dysfunction and reduced need for outpatient pulmonary care during the first 18-22 months' CA.

## **D. SPECIFIC AIMS**

The goal of this project is to understand better the etiology of symptomatic airway dysfunction among formerly premature infants during early childhood by examining the interaction of oxygen exposure (targeted SpO<sub>2</sub> range), surfactant therapy and early nasal CPAP in the newborn period.

SA#1 - Measure the effect of lower vs. higher targeted SpO<sub>2</sub> on the incidence of symptomatic airway dysfunction and volume of outpatient pulmonary care among infants born 24<sup>0/7</sup> - 27<sup>6/7</sup> weeks' gestation during the first 18-22 months' CA.

SA#2 - Measure the effect of early CPAP and permissive ventilator strategy compared with prophylactic surfactant and traditional ventilator strategy on the incidence of symptomatic airway dysfunction and volume of outpatient pulmonary care among infants born 24-27 weeks' gestation during the first 18-22 months' CA.

SA#3 – Among infants who develop CLD, determine whether CLD is milder in infants managed with low compared with high targeted SpO<sub>2</sub> by measuring incidence of symptomatic airway dysfunction and volume of outpatient pulmonary care. A similar analysis will be performed by SUPPORT Trial ventilatory strategy assignment, i.e. early CPAP and permissive ventilation compared with prophylactic surfactant and traditional ventilation.

**SA#4 – Among infants who do not develop CLD**, determine whether pulmonary outcome is better for infants managed with a low compared with high targeted SpO<sub>2</sub> range by measuring incidence of symptomatic airway dysfunction and need for outpatient pulmonary care. A similar analysis will be performed by SUPPORT Trial ventilatory strategy assignment, i.e. early CPAP and permissive ventilation compared with prophylactic surfactant and traditional ventilation.

## **E. RATIONALE/JUSTIFICATION**

Although synergy in producing airway injury may exist between oxygen toxicity and mechanical forces applied to the lung, animal and human data suggest that exposure to high concentrations of supplemental oxygen alone is sufficient to cause airway narrowing and greater airway dysfunction when exposed to subsequent environmental or infectious challenges. Understanding the relative contributions of oxygen toxicity and mechanical forces on airway growth and development may facilitate development of targeted therapies for preventing or reducing symptomatic airway dysfunction in premature infants.

*Why measure symptomatic airway dysfunction and outpatient pulmonary care as an outcome from a clinical NICU interventional trial?*

- 1) Important information will be available on the effect of oxidant gas exposure on airway development and later symptomatic airway dysfunction. Exposure to oxidant gas has been causally linked with later wheezing. Existing data on the relationship between supplemental oxygen therapy and wheezing come from longitudinal cohort studies, a design that suffers from intrinsic limitations that make controlling for potential confounders of respiratory outcome difficult. By randomizing infants to higher vs. lower target saturation ranges, and thereby presumably higher or lower concentrations of inspired oxygen, *the SUPPORT Trial creates a unique, and perhaps the only, opportunity to evaluate the effect of different levels of supplemental oxygen on subsequent symptomatic airway dysfunction and need for outpatient pulmonary care after NICU discharge.*
- 2) Using clinical measures of outpatient pulmonary morbidity, the effect of NICU based respiratory interventions on respiratory health and need for outpatient medical care can be directly quantified, allowing assessment of whether infants both with and without CLD have improved pulmonary health as a result of the study intervention.
- 3) The incidence of CLD, defined as an oxygen requirement at 36 weeks' PMA, is an incomplete measure of pulmonary outcome in formerly premature infants during early infancy. CLD as defined above reflects alveolar gas diffusion and NICU oxygen needs. However, outpatient pulmonary morbidity for formerly premature infants is often airway related, involving wheezing either as a primary symptom such as bronchiolitis or as a complicating symptom of lower respiratory tract infection such as pneumonia. The studies proposed here will directly measure the effect of a randomized NICU-based clinical intervention on symptomatic airway dysfunction and outpatient pulmonary morbidity.
- 4) The risk of a negative trial is reduced. Because the diagnosis of CLD does not completely predict need for outpatient pulmonary care, clinically significant improvements in pulmonary morbidity may occur with minimal or no change in the incidence of CLD. This result has occurred in other interventional trials in which no difference in CLD were observed (12).
- 5) At present, there is no standard way to measure symptomatic airway dysfunction in premature infants in NICHD pulmonary intervention trials. There is need for a better measure to assess clinical pulmonary outcome to recognize and promote therapies that reduce need for outpatient care of former extremely premature infants.

## **F. BACKGROUND / PREVIOUS STUDIES**

*Recurrent Wheezing In Preterm Infants is a Significant Public Health Problem*

Outpatient pulmonary morbidity, especially recurrent wheezing and need for outpatient pulmonary care, is an understudied but clinically important outcome measure for former premature infants with and without CLD. Infants born weighing < 1500 grams (very low birth weight, VLBW) and especially infants born weighing < 1000 grams are at increased risk for small airway narrowing, airway hyperreactivity, wheezing, and nighttime cough (1-11). Up to 30-40% of formerly extremely premature infants have episodes of wheezing after NICU discharge

with many requiring bronchodilators and frequent health care visits. Up to 40-50% of premature infants require re-hospitalization, mostly for treatment of respiratory illnesses (9;12;13). In analysis of cross sectional data from the National Maternal Infant Health Survey and 1991 Longitudinal Follow up Survey, the prevalence of asthma-like recurrent wheezing varied markedly with birth weight. Infants with normal birth weight (NBW, > 2500 grams) had a 6.7% prevalence of asthma compared to 10.9% of low birth weight infants (LBW, 1500-2499 grams) and 21.9% for VLBW (14). Mean per capita asthma related costs have been estimated to be 5 times greater for VLBW compared with NBW infants. The net effect is that VLBW infants, who comprise 2% of asthma patients, consume up to 7% of asthma-related therapy costs (14).

### *Animal Studies*

Animal studies suggest that exposure of the premature lung to hyperoxia (without concomitant mechanical ventilation) for relatively brief periods is sufficient to cause airway remodeling and smooth muscle changes that predispose toward airway narrowing and hyperreactivity to subsequent environmental challenges (15-18). In a rhesus monkey model of asthma, Schlegle et al. exposed infant monkeys to repeated cycles of inhaled House Dust Mite Allergen (HDMA), ozone or filtered air. While repeated exposure to either ozone or HDMA had mild effects, exposure to cycles of ozone followed by HDMA resulted in asthma like changes with significant increases in serum IgE, serum histamine, peripheral eosinophilia and greater airway reactivity. Using supplemental oxygen rather than the stronger oxidant ozone, Schulman et al. found that exposure of newborn guinea pigs to 70% oxygen for 96 hours resulted in airway hyperreactivity at 2 and 9 days after the cessation of oxygen. In cell models, intracellular glutathione buffers airway cells against oxidant injury during hyperoxia (19;20). Although the critical period for lung development is comparatively brief in laboratory animals compared with human infants, the duration of hyperoxic exposure (and risk of oxygen toxicity) for treatment of neonatal lung disease may extend for much longer periods in premature infants known to be deficient in anti-oxidant systems such as intracellular glutathione.

### *Premature Infants With CLD Are At Greatest Risk For Airway Dysfunction*

Among premature infants, infants with bronchopulmonary dysplasia (BPD) are at highest risk for poor pulmonary outcome after NICU discharge. Infants with CLD have small airway compromise with decreased forced expiratory flow velocities, airway hyperreactivity, and increased functional residual volume suggesting airway obstruction (2;5;9;21-24). In a pulmonary follow up of infants with RDS or BPD, De Klein et al. found infants with BPD had reduced FEV1 at baseline while infants with RDS but not BPD had significant improvements in FEV1 following bronchodilator therapy. In this study, a history of recurrent wheezing predicted abnormal pulmonary function (25). In a recent study of infants with CLD, Robin et al. found that 50% of infants with CLD had symptoms of recurrent wheezing and 35% showed significant airway responsiveness to bronchodilators, evidenced by a 24% increase in forced expiratory flow velocity at 75% of expired forced vital capacity (FEF<sub>75</sub>). This study demonstrated the relationship between recurrent wheezing as a clinical symptom and the physiologic measurement of airway obstruction. Infants with CLD and a history of recurrent wheezing showed greater hyperinflation, expiratory flow limitation and airway responsiveness to albuterol compared to those without a history of recurrent wheezing (24).

### *Premature Infants Without CLD Have Significant Airway Dysfunction*

Among VLBW infants who do not develop CLD, several studies of pulmonary outcome have found an association between neonatal oxygen exposure and increased prevalence of expiratory flow dysfunction and airway hyperreactivity (4;11;26-29). Some authors attribute reductions in airway function to intrinsically small airways as a consequence of poor intrauterine growth rather than superimposed airway injury or reactivity from neonatal respiratory disease (1;30). However, because small airways alone do not fully explain airway hyperreactivity, other mechanisms of small airway dysfunction are necessary to explain respiratory symptoms.

Several pulmonary outcome studies have reported significant increases (2-fold or more) in airway obstruction among VLBW infants without CLD following exposure to as little as 40% oxygen for 5 days (3;4;8;26). Not all studies have had similar results suggesting variability in effect or susceptibility of babies to oxygen exposure (31;32). In 1982, Coates et al. described increased small airway resistance at 10 year follow up of mildly

premature infants (mean gestational age 31 weeks and birth weight 2000 grams) treated with a high oxygen regimen and those exposed to a low oxygen regimen for the treatment of respiratory distress syndrome (RDS). Mechanical ventilation was not used in either group. Pulmonary function tests were performed on survivors receiving either the low or high supplemental oxygen regimen ten years after their initial illness. Infants treated with high levels of supplemental oxygen alone (no mechanical ventilation) had decrements in airway function similar to decrements in function reported for a historical cohort of RDS survivors treated with ventilation and high levels of supplemental oxygen. From these data, the authors concluded that neonatal exposure to high oxygen concentrations in the absence of mechanical ventilation is capable of causing long-term change in small airways (28). These studies suggest that use of lower supplemental oxygen concentration may improve respiratory health of infants who do not develop CLD.

#### *Premature Infants Without CLD Have Increased Risk of Symptomatic Airway Dysfunction and Need for Outpatient Pulmonary Care.*

For VLBW infants without CLD, the prevalence of parental or physician reported wheezing is increased compared with term infants, with estimates of the prevalence of wheezing ranging from 10-38% (4;8). Prevalence of wheezing requiring medications is greater compared with term infants. VLBW infants have a 2-4-fold increase in respiratory related re-hospitalization rates compared with term infants (4;8;33-35). Although most studies have found the risk of recurrent wheezing remains elevated throughout childhood, an Australian longitudinal follow-up cohort of VLBW infants found the prevalence of wheezing remained elevated for 2 years then returned to baseline (32;36).

#### *Prevalence of Symptomatic Airway Dysfunction in Formerly Preterm Infants During the Surfactant Era Remains High*

With the advent of surfactant therapy, survival of small infants increased dramatically and the incidence of CLD changed minimally (37-40). Classic BPD evolved into the "new CLD" characterized by reduced alveolarization and more variable airway changes (41). Pulmonary follow up studies during the surfactant era showed reduced pulmonary morbidity in surfactant treated patients. Typical of these studies, Sell et al. found the incidence of asthma was significantly lower in infants given synthetic surfactant compared with those given air placebo. Pelkonen et al. performed PFT measurements on 40 children aged 7-12 years who were born before 30 weeks of gestation with an immature surfactant system, and were randomized to one of three treatment groups: prophylactic surfactant, rescue surfactant and placebo (air). Spirometric parameters of children born preterm were compared with those of 20 children born at term. Bronchial obstruction was found in 53% of the prophylactically treated group, in 36% of the rescue group, in 67% of the placebo group, and in 0% of the control group (42). A recent report suggests that the introduction of surfactant therapy markedly altered the pulmonary outcome of premature infants. Published in 2001, the Newborn Lung Project Group reported results of a prospective 12-year follow-up of VLBW infants following the introduction of surfactant therapy (5;8;43). Among infants with CLD, wheezing symptoms decreased from 50 to 16% from the period before compared with the period after surfactant therapy became available. However, among infants without CLD the prevalence of wheezing increased from 14% to 38% with the introduction of surfactant. These data suggest that surfactant therapy has an effect on outpatient respiratory health and underscores the need to consider outpatient pulmonary outcomes in evaluating therapeutic strategies that potentially decrease surfactant replacement therapy.

#### *CLD is an Incomplete Predictor of Outpatient Pulmonary Morbidity*

Several authors have looked to respiratory symptoms and need for outpatient pulmonary care as outcome measures for neonatal lung disease (9;10;12;24). In 1988, from a retrospective chart review of 605 premature infants < 1500 grams, Shennan et al. found that the presence of BPD (oxygen requirement at 36 weeks PMA) had a 63% positive predictive value and a 90% negative predictive value for abnormal pulmonary outcome in the first 2 years of age. However, this study from before the era of exogenous surfactant therapy defined abnormal pulmonary outcome as death, oxygen requirement at 40 weeks PMA, 2 or more respiratory related hospital admissions, wheezing requiring drug therapy or persistent wheezing resulting in growth failure, handicap or hypotonia at 1 year of age. Such restrictive criteria for abnormal pulmonary outcome are likely to underestimate the burden of recurrent wheezing on former premature infants and their families. Several recent

interventional studies show that CLD is an incomplete predictor of clinical wheezing and need for outpatient pulmonary care and suggest that differences in oxygen exposure or oxidant stress may affect pulmonary outcome without affecting the incidence of CLD.

#### *Interventional Trials That Did Not Reduce CLD But Did Reduce Outpatient Pulmonary Morbidity.*

Recent data in preterm infants treated with human recombinant superoxide dismutase (SOD) found that anti-oxidant therapy did not reduce the incidence of CLD. However, among infants < 27 weeks gestation, SOD therapy resulted in significant reductions in the first year after NICU discharge in the number of emergency room visits and number of re-hospitalizations for respiratory problems and reductions in the need for bronchodilators suggesting a reduced prevalence of wheezing in patients treated with SOD (12). In a randomized, multi-center trial from Helsinki, N acetyl cysteine did not reduce the incidence of CLD. Outpatient pulmonary outcome of these patients has not been reported.

#### *Treatment of Premature Infants With Higher Targeted Oxygen Saturations Is Associated with Poorer Pulmonary Outcome*

In the STOP-ROP Study, infants exposed to higher levels of oxygen to achieve a targeted saturation of 96-99% compared with 89-94% had greater risk of adverse pulmonary events including pneumonia, chronic lung disease exacerbations and need for diuretics, oxygen and hospitalization at 3 months' corrected age. *Although all infants in this study had CLD at enrollment, different targeted oxygen saturations were associated with large differences in pulmonary morbidity.* Adverse pulmonary outcomes occurred with differences in FIO<sub>2</sub> of as little as 10% for patients treated with ventilation, CPAP or hood (36% ± 14% vs. 46% ± 20%, respectively for low vs. high saturation range) and 5% for infants treated with nasal cannula, (26% ± 6% vs. 31% ± 11%, respectively for low vs. high saturation range) (44). In a similar study, The Benefits of Oxygen Saturation Targeting (BOOST) Trial randomized infants < 30 weeks' gestation to higher (95-98%) or lower (91-94%) saturations ranges beginning at 32 weeks' PMA to determine whether infants managed with higher targeted saturation range showed better growth and neurodevelopment. As in the STOP-ROP study, need for oxygen therapy was prolonged. Trends towards an increased risk of pulmonary death and fewer outpatient office visits (median 27.5 vs. 31.3, p < .11) were seen in the lower targeted oxygen saturation group (13).

#### *Factors In Addition To Prematurity and Oxygen Contribute To Symptomatic Airway Dysfunction*

Multiple factors in addition to prematurity and oxygen contribute to the development of airway dysfunction in children (Table 1). In the SUPPORT TRIAL Breathing Outcomes Study, these potential covariates will be measured and controlled for using a randomized trial design. These covariates will also be evaluated as independent predictors of pulmonary outcome in multivariate analyses.

**Table 1. Important Covariates in Etiology of Recurrent Wheezing**

**Demographics** – race, sex, ethnicity, parental factors (educational level, poverty status, and age), and family history of wheezing or atopy.

**Environmental** – daycare, siblings, crowding, tobacco smoke or wood smoke in the home, pets

**Health Services** – health care and respiratory medication use appropriate for level of respiratory symptoms

**Medical-** congenital anatomic airway abnormalities, neonatal sepsis, RSV and other viral infections

## G. METHOD/ PROCEDURES

### NICHD SUPPORT Trial Breathing Outcomes Study

#### G.1 Description of study design

This study will add an 18-22 month longitudinal, prospective follow-up study of surviving infants enrolled, randomized and treated as part of the multi-center NICHD Neonatal Research Network SUPPORT Trial.

#### G.2 Definition of study population

Infants with gestational age of 24<sup>0/7</sup>-27<sup>6/7</sup> weeks' gestation by best obstetrical estimate.

##### Inclusion criteria:

- Enrollment in the SUPPORT Trial
- Survival to hospital discharge
- Consent for enrollment into the Breathing Outcomes Study, obtained either at the time of enrollment into the SUPPORT Trial or separately.

##### Exclusion criteria

- Refusal of informed consent

#### G.3 Description of study intervention

Before delivery, infants will be randomized to subsequent management with high vs. low target oxygen saturation according to the SUPPORT Protocol. The SUPPORT Breathing Outcomes Study begins just prior to NICU discharge (Figure 1).

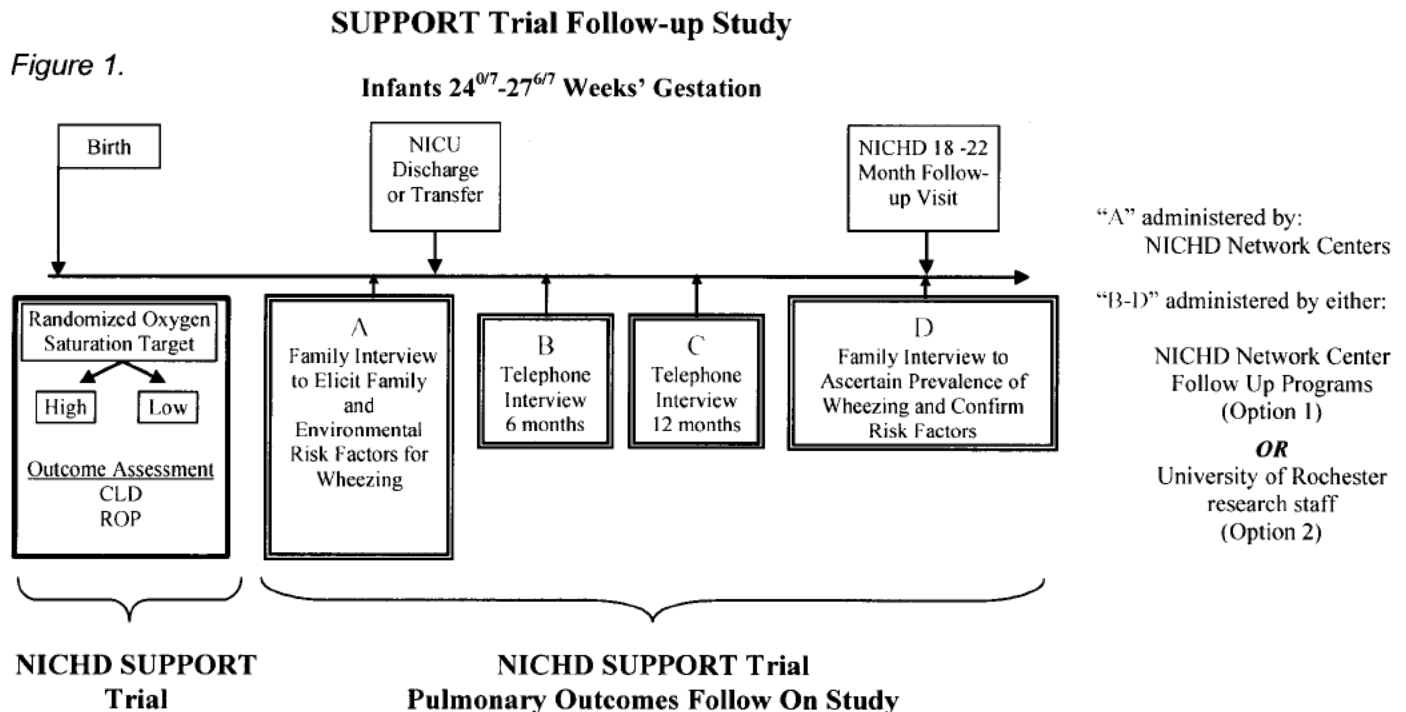


Fig 1, A. Parent (Guardian) Interview to Elicit Family and Environmental Risk Factors for Wheezing and Cough The family interview will be administered either face to face or by telephone to study



participants by site study staff prior to or within 30 days of NICU discharge. The questions are based on intake questions used by the Tucson Respiratory Study and are designed to elicit family history of asthma, atopy, and home environmental exposures and to identify likely care givers (NICU Discharge – Baseline Interview).

Fig 1, B. Interview at 6 months PMA – respiratory interval history

Fig 1, C. Interview at 12 months PMA – respiratory interval history

Interviews will be undertaken at 6 and 12 months to obtain an interval history of respiratory problems including wheezing, cough, medications used, and health services sought for respiratory related problems (6 and 12 Month Questionnaire). Interviews may be administered either by telephone or face to face.

Fig 1, D. Parental Interview to Ascertain Incidence of Wheezing and Cough and Confirm Risk Factors

This parent interview may also be administered either by telephone prior to the regularly scheduled 18-22 month NICHD developmental follow up clinic visit or face to face at the time of the visit. Contacting parents prior to the office visit will help improve the Developmental Follow Up Clinic attendance rate and will allow the clinic visit to provide a back up means to contact the family. The 6, 12 and 18-22 month interviews will be conducted either by the local NICHD Follow Up Program (Option 1) or long distance from Rochester (Option 2), based on center preference (see table 2 below). The interview questionnaires are based on questionnaires administered by the Tucson Respiratory Study at approximately one year of age (18-22 Month Questionnaire). Questions are designed to ascertain the frequency and severity of wheezing and cough episodes and to assess need for outpatient pulmonary care. In addition, risk factors obtained at the 1<sup>st</sup> interview will be confirmed.

Each interview will collect a 6 month interval history, which, when taken together, will provide a complete respiratory history over the first 18-22 months' corrected age. If one questionnaire is not completed, the subsequent questionnaire will include the full interval history since the last completed questionnaire.

To standardize administration of the interview, the Rochester site will lead an interviewer training program consisting of two parts. Part 1 will consist of a teleconference to discuss study questions and interview script in question by question detail. Part 2 will consist of a practice interview in which interviewers from each center interview the Rochester trainer, who simulates a standardized patient. Following the practice interview, the Rochester trainer and practice interviewer will discuss the interview and give feedback. All interviewers will be required to complete this training.

<b>Table 2. SUPPORT Trial - Breathing Outcomes Study</b>		
<i>6, 12 and 18-22 Month Pulmonary Questionnaires</i>		
<u>NICHD Site</u>	<u>Administered By</u>	<u>Option Number</u>
Alabama	Alabama	1
Brown	Brown	1
Cincinnati	Cincinnati	1
CWRU	CWRU	1
Dallas	Dallas	1
Duke	Rochester	2
Emory	Rochester	2
Houston	Rochester	2
Indiana	Indiana	1
Miami	Miami	1
Rochester	Rochester	2
Stanford	Rochester	2
UCSD	UCSD	1
Wake Forest	Wake Forest	1
Wayne State	Wayne State	1
Yale	Yale	1

## **G.4 Precise definition of co primary/secondary outcomes**

### **G.4.1 Definition of primary outcomes- parental report of recurrent wheezing and chronic cough.**

Two primary outcomes will be measured, the incidence of recurrent wheezing and incidence of chronic cough. Whether individual symptoms (recurrent wheezing or chronic cough, alone) or a combination of these symptoms (wheezing and/or chronic cough, together) best quantifies symptomatic airway dysfunction following premature birth is controversial. Many studies have used wheezing alone as a primary outcome measuring pulmonary morbidity in formerly premature infants (10;12;14;48). In 1996, Greenough, using a combined outcome of either wheezing or chronic cough as a measure of symptomatic airway dysfunction, found that greater pulmonary symptoms were associated with longer durations of supplemental oxygen and mechanical ventilation (49;50). Later, in a follow-up study of infants enrolled in The United Kingdom Oscillator Study (UKOS), Greenough found that frequent wheezing episodes but not chronic cough were associated with neonatal respiratory events (51;52). In our study, to address this issue most conservatively, recurrent wheezing and chronic cough will be measured as co-primary outcomes. Secondary analyses will consider these outcomes in combination.

The incidence of wheezing will be ascertained using the primary question used and validated in the Tucson Children's Respiratory Study (a large prospective birth cohort study of term infants) (53-59), "Has his/her chest ever sounded wheezy or whistling?" (53). Likewise, the incidence of cough will be ascertained using the Tucson question, "Has this child ever had a cough when he/she did not have a cold?" (53). As in Greenough's study, recurrent wheezing will be defined as episodes of wheezing occurring more than twice/week. Chronic cough will be defined similarly, cough occurring as more than twice/week. Additional questions will further characterize the wheezing and coughing episodes, including whether symptoms were associated with a viral illness (parental report of a "cold") or an environmental exposure. A symptom diary will be offered to study participants to help facilitate recall of pulmonary symptoms and need for outpatient pulmonary care.

The Tucson Children's Respiratory Study administered the questionnaires both in person and by phone, depending on patient availability. The investigators did not undertake a formal validation of phone vs. face-to-face administration of the questionnaire. Anecdotally, based on phone conversation with the study coordinator, investigators did not observe a difference in quality of responses between phone and questionnaires administered in person.

#### **G.4.1.1 Standard Definition of Wheezing**

Several studies have found that multiple colloquialisms in both English and Spanish can be used to describe wheezing (60-64), creating opportunity for misinterpretation of respiratory sounds and potential for over or under estimation of the incidence of wheezing. Other studies have found that clips of respiratory sounds played for families improve accuracy of symptom reporting (65;66), providing data relatively free from biases due to language, culture, literacy or interviewing techniques. To minimize misinterpretation of other respiratory sounds as wheezing, we will provide a verbal AND a brief audio clip that can be played for the interviewee at the beginning of the interview (electronic clip included separately). Accompanying the audio clip, wheezing will be defined verbally by the interviewer as an expiratory sound (a sound that is made when breathing out, not in) coming from the chest, sometimes described as whistling or musical. Although not yet widely used, use of audio clips to standard symptom definition is the best approach to bridge the language gap that exists between English and Spanish and among Spanish speaking populations using different dialects or colloquialisms.

In administering the questionnaires, every effort will be made to accurately measure the occurrence of pulmonary symptoms and health care and medication use, thus establishing the true incidence of pulmonary morbidity in the study population as a whole. Most importantly, however, because pulmonary morbidity is a blinded outcome of a randomized controlled trial, bias favoring one study arm over another should not occur.

#### **G.4.1.2 Parental Report for Non-English Speaking Populations**

Upon finalization of the questionnaires, Spanish language versions will be created and made available to all centers. The Cornell Translation Service, a University based professional translation service, will be contracted to perform the translation. For centers choosing to administer the questionnaires locally (Option 1), each center will be free to choose their primary interviewer who has the necessary skills. Administration of the questionnaire by a native speaker of the local Spanish dialect is recommended. For centers choosing Rochester to administer the questionnaire to their patients (Option 2), English and Spanish speaking individuals, trained to administer the questionnaires, will conduct the telephone or face to face interviews. An audio clip and verbal definition of wheezing will be presented to the respondent to standardize interpretation of wheezing and to minimize ascertainment biases due to language, culture, literacy or interviewing techniques.

#### **G.4.1.3 Parental Report of Pulmonary Symptoms Is a Reliable Outcome Measure of Airway Dysfunction**

Evaluation of frequency and severity of respiratory symptoms by parental questionnaire and need for pulmonary care has been used as the primary outcome in multiple follow up studies of term and premature infants (10;12;14;48). A recent review evaluated the value of respiratory symptom history ascertained by parental questionnaire in determining the risk for developing asthma in early childhood. By evaluating 9 large, longitudinal, full term birth cohort studies and reviewing the original questionnaire from 7 of these studies, Koopman found that the questions posed to parents eliciting a history of wheezing in their infants were similar. Parental report of wheezing predicted an increased risk for later respiratory symptoms, including asthma. In the studies proposed here, incidence of recurrent wheezing and chronic cough ascertained by parental report will be primary outcomes, rather than physiologic measurements of airway dysfunction, for several reasons.

#### **G.4.1.4 Reasons to Use Parental Report of Recurrent Wheezing and Chronic Cough as Primary Outcomes**

- Parental interview can be performed more readily on large numbers of patients. The validity of this approach has been shown in several longitudinal studies including The Tucson Respiratory Study.
- Recurrent wheezing is highly correlated with changes on pulmonary function testing (PFT). In infants with CLD, a history of wheezing was associated with greater expiratory flow limitation, hyperinflation and airway responsiveness to albuterol on PFT compared to those without such a history (24).
- Parental recall of respiratory illnesses has been shown to correlate strongly with review of medical office records. For asthma and bronchitis in the past year, Pless et al. found good agreement between recall of 288 parents and physician office chart review. Parental education and occupation were not predictive of a parent's ability to recall the illness (67). In an assessment of parental recall done to evaluate minor injury in children, Harel found recall declined with time, with the best recall occurring in the first 3 months after injury with further decline after 6 months from the time of the injury (47;68;69).
- Symptomatic airway dysfunction can be assessed in a standardized way. The NHLBI Consensus Expert Report developed standardized questions to assess severity of airway dysfunction. Three standardized questions from this report will be administered at 6, 12 and 18 months to assess symptom severity (70).

**G.4.2 Definition Of Secondary Outcomes - Physician Diagnosed Wheezing.** A secondary outcome will be parental report of physician diagnosed wheezing, defined as an episode of wheezing occurring at a health care visit. Physician diagnosed wheezing will be collected by parental report during the telephone or face to face interviews, using the question "Has your child been diagnosed with wheezing by a doctor?"

**G.4.3 Definitions of Secondary Outcomes - Measures Need and Volume of Outpatient Pulmonary Care** Important secondary outcomes of outpatient pulmonary morbidity will be collected (Table 3).

<b>Outcomes</b>	<b>Source</b>
<b>Secondary Outcomes</b>	
Number and duration of outpatient pulmonary medications including bronchodilator, diuretic, methylxanthine, and inhaled and systemic steroid therapy.	Family interview
Number of office visits for respiratory illnesses including pneumonia, bronchiolitis, asthma, bronchitis	Family interview
Number of emergency room visits for respiratory illnesses including pneumonia, bronchiolitis, asthma, bronchitis	Family interview
Number of re-hospitalizations for respiratory illnesses including pneumonia, bronchiolitis, asthma, bronchitis	Family interview
Growth at 18 months PMA (height, weight and head circumference)	NICHD follow up clinic data

#### **G.4.4 Data Collection**

Data collection for The Breathing Outcomes Study will be accomplished using one of two options (Figure 2, Table 2). Regardless of Option chosen, each local center will be responsible for obtaining informed consent and tracking patients following discharge.

**Consent:** For both options, every effort will be taken to enroll ALL SUPPORT patients into the Breathing Outcomes Study, including currently enrolled SUPPORT patients (both patients still in NICU and those discharged) and future enrollees. By obtaining pulmonary outcome data for both current and future SUPPORT patients, death or adverse pulmonary outcome can be analyzed as competing outcomes. Sample consent forms for currently enrolled and future SUPPORT patients are attached.

	Option 1		Option 2	
	Local Center	Local Center	Local Center	Rochester
Consent / IRB	✓	✓		
Questionnaire at Discharge	✓	✓		
Patient Tracking	✓	✓		
Questionnaire at 6 & 12 mo.	✓			✓
Questionnaire at 18-22 mo.	✓			✓
Data Entry (questionnaires)	✓			✓

##### **G.4.4.1 Data Collection: Ascertainment of Outcomes - Field Work**

###### **A. Ascertainment of Wheezing and Outpatient Pulmonary Morbidity By Interview.**

There will be 4 parental interviews over 18-22 months, one face to face interview or telephone prior to or within 30 days of NICU discharge and 3 subsequent interviews (by telephone or face to face) at 6 month intervals to collect data on recurrent wheezing, chronic cough and volume of outpatient pulmonary care (Figure 1, A-D above). Based on review of longitudinal studies of full term infants in which follow up patient contacts occurred quarterly to once every 18 months', a 6 month interval for follow up patient contacts is planned in an effort to reduce parental recall omissions which are more likely to occur with less frequent follow up (48;68). The 4 interviews are designed to collect the primary and secondary outcomes of the follow-up study. Other inpatient and outpatient data will be collected as part of the NICHD Neonatal Network Generic Database (GDB) and Follow-up Program.

**B. Interview Instruments** – Questionnaires are based on the Tucson Children's Respiratory Study, a longitudinal cohort study that followed healthy term infants from birth to over 20 years of age. Questionnaires have been updated with validated symptom severity and tobacco smoke exposure questions, a current list of available respiratory medications and modifications that address health issues faced by formerly premature infants such as use of palivizumab for RSV prophylaxis. The original Tucson questionnaires are designed to elicit a thorough history of possible covariates, such as environmental and infectious exposures and family histories of atopy, asthma or respiratory disease.

**C. Administration of Interview Instruments** – Six, 12 and 18-22 month interviews will be initiated in one of two ways (table 2):

###### **C.1 Option 1 - NICHD Network Center Follow Up Programs (local contact)**

Individual NICHD Network Centers may choose to undertake administration and tracking of patients enrolled in the SUPPORT Breathing Outcomes Study. Local administration of the questionnaires capitalizes on existing NICHD resources available at local centers. Each Network Center choosing local administration of the telephone or face to face questionnaire will identify one or more interviewers who will undergo training in the administration of the questionnaire and tracking of enrolled patients. The Rochester Health Service Research Group will provide training and server as a resource to answer questions regarding administration of the questionnaire (outlined above).

Conducting the telephone interviews from Local Centers will:

- 1) reduce risk for HIPPA violation
- 2) capitalize on existing rapport between the patient's family and their local center
- 3) avoid redundancy in making tracking calls to families

### **C.2 Option 2 - University of Rochester research staff (long distance contact)**

The University of Rochester Neonatology Research Group has conducted similar telephone interview designs as part of an ophthalmologic outcome study of patients enrolled in a randomized trial of cryotherapy to treat ROP and a 15-year, longitudinal neurological assessment conducted by telephone survey among 132 infants treated with surfactant. Telephone follow up rates were 96% follow up at 7 years and 95% follow up at 15 years (71). In the study proposed here, the University of Rochester Health Services Research Group (HSR Group), will conduct the telephone interviews.

In telephone follow up surveys conducted by the HSR Group, follow up rates at 12 months' have exceed 75% in populations at high risk for being lost to follow up (72-78). Working with NICHD Network Centers to assist in tracking local families, follow up rates for this Follow-up Study are expected to exceed 80% and should approach the average annual NICHD follow up rate of 83%.

To facilitate tracking and record keeping, Network Centers choosing Rochester to administer questionnaires to their patients (table 2) will provide contract information to the Rochester site. RTI International will provide monthly updates of patients due for interviews. Local centers will be responsible to maintain updated contact information. Each interview will close with a question as to whether the family plans a new address or phone number prior to the next interview. The names and phone number of a friend or relative will be sought so that they may be contacted in the event that contact with the patient is lost. If contact information is updated, the new contact information will be transmitted back to the local center. By interviewing families every 6 months, a higher follow up rate will be achieved because family contact information will not become so out of date that the family is lost or that re-contacting them is inefficient. We anticipate that each interview will require 2 hours of staff time, with 20-30 minutes to conduct the interview and 90 minutes to contact family and enter data.

### **Advantages of Conducting Telephone Interviews From a Central Research Facility**

Conducting the telephone interviews from Rochester will:

- 1) require less effort from the individual Network Centers
- 2) allow standardization of the telephone interview by a core group of trained interviewers
- 3) blind the telephone interviewer to the SUPPORT Trial study group designation
- 4) reduce the cost of the study by consolidating the telephone training and follow up at one site.

### **G.4.4.2 Data Collection: Ascertainment of Environmental and Genetic Covariates**

Ascertainment of important environmental exposures and genetic risk factors that might confound the relationship between supplemental oxygen exposure and symptomatic airway dysfunction will be obtained along with the primary outcomes during the same interviews (Table 4). Tobacco smoke exposure is a potentially significant risk factor for airway dysfunction. The tobacco smoke question in the Tucson Study has been replaced by a question shown by Dr. Wakefield et al to correlate with cotinine levels in infants (79;80).

#### **Table 4. Postnatal and Genetic Covariates Evaluated as Potential Confounders of Oxygen and Wheezing**

**Covariates in Home Environment and Exposures** The initial questionnaire and 6 month interviews will gather information on other *inhaled exposures* (tobacco, wood stoves, cold air), *residence* (crowding, siblings, daycare), *infectious exposures* (RSV, palivizumab) and medical risk factors (congenital anatomic airway abnormalities)

**Covariates in Family History** Questionnaires will elicit *family history* of atopy (family history of asthma, eczema or allergy to foods, pets).

**G.4.4.3 Data Collection: Ascertainment of Primary Exposure**

**Oxygen Exposure**

In the SUPPORT Trial, it is assumed that managing infants with a higher vs. lower targeted oxygen saturation range will result in different levels of supplemental oxygen exposure. The SUPPORT Trial will collect data on FIO2 exposure to quantify the anticipated difference. As part of the SUPPORT Trial, FIO2 values will be recorded and analyzed at many time points including time of admission, first blood gas, and as described in the SUPPORT Manual of Operations, Chapter 10 Safety Monitoring Form. Because oxygen is the primary exposure in the SUPPORT Breathing Outcomes Study and plays a central role in the disease model proposed, oxygen exposure will be quantified as described in the main SUPPORT trial and analyzed as a predictor of later symptomatic airway dysfunction.

**G.5 Sample size estimate with some statistical support based upon primary outcome**

**G.5.1 Sample Size**

The SUPPORT Trial anticipates enrollment of 1310 patients  $\geq 24^{0/7}$  and  $\leq 27^{6/7}$  weeks' gestation, providing 80% power to detect a 10% difference between treatment groups in the incidence of death/CLD and death/stage III Retinopathy of Prematurity (ROP). Assuming mortality of 22% for infants in this GA range (NICHD 2001-2002 data), 1021 infants would be expected to survive and be eligible for the SUPPORT Breathing Outcomes study.

**Power for detecting a difference between the high vs. low saturation groups for the primary outcome**

First we consider power for detecting a difference between the high and low saturation groups for the first primary outcome, recurrent wheezing. We expect the incidence of wheezing to be about 0.17 in the low saturation group and about 0.31 in the high saturation group (12). For the power calculations, we also consider a scenario with a smaller difference between groups: 0.19 for the low saturation group and 0.29 for the high saturation group. We expect the follow up rate to be about 80% (NICHD historical average follow up rate), which would result in data on about 816 patients.

We also consider a lower follow up rate of 65%, which would result in about 663 patients. Power to detect a difference between groups based on a chi-square test with type I error alpha set at 0.05 is given in Table 5 for each scenario. From those results, we expect to have more than 80% power for the primary outcome.

**Table 5. Power for primary outcome.**

Follow-up rate	Low Saturation	High Saturation	power
80%	0.17	0.31	0.99
80%	0.19	0.29	0.90
65%	0.17	0.31	0.98
65%	0.19	0.29	0.83

Also of interest are subgroup analyses, where we look separately at the CLD and non-CLD subjects. Of survivors, we expect 37% or 378 infants to have CLD. For the CLD group, we expect the incidence of wheezing to be about 0.5 in the high saturation group and 0.3 in the low saturation group. If there is a 80% follow up rate, we will have 95% power to detect a difference between the two groups. For the non-CLD subgroup, we expect the incidence to be 0.2 and 0.1 in the high and low groups, respectively. With 80% follow up, we will have 92% power. Thus, we expect to have adequate power for the primary outcome even in the analyses stratified by CLD.

**Power for detecting a difference between the high vs. low saturation groups for secondary outcomes**

We expect the study to be adequately powered for analysis of important secondary outcomes such as use of pulmonary medications. Based on results reported in Davis et al. for infants less than 27 weeks' gestational age [22], we expect the rate of pulmonary medication use to be 0.42 in the high saturation group and 0.19 in the lower saturation group. In that case, even with a 65% follow up rate, we would have more than 99% power to detect a difference between the groups with a chi-square test. Similarly, the CLD subgroup analyses would have more than 80% power under those assumptions. Based on the power numbers above, we could potentially enroll fewer subjects in the trial and still have adequate power. However, we choose to over enroll slightly to make up for the fact that some patients will likely be lost to follow up. The recruitment time will be that of the SUPPORT Trial (2 years) with a run out period of 18-22 months to ascertain follow-up outcomes. The total study period is 36-40 months.

### G.5.2 Data Analysis

Analysis of primary dichotomous outcomes will be performed by chi square test and presented as a relative risk for development of that outcome. Number of outpatient pulmonary visits for respiratory illnesses will be presented as median values. The Wilcoxon Rank Sum test, a non-parametric alternative to the two-sample t-test, will be used to test for differences between the two groups. Statistical analyses will need to consider the effect of multiple comparison groups on the level of statistical significance. All analyses will be performed in conjunction with the Research Triangle Institute (RTI, North Carolina). Data will be presented as shown in tables 6-7. Mean FIO2 values in the high and low SpO2 groups will be compared by two sample t-test. Analyses will be done to evaluate the effect of ventilator strategy on pulmonary outcome and presented similarly to table 6 and 7. Other secondary analyses will be performed, including analyses of respiratory outcomes by presence or absence of CLD (oxygen at 36 weeks' PMA determined by SUPPORT study criteria). The incidence of outpatient respiratory diagnoses, such as asthma or reactive airway disease, will be compared between intervention groups and, in sub group analyses, between intervention groups by presence or absence of CLD.

<b>Table 6. Primary Dichotomous Outcomes</b>	<b>Low Saturation</b>	<b>High Saturation</b>	<b>RR</b>	<b>CI</b>	<b>p-value</b>
Parental Report of Recurrent Wheezing (%)					
Parental Report of Chronic Cough (%)					
Need for Outpatient Pulmonary Medications (%)					
Need for Physician Visit for Respiratory Illness (%)					
Need for Re-hospitalization for Respiratory Illness (%)					

<b>Table 7. Primary Outcomes – Continuous Outcomes</b>	<b>Low Saturation</b>	<b>High Saturation</b>	<b>p-value</b>
Number of Physician Visit for Respiratory Illness (Median)			
Number of Emergency Visits for Respiratory Illness (Median)			
Number of Re-hospitalization for Respiratory Illness (Median)			

### G.5.2 Expected Results

We predict that premature infants managed with a lower targeted oxygen saturation range compared to those managed with a higher targeted oxygen saturation are exposed to lower levels of supplemental oxygen and have reduced risk of recurrent wheezing in the first 18-22 months' CA.

### G.5.2 Anticipated Problems and Solutions

- 1) Participant attrition. As seen in the sample size calculation, the potential for patients to be lost to follow up over time will be offset by over enrolling patients to participate in the follow up. Because patients who enroll in the SUPPORT Trial are randomized, there should be no systematic bias favoring one group over another among patients who are lost to follow up. However, if loss to follow up is in part caused by the treatment or outcomes, this could bias the results. We will therefore investigate whether there are differences in key variables for subjects who are lost to follow up compared to those who remain in the study. For example, we will test whether subjects in one treatment arm were more likely to be lost to follow up than in the other arm. Similarly, we will compare wheezing rates at 6 months' for those who are later lost to follow up compared to those who remain in the study. We do not expect to see any major differences.
- 2) Difficulty tracking families. With mobile families, keeping contact information up to date may be difficult. To promote successful follow up in both the Breathing Outcome Study described here and the routine NICHD neurodevelopmental follow up visit at 18 - 22 months, each center will be responsible to track families to maintain current contact information for both the family and primary care physician.

- 3) Center variability in administering the questionnaire. With 11 centers administering the questionnaires, variation in techniques and styles in administering the questionnaires has the potential to introduce ascertainment bias. To minimize this risk, staff administering the questionnaires will undergo an interviewer training program conducted by the Rochester Site. The program will consist of a conference call and a practice interview of a standardized patient.
- 4) The SUPPORT Breathing Outcomes Study has been prepared as the central project for Dr. Stevens' Patient Oriented Clinical Research Grant (K23 Award), revised submission 7/1/05. If approved, funds from the K23 will be available to offset a portion of the cost of conducting this Follow-up Study. If not approved, NICHD funding has been approved to support the project.
- 5) Initiation of the Breathing Outcomes Study after enrollment into SUPPORT has begun.
  - 5.1 *Babies already enrolled in SUPPORT*

To help assure pulmonary outcome assessment for all SUPPORT patients, families of babies already enrolled in SUPPORT will be approached with a separate consent to enroll in the Breathing Outcomes Study. IRB approval of this consent form will be required.
  - 5.2 *Future babies eligible for enrollment in SUPPORT*

Going forward, a modified SUPPORT Consent Form, which includes consent for the Breathing Outcomes Study, will be need to be prepared at each center. The revised SUPPORT Consent will require enrollment into both the SUPPORT Trial and the Breathing Outcomes Study prior to delivery. Because a significant amount of time may elapse between enrollment and the first interview, the Breathing Brochure will be discussed with families, either prior to NICU discharge or within 30 days after NICU discharge.

#### **G.6 Available population/compatibility with other ongoing protocols**

Another secondary study proposed by a group independent from ours is looking at the genetics of reactive airways disease in patients enrolled in the SUPPORT Trial. The follow on study proposed here should be complementary to the genetics study, enhancing the both the quality and quantity of data on the prevalence of wheezing and need for outpatient pulmonary care in patients enrolled in the SUPPORT Trial.

#### **G.7 Estimate of projected recruitment time**

The recruitment time will be that of the SUPPORT Trial with a 18-22 month period of follow up to ascertain primary and secondary outcomes.

#### **H. RISKS / BENEFITS, WITH ESTIMATE OF FREQUENCY / SEVERITY OF RISKS.**

By using clinical measures of outpatient pulmonary morbidity, the effect of NICU based respiratory interventions on respiratory health and need for outpatient medical care may be quantified, allowing assessment of whether infants who develop CLD and those who do not have improved pulmonary health as a result of the study intervention. In addition to creating a potential model for outpatient pulmonary follow up, the proposed follow on study may improve follow up at the 18-22 month NICHD visit by maintaining contact with families during the interval between NICU discharge and the follow up visit. We anticipate no risk to the patient of this observational follow on study.

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**SUPPORT Trial  
Breathing Outcomes Study**

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

NICHD Neonatal Research Network

**Manual of Operations**

December 12, 2005

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# Chapter 1 Overview and Trial Design

## 1.1 Introduction

This manual provides detailed instructions of study procedures for the Breathing Outcomes Study of the NICHD SUPPORT Trial (The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants). This manual should be used as a reference guide for study staff including investigators, data managers, coordinators, and telephone interviewers, if different from the coordinators. The trial objectives and design are summarized briefly below. For further discussion to the study background and design, please refer to the Breathing Outcomes Study Protocol.

## 1.2 Study Design

This study is a longitudinal follow-up of surviving infants enrolled, randomized and treated as part of the SUPPORT Trial, which was a prospective, randomized, factorial 2X2 design multi-center trial conducted by the NICHD Neonatal Research Network. This follow-up study will determine the effect of lower targeted oxygen saturation ranges and more aggressive use of CPAP on the incidence of symptomatic airway dysfunction (defined as recurrent wheezing or chronic cough) and volume of outpatient care in the first 18-22 months' corrected age (CA). The individual factors to be tested in this follow-up study are:

- 1) Symptomatic airway dysfunction and need for outpatient pulmonary care in the first 18-22 months among infants managed with a lower SpO<sub>2</sub> range (85% to 89%) as compared to a higher, more conventional SpO<sub>2</sub> range (91% to 95%).
- 2) Symptomatic airway dysfunction and need for outpatient pulmonary care in the first 18-22 months corrected age among infants managed with CPAP and a permissive ventilatory strategy versus infants managed with prophylactic surfactant and conventional ventilation begun in the delivery room and continuing in the NICU.

Table 1 below describes the study treatment groups. Refer to the SUPPORT Trial Protocol for further details regarding the projected outcomes relative to the study interventions

Table 1: SUPPORT Trial Study Treatment Groups

<b>Randomized Intervention</b>	<b>Low SpO<sub>2</sub> 85% to 89%</b>	<b>High SpO<sub>2</sub> 91 to 95%</b>
<b>Treatment</b>	Early CPAP +	Early CPAP +
<b>Early CPAP</b>	Low SpO <sub>2</sub>	High SpO <sub>2</sub>
<b>Control</b>	Control +	Control +
<b>Prophylactic/Early Surfactant</b>	Low SpO <sub>2</sub>	High SpO <sub>2</sub>

## 1.3 Primary Hypotheses

- 1) We hypothesize that relative to infants managed with a higher SpO<sub>2</sub> range (91% to 95%), infants managed with a lower SpO<sub>2</sub> range (85% to 89%) will have less frequent episodes of

symptomatic airway dysfunction and reduced need for outpatient pulmonary care at 18-22 months' CA.

2) We hypothesize that relative to infants managed with prophylactic surfactant and conventional ventilation, infants managed with early CPAP and permissive ventilator strategy will have less frequent episodes of symptomatic airway dysfunction and reduced need for outpatient pulmonary care in the first 18-22 months' CA.

#### **1.4 Secondary Hypotheses**

1) We hypothesize that **among infants with CLD**, infants managed with a lower SpO<sub>2</sub> range relative to those managed with a higher SpO<sub>2</sub> target range and infants managed with early CPAP and permissive ventilator strategy compared with those managed with prophylactic surfactant and conventional ventilation will have less frequent episodes of symptomatic airway dysfunction and reduced need for outpatient pulmonary care during the first 18-22 months' CA.

2) We hypothesize that **among infants without CLD**, infants managed with a lower SpO<sub>2</sub> range relative to those managed with a higher SpO<sub>2</sub> target range and infants managed with early CPAP and permissive ventilator strategy compared with those managed with prophylactic surfactant and conventional ventilation will have less frequent episodes of symptomatic airway dysfunction and reduced need for outpatient pulmonary care during the first 18-22 months' CA.

#### **1.5 Summary of Data Forms**

The following is a summary of the data forms used in this study. Further details on each form are provided in subsequent chapters. A complete set of forms can be found in Appendix B.

##### **Enrollment Log (SUPF00)**

The purpose of this form is to record all study infants who participated in the SUPPORT Trial, making them eligible for participation in the Breathing Outcomes Study. Record the child's first and last name, date of birth, mother's initials (optional), birth number (only recorded in cases of multiple births), Network study number ( \_ \_ \_ \_ ), SUPPORT Follow-up number ( \_ \_ \_ \_ ), whether consent was granted (Yes, No, or Refused), and any comments that are relevant. The Enrollment Log should be comprehensive for all infants who participated in the SUPPORT Trial. Identifying information on this log will not be transmitted to the DCC but should be used by the centers as an internal management tool. Whether or not consent is granted will be transmitted to the DCC and will be used in sending the monthly reminder lists for the 6 month, 12 month, and 18-22 month interviews. This is particularly relevant for the infants that were already enrolled in the SUPPORT Trial at the initiation of the Breathing Outcomes Study.

##### **NICU Discharge-Baseline Interview (SUPF01)**

This interview will be administered to the parent or guardian by trained study staff prior to NICU discharge or within 30 days after NICU discharge. For patients enrolled into the Breathing Outcomes Study after NICU discharge, this questionnaire can be administered prior to the 6 month questionnaire. Questions concerning family medical history, anticipated living arrangements, and alternate contact information will be asked.

The purpose of the discharge questionnaire is to assure adequate randomization of important covariates affecting outpatient respiratory health and to obtain baseline data on home environment and family history of respiratory diseases.

**6 Month and 12 Month Interview (SUPF02)**

This interview will be administered by telephone or face to face to the parent or guardian by a trained interviewer at 6 months' CA and again at 12 months' CA.

The purpose of these questionnaires is to obtain an **interval** respiratory history. Questions are designed to collect respiratory history since the last contact with the interviewee, such that when the 6, 12 and 18-22 month questionnaires are taken together, a complete respiratory history over the time period is collected.

**18-22 Month Interview (SUPF03)**

This interview will be administered to the parent or guardian at 18-22 months CA by either telephone interview prior to the regularly scheduled 18-22 month NICHD developmental follow up clinic visit or face to face at the time of the visit.

The purpose of these questionnaires is to obtain an **interval** respiratory history and to identify environmental exposures that may increase the likelihood of symptomatic airway dysfunction.

## Chapter 2 Administration

### 2.1 Organizational Structure

The NICHD Neonatal Research Network is conducting this study. The Network is funded by the NICHD under cooperative agreements with seventeen institutions comprised of sixteen clinical centers and a data coordinating center. The Steering Committee for the Network consists of the Principal Investigator from each clinical center, the data center, and the NICHD project officer. The Steering Committee Chairman is appointed by NICHD and is not a Principal Investigator from any of the Clinical Centers.

#### *SUPPORT Trial Follow-up Subcommittee*

The SUPPORT Protocol Subcommittee is responsible for the preparation and maintenance of the protocol, data forms, and manual of operations. This subcommittee will monitor the overall study performance (including protocol compliance) and will report the progress of the trial to the Steering Committee. SUPPORT Subcommittee members are:

Neil Finer, MD

Waldemar A. Carlo, MD,

Edward F. Donovan MD

Michele Walsh, MD

Shahnaz Duara, MD

Rosemary D. Higgins, MD

Abhik Das, PhD

Ruth Everett, RN

Wade Rich, RRT

In addition, Dr. Vohr, as director of the Follow Up Program, will coordinate input from the Follow-up PIs. Timothy P. Stevens, MD, MPH and Peter Szilagyi, MD, MPH from the Department of Pediatrics at the University of Rochester will be instrumental in designing, implementing and executing the clinical studies outlined here and will have significant ongoing involvement with the project.

### 2.2 Participating NICHD Neonatal Research Network Centers

Centers from the NICHD Neonatal Research Network participating in the trial are listed below. The NICHD center number is indicated in parentheses next to the name of each center. The Neonatal Research Network principal investigators (PIs) are located in the second column, the Follow-up PIs in the third column and the SUPPORT Study PIs in the fourth column.

<b>PARTICIPATING CENTERS</b>	<b>NRN PI</b>	<b>NRN Follow Up PI</b>	<b>SUPPORT STUDY PI</b>
Case Western Reserve Univ. (3) Rainbow Babies and Children's Hospital	Michele Walsh, MD	Dee Wilson, MD	Michele Walsh, MD
University of Texas-Dallas (4)	Charles Rosenfeld, MD	Roy Heyne, MD	Walid Salhab, MD
Wayne State University (5) Children's Hospital of Michigan	Seetha Shankaran, MD	Yvette Johnson, MD	Seetha Shankaran, MD
University of Miami (8) Jackson Memorial Hospital	Shahnaz Duara, MD	Charles Bauer, MD	Shahnaz Duara, MD
Emory University (9) Grady Memorial Hospital	Barbara J. Stoll, MD	Ira Adams-Chapman, MD	Susie Buchter, MD
University of Cincinnati (11) University of Cincinnati Hospital	Edward F. Donovan, MD	Jean Steichen, MD	Vivek Narendran, MD Kurt Schibler, MD
Indiana University (12)	James A. Lemons, MD	Anna M. Dusick, MD	Brenda Poindexter, MD
Yale University (13) The Children's Hospital at Yale – New Haven	Richard A. Ehrenkranz, MD	Richard A. Ehrenkranz, MD	Vineet Bhandari, MD
Brown University (14) Women and Infant's Hospital	William Oh, MD	Betty R. Vohr, MD	Abbot Laptook, MD
Stanford University (15) Stanford University Med Center	David K. Stevenson, MD	Susan R. Hintz, MD	Krisa Van Meurs, MD
University of Alabama (16) University of Alabama at Birmingham	Waldemar A. Carlo, MD	Myriam Peralta, MD	Waldemar A. Carlo, MD
University of Texas- Houston (18)	Jon E. Tyson, MD	Jon Tyson, MD	Brenda Morris, MD
Duke University (19)	Ronald Goldberg, MD	Ricki Goldstein, MD	C. Michael Cotten, MD
Wake Forest University (20)	Michael O'Shea, MD	Robert Dillard, MD	Michael O'Shea, MD
Golisano Children's Hospital at Strong (21) University of Rochester	Dale L. Phelps, MD	Gary Myers, MD	Nirupama Laroia, MD
University of California-San Diego (22)	Neil Finer, MD	Yvonne Vaucher, MD	Neil Finer, MD

### **2.3 Responsibilities of Clinical Centers**

The minimum staff required for network participation at each clinical center is the physician Principal Investigator (PI), the Research Coordinator, and telephone interviewers, if interviews are not conducted by the Research Coordinator.

The research coordinator may identify another individual to conduct the telephone interviews. In this situation, it will be the coordinator's responsibility to assure that the interviewer is certified in standardized administration of the questionnaire (see below). The responsibilities of these individuals are described briefly in this chapter and in more detail in subsequent chapters.

The PI or designee is responsible for ensuring the proper conduct of the trial at his or her clinical center (including recruitment and treatment of patients as specified in the protocol), accurate collection of data and transmission of information to the Data Coordinating Center (DCC). Other specific duties include the following:

- Presenting an in-service to the other physicians
- Applying for IRB approval
- Introducing the study to the parents of prospective patients, and obtaining signed informed consent from the parents of eligible infants (in some centers this responsibility may be delegated)
- Reviewing all infants for whom informed consent has been obtained to confirm their eligibility
- Informing the IRB of the study progress.

The Research Coordinator will be responsible for the day-to-day operations of the study at the clinical center, including data collection and management. This responsibility includes the following:

- Collecting information necessary to complete the data collection forms, and coordinating data entry
- Training and certifying the staff in the use of the network computer
- Controlling access to the network computer and ensuring that required back-up, security and confidentiality are maintained
- Responding to edit messages and other communications from the data center
- Distributing updates of the protocol and of the manual of operations to clinical center staff
- Further responsibilities are based on the study administration option chosen by the center.

### **2.3.1 Delineation of Responsibilities by Study Administration Option**

Clinical Centers have the option of administering the follow-up questionnaires to their own patients (Option 1) or having telephone interviewers of the University of Rochester Health Services Research Group administer the follow-up questionnaires to their patients (Option 2). Table 2 indicates which option the centers have chosen.

**Table 2. SUPPORT Trial - Breathing Outcomes Study**

*6, 12 and 18-22 Month  
Pulmonary  
Questionnaires*

<u>NICHD Site</u>	<u>Administered By</u>	<u>Option Number</u>
Alabama	Alabama	1
Brown	Brown	1
Cincinnati	Cincinnati	1
CWRU	CWRU	1
Dallas	Dallas	1
Duke	Rochester	2
Emory	Rochester	2
Houston	Rochester	2
Indiana	Indiana	1
Miami	Miami	1
Rochester	Rochester	2
Stanford	Rochester	2
UCSD	UCSD	1
Wake Forest	Wake Forest	1
Wayne State	Wayne State	1
Yale	Yale	1

Regardless of the option chosen, each local center is responsible for obtaining informed consent, completing the Enrollment Log (SUPF00), administering the NICU Discharge-Baseline Interview (SUPF01) and distributing the respiratory brochure to parents, as well as tracking patients following discharge. Table 3 further describes the responsibilities of the local center and Rochester in Option 1 and Option 2.

*Table 3.*

	Option 1	Option 2	
	Local Center	Local Center	Rochester
Consent / IRB	✓	✓	
Questionnaire at Discharge	✓	✓	
Patient Tracking	✓	✓	
Questionnaire at 6 & 12 mo.	✓		✓
Questionnaire at 18-22 mo.	✓		✓
Data Entry (questionnaires)	✓		✓

Each of the responsibilities discussed in Table 3 above will be discussed separately below.

**2.3.2 Consent**

For both options, every effort will be taken to enroll ALL SUPPORT patients into the Breathing Outcomes Study, including both currently enrolled SUPPORT patients (both patients still in NICU and those discharged from the NICU) and all future enrollees. By obtaining pulmonary outcome data for both current and future SUPPORT patients, death or

adverse pulmonary outcome can be analyzed as competing outcomes. Sample consent forms for currently enrolled and future SUPPORT patients are included in Appendix C.

### **2.3.3 Discharge-Baseline Questionnaire**

The purpose of the discharge-baseline questionnaire is to assure adequate randomization of important covariates affecting outpatient respiratory health and to obtain baseline data on home environment and family history of respiratory diseases. There are a total of 25 questions on the questionnaire; the first 6 are demographic, 11 questions are on home environment and exposures, 2 questions are on diet, 1 question is on alternate contact information, and 5 questions are on family history of allergy and respiratory problems.

Each center, regardless of study option chosen, will administer the discharge-baseline questionnaire. This will allow ascertainment of baseline data as well as confirming contact information for the family. For patients enrolled into the Breathing Outcomes Study after NICU discharge, this questionnaire can be administered prior to the 6 month questionnaire.

After completing the discharge - baseline questionnaire, parents will be given the respiratory brochure ("My Baby's Breathing Book"), which will have space for families to note how often their baby has wheezing or coughing, whether the baby visited a doctor's office, emergency room or was hospitalized for breathing problems. By presenting the brochure to the family and discussing it with them as they leave the NICU or at a follow-up clinic visit, each family will have opportunity to review the study with study personnel. This is especially important because many families will have committed to the follow up study several months before discharge. When the interviewer calls in six months, parents should be asked to gather any notes, medications or other information about their baby's breathing.

### **2.3.4 Tracking**

All centers (Option 1 and 2 centers) will track their own patient's telephone and contact information for the purpose of administering telephone questionnaires at 6, 12 and 18-22 months. This will also help assure attendance at the routine NICHD neurodevelopmental follow up clinic visit 18-22 months.

The following core set of contact information is recommended for all enrolled patients.

- Network number
- Patient Name
- DOB
- Gender
- Name of Prior Interview Respondent (if different than primary care taker)
  - Primary Caretaker Contact Information
    - Name
    - Relationship to patient
    - Mailing address
    - Telephone number #1
    - Telephone number #2
  - Secondary (Backup) Caretaker Information
    - Name
    - Relationship to patient
    - Mailing address



- Telephone number #1
- Telephone number #2

### **2.3.5 Responsibility of Option 1 Centers In Administering Questionnaires at 6, 12 And 18 Months' Corrected Age**

Clinical Centers will have the option of administering the follow-up questionnaires to their own patients (Option 1) or having telephone interviewers from the University of Rochester Health Services Research Group administer the follow-up questionnaires to their patients (Option 2).

- Standardization of Interview Technique
  - In order to assure that interviews are administered in a standard and consistent manner, the University of Rochester Health Services Research Group will conduct an Interviewer Certification Program to train interviewers at Option 1 centers and Rochester-based interviewers. All interviews must be performed by certified interviewers (see 2.3.7 below).
- Conducting the Interviews
  - Prior to each interview, a postcard will be mailed to the family reminding them to expect a telephone call.
  - For centers that see patients in an office setting, the questionnaire may be administered face to face.

### **2.3.6 Responsibility of Option 2 Centers In Administering Questionnaires at 6, 12 And 18 Months' Corrected Age**

- Upon receipt of RTI reminder, Option 2 Centers will send a postcard to the family reminding them to expect a telephone call.
- Review and update contact information as necessary and fax contact information to the Rochester Health Services Research Group (RHSRG).
- The RHSRG will conduct the telephone interview.
- At the conclusion of each interview, contact information will be confirmed and updated contact information faxed back to the Option 2 Center.

### **2.3.7 Responsibilities of the University of Rochester Health Services Research Group**

- The certification program will consist of two parts.
  - Part 1 will consist of a teleconference training session during which each question on the questionnaires is reviewed and discussed with the interviewers. The goal is to assure that interviewers understand the purpose of each question and, in a standard way, how to deliver the question, elicit an answer and record the interviewee's response.
  - Part 2 will consist of a practice interview in which interviewers from each center interview the Rochester trainer, who simulates a standardized patient. Following the practice interview, the Rochester trainer and practice interviewer will discuss the interview and give feedback.

- Other responsibilities include:
  - Development and distribution of an audio clip of wheezing to be presented along with a verbal definition to the interview respondent to standardize interpretation of wheezing and to minimize ascertainment biases due to language, culture, literacy or interviewing techniques.
  - Maintaining trained Spanish-speaking individuals to conduct the telephone interviews with Spanish-speaking participants from centers choosing Rochester to administer the questionnaire to their patients (Option 2).
  - Spanish language versions of the questionnaires will be created and made available to all centers. The Cornell Translation Service, a University-based professional translation service, will be contracted by the University of Rochester to perform the translation.

#### 2.4 Responsibilities of the Data Coordinating Center

The DCC at RTI International is responsible for all aspects of statistical design and analysis as well as data management of the study. In particular, this includes:

- Processing, updating and distributing the protocol and manual of operations
- Developing and distributing the data forms, including periodic updates as necessary
- Developing, testing and implementing the database and other software. Ensuring that data are correct and complete by implementing editing and auditing procedures
- Monitoring the progress and quality of the study
- Preparing interim and final analyses and reports
- Participating in the preparation of presentations and publications relating to the study

The DCC is also responsible for sending monthly reminder reports to Network Centers. For patients enrolled in the Pulmonary Outcomes Study, the DCC will send a monthly reminder to each center with a list of IDs that are due to have questionnaires conducted. The report will include the following:

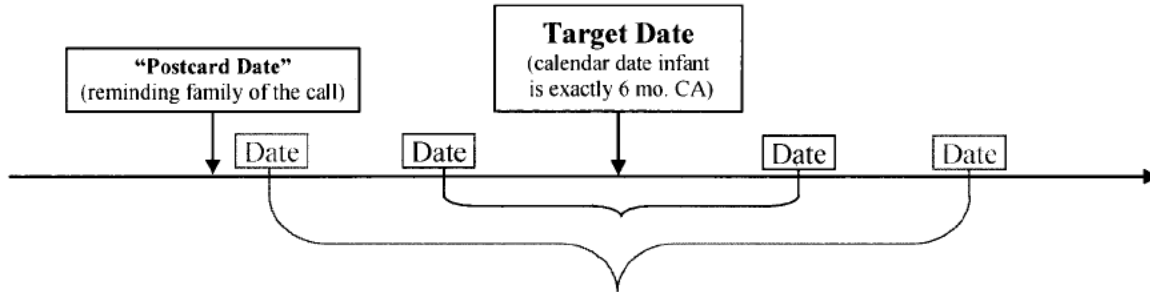
- Network number
- Gestational age
- Gender
- Date of last interview
- Care taker (relationship code) providing the previous interview
- Whether the previous interviews were conducted face to face or by telephone
- List of the 4 interviews that have been completed (CA = corrected age)
- Completed interview dates, dates of previous interviews and interviewee information may be presented as outlined in the table below.

*Example table*

<u>Required Interviews</u>	<u>Date</u>	<u>Caretaker Interviewed</u>	<u>Face to Face?</u>
----------------------------	-------------	------------------------------	----------------------

- Discharge                    / / /                    \_\_\_\_\_                    Y or N
- 6 month CA                    / / /                    \_\_\_\_\_                    Y or N
- 12 month CA                    / / /                    \_\_\_\_\_                    Y or N
- 18-22 month CA                    / / /                    \_\_\_\_\_                    Y or N

- Target date for the current interview with windows within which interview should be accomplished, goal window ( target date  $\pm$  2 weeks ) and acceptable window ( target date  $\pm$  4 weeks )
- A “postcard date”, 5 weeks prior to the contact, when a postcard might be sent to the family reminding them of the upcoming call or visit



**2.5 Responsibilities of NICHD**

In addition to its role as a funding agency, the NICHD participates in the activities of the cooperative agreement by being represented on the Steering Committee. The Program Official also participates in the development of protocol and in assisting the Steering Committee in the coordination of the studies conducted by the Network. The NICHD Program Official, in conjunction with the RTI Principal Investigator is responsible for monitoring site performance of all participating centers. The Program Official has the following responsibilities:

- Assistance in the development of the study protocol.
- Assistance in the development of capitation-based budgets, including the identification of study costs and special institutional needs.
- Allocation of network resources to meet study needs.
- Facilitation of training meetings, site visits, and subcommittee meetings.
- Participating in preparation of publications.

## Chapter 3 Screening, Eligibility, Consent

### 3.1 Study Population

This follow-up study will include all surviving infants enrolled, randomized and treated as part of the multi-center NICHD Neonatal Research Network SUPPORT Trial, which were inborn infants of 24 0/7<sup>th</sup> to 27 6/7<sup>th</sup> weeks at birth for which a decision was made to provide full resuscitation as required. Infants 27 weeks or less gestation (completed weeks by best obstetric estimate) were enrolled.

### Inclusion Criteria

- Enrollment in the SUPPORT Trial
- Survival to hospital discharge
- Consent for enrollment into the Breathing Outcomes Study, obtained either at the time of enrollment into the SUPPORT Trial or separately.

### 3.2 Exclusion Criteria

- Refusal of informed consent

### 3.3 Informed Consent

Every effort will be taken to enroll ALL SUPPORT Trial patients into this follow-up study, including currently enrolled SUPPORT patients (both patients still in NICU and those discharged) and future enrollees. By obtaining pulmonary outcome data for both current and future SUPPORT patients, death or adverse pulmonary outcome can be analyzed as competing outcomes. Each local center will be responsible for obtaining informed consent for the Breathing Outcomes Study regardless of whether they are administering the follow-up questionnaires to their patients or Rochester is conducting the telephone interviews.

For future enrollees in the SUPPORT Trial, consent for the Breathing Outcomes Study will be obtained at the time of enrollment in the main trial. As described in the SUPPORT Trial Manual of Operations, these infants will be recruited for the study by approaching one or both parents at the time of admission to the hospital at risk for premature delivery at 27 weeks or less. It is anticipated that, whenever possible, the parents will be approached by study personnel to discuss the trial and obtain an informed consent for the participation of the infant at delivery. Randomization will be by family, thus all offspring will be randomized to the same trial arms, provided adequate equipment and personnel are available at the time of delivery. Sample consent forms for currently enrolled and future SUPPORT patients are attached (Appendix C).

A Study Brochure will be given to each family at the time of the discharge interview. The brochure reviews the study and its commitments and also asks families to make observations about the baby's breathing symptoms and treatments. Reviewing the brochure is especially important because many families will have committed to the follow-up study several months before discharge.

### **3.4 Screening Procedures**

This follow-up study will include all surviving infants enrolled, randomized and treated as part of the NICHD Neonatal Research Network SUPPORT Trial.

For future enrollees in the SUPPORT Trial, all admissions for threatened premature delivery will be screened on a daily basis to ensure that eligible patients can be enrolled. Obstetrical colleagues at each participating institution will be informed of the nature of this study and encouraged to discuss this study with their patients at risk of premature delivery. The study coordinator at each site will maintain a screening log of potentially eligible patients. In addition, the usual practice of neonatal consultation for all such at risk deliveries will provide a second opportunity to approach mothers with fetuses at risk of preterm delivery.

## **Chapter 4 Randomization**

### **4.1 Randomization Procedures**

Randomization for the NICHD Neonatal Research Network SUPPORT Trial was stratified by gestational age group (24 - 25 6/7 and 26 - 27 6/7) and occurred prior to delivery for consented deliveries. The randomizations were performed by utilizing specially prepared envelopes. The Data Center prepared brown sealed envelopes which contained the identity of the treatment combination that were assigned to the infants enrolled into the study. Deliveries were randomized as a unit, thus multiples, twins, triplets etc were randomized to the same arm of the trial. One envelope corresponded to the delivery of a consenting mother regardless of the number of babies delivered so that all babies from a given delivery received the same treatment combination.

Refer to Section 4.1.1 of the NICHD Neonatal Research Network SUPPORT Trial Manual of Operations (MOO) for more information on randomization and masking as well as storing and assigning oximeters that occurred during the main study.

During the Breathing Outcomes Study activities, research coordinators and telephone interviewers, if different from the research coordinators, will remain blinded as to whether infants were randomized to the control or treatment group.

## Chapter 5 Breathing Outcomes Study Procedures

### 5.1 SUPPORT Trial Study Interventions

Refer to Chapter 5 of SUPPORT Trial Manual of Operations (MOO) for more information on the study interventions and the procedures for the treatment groups. The same questionnaires will be administered to both treatment groups in the Breathing Outcomes Study.

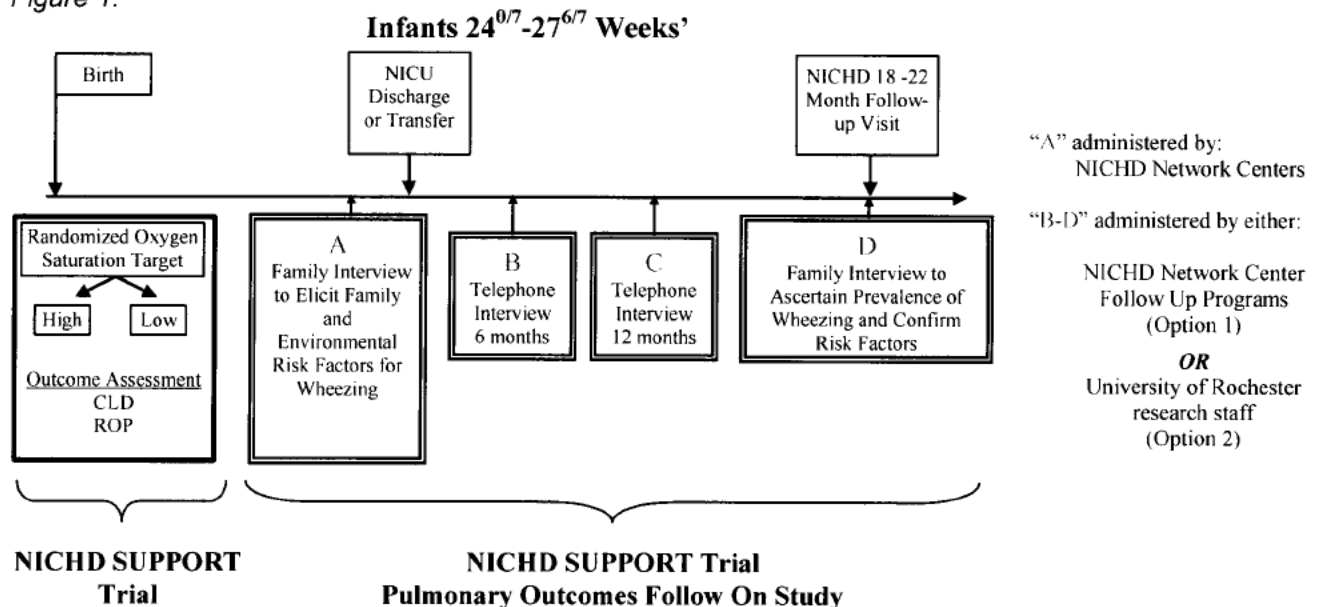
### 5.2 Breathing Outcomes Study Interventions

The SUPPORT Breathing Outcomes Study begins just prior to NICU discharge. See Figure 1 for a diagram of the SUPPORT Trial Breathing Outcomes Study procedures.

Four questionnaires will be administered at approximately 6 month intervals until the baby is 18-22 months' corrected age according the schedule outlined in Figure 1. Each interview will collect a 6 month interval history, which, when taken together, will provide a complete respiratory history over the first 18-22 months' corrected age. If a questionnaire is not completed, the subsequent questionnaire will include the full interval history since the last completed questionnaire.

**SUPPORT Trial Follow-up Study**

Figure 1.



### DESCRIPTION OF QUESTIONNAIRES

**A) Discharge-Baseline Questionnaire Administered by Network Centers**

The discharge-baseline interview consists of a primary caretaker (parent or guardian) interview to elicit family and environmental risk factors for wheezing and cough. The family interview will be administered at each participating Network Center by trained study staff prior to NICU discharge or transfer. The questions are based on intake questions used by the Tucson Respiratory Study and are designed to elicit family history of asthma, atopy, and home environmental exposures and to identify likely care givers. This interview will be administered to the parent or guardian by trained study staff prior to NICU discharge or within 30 days after NICU discharge. For patients enrolled into the Breathing Outcomes Study after NICU discharge, this questionnaire can be administered prior to the 6 month questionnaire.

The purpose of the discharge-baseline questionnaire is to assure adequate randomization of important covariates affecting outpatient respiratory health and to obtain baseline data on home environment and family history of respiratory diseases. There are a total of 25 questions on the questionnaire; the first 6 are demographic, 11 questions are on home environment and exposures, 2 questions are on diet, 1 question is on alternate contact information, and 5 questions are on family history of allergy and respiratory problems.

Each center, regardless of study option chosen, will administer the discharge questionnaire and perform data entry. This will allow ascertainment of baseline data as well as confirming contact information for the family.

**B) Respiratory History Questionnaires Administered at 6 and 12 Months' Corrected Age**

The purpose of this questionnaire is to obtain an interval respiratory history. Questions are designed to collect respiratory history in areas outlined in the table at right. For centers choosing Option 1, interviews may be conducted either by telephone or face to face. For centers choosing Option 2, interviews will be conducted long distance by telephone from The Rochester Health Services Research Group to the family.

Outcome	Question No.
Respiratory Symptoms	9, 10, 13-15
Quality of Life	11, 12
Health Services Utilization	
Office	6
Emergency Department	7
Hospitalization	8
Medication Use	27
Oxygen Use	26
Preventive Services	24, 25
Exposures	16-23

**C) Respiratory and Environmental Exposure History Questionnaires Administered at 18-22 Months' Corrected Age**

The purpose of this questionnaire is to obtain an interval respiratory history and to identify environmental exposures that may increase the likelihood of symptomatic airway dysfunction. Questions are designed to ascertain the frequency and severity of wheezing and cough episodes and to assess the need for outpatient pulmonary care. In addition, a history of atopy is elicited. There are a total of 34 questions, encompassing the 27 questions



from the discharge and 6 and 12 month questionnaires and 7 concerning infection and allergy history.

This parent interview may also be administered either by telephone prior to the regularly scheduled 18-22 month NICHD developmental follow-up clinic visit or face to face at the time of the visit. Contacting parents prior to the office visit will help improve the Developmental Follow Up Clinic attendance rate. Otherwise, the clinic visit will provide a back up means to contact the family. The 18-22 month interview will be conducted either by the local NICHD Follow Up Program (Option 1) or long distance from Rochester (Option 2), based on center preference (see table 2 below).

### **5.3 Administration of the Breathing Outcomes Questionnaires**

- The questionnaires are for research only. Caretakers, parents or guardians expressing concern regarding the child's breathing should be encouraged to discuss their concern with the family's primary care physician. Diagnostic or treatment advice should NOT be offered as part of the interview.

### **5.4 Protocol Violations**

The occurrence of any one of the following criteria will determine whether an individual infant will be considered a protocol violation:

- Interview occurring outside the acceptable window ( target date  $\pm$  4 weeks )
- Missed interview

In both of these cases the interview should be conducted at the next available opportunity and should encompass respiratory health since the prior interview.

All protocol violations will be reviewed by the center PI who will discuss each protocol violation with the involved clinicians, identifying steps to avoid future violations.

### **5.5 Adverse Events**

We anticipate no risk to the patient from this observational follow-up study.

Serious adverse events were anticipated in the main SUPPORT Trial for this vulnerable population. Refer to Section 5.5 of the NICHD Neonatal Research Network SUPPORT Trial MOO for more information on adverse event reporting and monitoring.

## Chapter 6

### NICU Discharge-Baseline Interview

#### Introduction

The purpose of the discharge-baseline questionnaire is to assure adequate randomization of important covariates affecting outpatient respiratory health and to obtain baseline data on home environment and family history of respiratory diseases. There are a total of 25 questions on the questionnaire; 6 questions on demographics, 11 questions on home environment and exposures, 2 questions on diet, 1 question on alternate contact information, and 5 separate questions on family history of allergy and respiratory problems.

Each center, regardless of study option chosen, will administer the discharge-baseline questionnaire and perform data entry. This will allow ascertainment of baseline data as well as confirming contact information for the family. Each center is also responsible for maintaining an Enrollment Log (SUPF00). See Section 1.5 (Summary of Data Forms) for a description of the log and instructions for completing it.

#### Instructions for Completing the NICU Discharge-Baseline Interview (SUPF01)

##### Timing of the Interview:

This interview should be administered to the parent/guardian by a trained study staff member prior to or within the first 30 days following NICU discharge. If for any reason the infant is enrolled into the Pulmonary Outcome Study later than 30 days following NICU discharge, the questionnaire should be administered prior to interval questionnaires (SUPF02 or SUPF03)

##### Heading- Infant's Identification

The following information is included in the heading section of all patient specific data forms: Center, Site, Network Number, SUPPORT Follow-up Number, Birth Number and Mother's Initials (**optional**). This information should be completed on each page of the interview in case the completed form pages are separated.

##### Interview Outcome Information

The interview outcome information is located on the cover page of each form after the interview scripting. The outcome information is placed at the beginning of the form to be consistent with the data entry system. If an interview is not conducted, then the data entry person will be able to indicate why without having to scroll through pages of interview questions. Check "Yes" or "No" whether the interview was conducted. If "No", indicate why by checking: 1-Loss of contact, 2-Interviewee refused, 3-Child died, or 4-Other. If "Other", indicate why the interview was not conducted in the space provided. By indicating "Loss of Contact" you have exhausted all means of reaching the family and you do not know how to contact them. If you are still actively trying to reach the family at the end of the open window, then wait to complete the interview outcome information until: 1- the interview is conducted or 2- it is determined that the family is a "loss of contact". Record the initials of the person completing the form.

#### 6.1 Conducting the Interview

##### 6.1.1 Initiating the interview:

**Script Introducing the Study:**

**N.B. The interviewer's script is in italics and enclosed in quotations.**

*"Premature babies are more likely than full term babies to have breathing problems after discharge from the NICU. The purpose of this study is to see whether or not the treatments your baby received as part of the SUPPORT Study improves your baby's breathing in the 18-22 months following the baby's due date.*

*As part of this study, we will contact you every 6 months or so to ask you questions about your baby's breathing. The questions will be about your baby's breathing symptoms, especially wheezing and coughing, and about your baby's need for medical visits and treatments for breathing problems.*

*By wheezing we mean an expiratory sound (a sound that is made when breathing out, not in) that comes from the chest, sometimes described as whistling or musical.*

*We have prepared a brochure for you that describes the study and outlines important characteristics of your baby's breathing, especially breathing problems and treatments.*

*Give brochure*

*When we call, we'd like you to gather any notes, medications or other information about your baby's breathing. We will ask questions about how often your baby has wheezing or coughing, whether your baby visited a doctor's office, emergency room or was hospitalized for breathing problems, and whether your baby has needed breathing medicines or treatments. If you wish, you may use the brochure to make notes about your baby's breathing.*

*In order to help us understand your baby's breathing and risk for breathing problems at home, we'd like to ask you a few questions about your home and about whether breathing problems run in the family. As with all information we collect, the answers to these questions will be kept confidential."*

Please confirm the study baby's identity.

*"We will be discussing, patient name. He/she is a boy/girl born on birth date"*

**Question 1.**

**Child's Name:**

Please enter the child's name including, nickname that he/she will be called.

**Question 2.**

Enter the date of the interview in "mm/dd/yyyy" format.

**Question 3.**

**Child's Sex:**

Please enter the child's sex.

**Question 4.**

**Child's Birthdate:**

Please enter to the child's birth date in "mm/dd/yyyy" format.

Please confirm the identity of the caretaker being interviewed.

**Question 5.**

*"With whom am I speaking?"*

**Question 5a.**

*"What is your relationship to the baby?"*

Please specify the primary caretaker's name and relationship to the infant using the relationship codes used in the Network Follow up Program, Appendix D.

Every effort should be made to interview the primary caretaker during this interview and all subsequent interviews (6, 12 and 18 months). If the mother resides in the same household as the child, the mother is the primary caretaker. If each caretaker has exactly 50% custody, record as the primary caretaker, the person who comes in for the discharge. This person should answer all subsequent interviews, if possible.

**APPENDIX B OF THE BREATHING OUTCOMES MANUAL OF PROCEDURES**

**RELATIONSHIP CODES**

The following codes are used to identify the primary caretaker.

- 001 - Mother of Child
- 002 - Father of Child
- 011 - Husband, Significant Other (SO)(if different from 002)
- 012 - Wife, Girlfriend (if different from 001)
- 021 - Maternal grandmother
- 022 - Paternal (SO) grandmother
- 031 - Maternal grandfather
- 032 - Paternal (SO) grandfather
- 041 - Maternal aunt
- 042 - Paternal (SO) aunt
- 051 - Maternal uncle
- 052 - Paternal (SO) uncle
- 061 - Brother
- 062 - Step Brother
- 071 - Sister
- 072 - Step Sister
- 081 - Maternal female cousin
- 082 - Paternal (SO) female cousin
- 091 - Maternal male cousin
- 092 - Paternal (SO) male cousin
- 101 - Other maternal relative
- 102 - Other paternal (SO) relative
- 201 - Foster mother
- 202 - Foster father
- 301 - Adoptive mother
- 302 - Adoptive father
- 401 - Other non-relative
- 402 - Social worker/case worker
- 501 - Staff in congregate care
- 502 - Still hospitalized
- 504 - Unknown

**Question 6.**

**Type of Interview:**

Record whether the interview conducted face to face or by telephone.

Interview Begins

(N.B. The interviewer's script is in italics and enclosed in quotations)

Script: *"At this time, we would like a little information about the environment in which your new child will grow up."*

**Question 7.**

*"First, how many people normally live with you in your home for at least 6 months of the year?"*

Enter the total number of household members. A household member is a person who spends more than 7 nights in the home over a two week period for at least 6 months of the year. The interviewee as well as the child should be included in this number.

**Question 8.**

*"After the first few months, will your child be sharing a room with other family members on a regular basis?"*

Enter YES if child shares a room with another household member more than 7 nights in a 2 week period.

**Question 8a.**

If answer to 8 is YES: *"How many other people will sleep in the same room with him/her?"*

Please record how many people will sleep in the same room with the child.

**Question 9.**

*"How many rooms are there in your house, excluding closets and bathrooms?"* Record how many rooms in the space provided.

A room is a space within the house in which residents play, sleep, work or eat.

**Question 10.**

*"Do you have any pets inside the home?"*

If yes record, *"How many dogs in the home? Cats in the home? Do you have other pets in the home? What kinds? How many?"*

If interviewee reports pets, please record the number of dogs and cats separately. Group all other pets together and record total number of pets that are neither a dog nor a cat.

**Question 11.**

*"Does your home or apartment have air conditioning or some kind of cooling where the baby will sleep at night?"*

Please enter "Yes" or "No"

This question assesses whether there is air conditioning or some kind of cooling where the baby sleeps at night. This excludes fans such as floor, table or ceiling fans.

Question 11.a-11.c Please record whether family has air conditioning or evaporative cooling. If family uses another type of home cooling system, please answer YES and record type.

**Question 12.**

*“How is your home heated?, With steam or hot water, with a gas furnace, with electricity, with a wood stove, or something else? ”*

Please prompt by reading each of the listed heating options. Record all heating methods used in the home or apartment. If more than one heating type is used, please record all heating types used. Steam or hot water heat uses upright radiators or baseboard units. A central gas furnace uses forced air vents that blow air into the room. Included in wood stove heat is use of a fireplace for heat, including fireplaces with energy efficient “inserts”.

**Question 13.**

*“What fuel is used most for cooking in your home?”*

There is no need to prompt with each alternative cooking fuel. Please record one primary cooking method used in the home or apartment.

**Scripting: “The next questions are about your baby’s diet .....**”

**Question 14.**

*“Is your child receiving only breast milk, only formula, or both breast milk and formula?”*

Record response. If “other” specify. For example, if the child is not receiving enteral nutrition, then “other” should be recorded and the type of nutrition specified.

Question 14a.

If reply to 14 is only breast milk (choice #1),

*“Will the breast milk be supplemented with formula in the next 6 months?”*

Please record “Yes”, “No” or “Don’t Know”

Question 14b.

*“If so, when do you think the supplement will begin?”*

If YES was entered for 14a (breast milk will be supplemented with formula) then enter the number of months from date of interview that breast milk will be supplemented with formula.

**For interviews conducted after the target period of 30 days following NICU discharge, Question 14 should be stated as, “At the time of NICU discharge was your child receiving” (read all answer choices).**

**Scripting: “The next question are about your baby’s care environment .....**”

**Question 15.**

*“Does the mother plan to work outside the home within the next year?”*

Select from responses below.

1. Yes
2. No
3. Don’t Know

**For interviews conducted after the target period of 30 days following NICU discharge, Question 15 should be stated as, “Does the mother plan to work outside of the home within the first year of the child’s life?”**

**Scripting: “The next questions are about smoke exposure.....”**

**Question 16.**

*"Which one of the following 3 statements best describes the situation regarding smoking in your child's home? .....Read all options to the interviewee before recording a response: Smoking is allowed in any common room of the home, smoking is limited to part of the house where the child rarely goes, there is no smoking inside at all?"*

**Question 16a.**

If answer to question 16 is "there is no smoking in the house at all", then ask question 13a, "Are there any exceptions to this situation?"

If respondent reports any exceptions, record "Yes". If no, skip to question 17.

**Question 16b.**

If answer to 16a is "Yes", then ask question 16b.

*"Under what circumstances are the exceptions allowed?"*

Record a brief response as free text.

**Question 17.**

*"Which one of the following 5 statements best describes the situation regarding smoking in your car? .... Read all options to the interviewee before recording a response: Smoking is usually or always allowed, smoking is sometimes allowed, smoking occurs in the car only when the child is not inside, there is no smoking inside the car"*

Record the response as it applies to the main automobile in which the baby rides. If family does not ride in a car (public transportation only or baby doesn't leave home), record response #1.

**Questions 17a and 17b.** Responses questions to 17a and 17b are completed similarly to questions 16a and 16b.

**Question 18.**

*"How often have you smoked since this child was born?"*

Please record response, never means never, daily means at least once per day, record occasionally for any quantity between never and daily.

**Question 19.**

*"Altogether, how many people in the child's home smoke?" \_\_\_\_\_ people*

Record the number of people who reside in the home (spend more than 7 out of 14 nights in the home) who smoke. Any smoker counts, whether they smoke in the home, outside the home or at some distant location.

**Family History Form**

**Scripting:** *"In the next section, we'd like to know what breathing and allergy problems run in the family."*

**Administer the attached Family History Questionnaire using the follow script.**

**Mother:**

*"We'll start with the baby's mother. How old is the baby's biologic mother? Does she have bronchitis, emphysema, COPD, bronchiectasis, asthma, inhaled allergies, or food allergies?"*

*Circle Yes, No, or DK (Don't Know).*

*“Does she (you) have any other chronic respiratory illnesses?”*

*“How often do you smoke in the baby’s home?”*

**Father:**

*“For the baby’s biologic father, is he living? How old is he? Does he have bronchitis, emphysema, COPD, bronchiectasis, asthma, inhaled allergies, or food allergies?”*

*“Does he have any other chronic respiratory illnesses?”*

*Circle Yes, No, or DK (Don’t Know).*

*“How often does he smoke in the baby’s home?”*

Complete the remainder of the table by collecting the same medical history using the script above.

Please complete a family history for each of the family relationships listed, mother, father, maternal grandmother (Mom’s biologic Mother), maternal grandfather (Mom’s biologic Father), paternal grandmother (Dad’s biologic Mom), and paternal grandfather (Dad’s biologic Father). For each relative above, enter whether they have ever had any of the listed respiratory problems. The interviewer need not explain each diagnosis, but may offer an explanation if asked. Record only those responses that pertain to the baby’s biologic relatives. If information is not known by the respondent, record as “DK” (Don’t Know).

**Question 20.**

“Finally, which friend or relative is most likely to be able to contact you 6 months from now in case we lose contact with you?”

Record the information for an alternate contact person who is unlikely to move and the most likely to know the baby’s family most recent residence / phone number.



## Chapter 7

### 6 and 12 Month Pulmonary Outcome Questionnaires

#### Introduction

The purpose of this questionnaire is to obtain an **interval** respiratory history, such that when the 6, 12 and 18-22 month questionnaires are taken together, a complete respiratory history over the time period is collected.

The questionnaire will be administered to the parent or guardian by a certified telephone interviewer at 6 months' CA and again at 12 months' CA.

Centers choosing Option 1 will administer the questionnaire using a certified local interviewer and locally maintained contact information. For centers choosing Option 2, a Rochester Health Services Research Group (RHSRG) certified interviewer will conduct the interview via long distance telephone call using contact information maintained by the local center and faxed or emailed to the RHSRG.

*Instructions for Completing the 6 and 12 Month Questionnaire (SUPF02)*

#### Instructions for Completing the NICU Discharge-Baseline Interview (SUPF01)

##### Timing of the Interview:

This interview should be administered by a certified study interviewer. The target window for this interview is at the following corrected ages: 6 months  $\pm$  2 weeks and 12 months  $\pm$  2 weeks, with an acceptable window of 6 months  $\pm$  1 month and 12 months  $\pm$  1 month. If for any reason the infant is enrolled into the Pulmonary Outcomes Study later than this time window or becomes available for a Pulmonary Outcomes Interview outside this window, the questionnaire should be administered, collecting an interval history from the time of NICU discharge or the most recent interview, whichever is most recent.

##### Heading- Infant's Identification

The following information is included in the heading section of all patient specific data forms: Center, Site, Network Number, SUPPORT Follow-up Number, Birth Number and Mother's Initials (**optional**). This information should be completed on each page of the interview in case the completed form pages are separated.

##### Interview Outcome Information

The interview outcome information is located on the cover page of each form after the interview scripting. The outcome information is placed at the beginning of the form to be consistent with the data entry system. If an interview is not conducted, then the data entry person will be able to indicate why without having to scroll through pages of interview questions. Check "Yes" or "No" whether the interview was conducted. If "No", indicate why by checking: 1-Loss of contact, 2-Interviewee refused, 3-Child died, or 4-Other. If "Other", indicate why the interview was not conducted in the space provided. By indicating "Loss of Contact" you have exhausted all means of reaching the family and you do not know how to contact them. If you are still actively trying to reach the family at the end of the open window, then wait to complete the interview outcome information until: 1- the interview is conducted or 2- it is determined that the family is a "loss of contact". Record the initials of the person completing the form.

## 7.1 Conducting the Interview

### 7.1.1 Initiating the interview:

Please request and confirm the identity of the caretaker who completed the initial interview.

Every effort should be made to interview the primary caretaker who completed the initial interview (hereafter referred to as the primary respondent) during this interview and all subsequent interviews (6, 12 and 18 months). If the mother resides in the same household as the child, the mother is the primary caretaker. If each caretaker has exactly 50% custody, record as the primary caretaker, the person who comes in for the discharge. This person should answer all interviews, if possible.

The interviewer will need to ask for the primary respondent. In the event that the primary respondent is not available, arrangements should be made to call back at a time when the primary respondent will be free to complete the interview. At least 3 call attempts should be made to reach the primary respondent, after that a secondary respondent, who is familiar with the baby and his or her respiratory health, can be identified to complete the interview.

#### Introduction Script:

When parent or primary care giver is on phone:

***“Hello, my name is <your name>. I am calling from the <NICHD Center>. As you probably remember, when you were in the NICU you enrolled in our study about respiratory health of premature infants. I am calling to ask you some questions about your baby’s breathing. It will take about 10-20 minutes to complete. Is this a good time for you?”***

***“Before we begin this interview, it would be helpful if you could gather the Breathing Brochure any notes you have about your baby’s breathing as well as any medications your child has been prescribed or has been taking and have them in front of you. As with all information we collect, the answers to these questions will be kept confidential.”***

#### **Question 1.**

Please enter date of the interview.

Please confirm the identity and contact information for the study baby to be interviewed.

*“We will be discussing, patient name. He/she is a boy/girl born on birth date”*

#### **Child’s Name:**

Please enter the child’s name.

#### **Child’s Birthdate:**

Enter to the child’s birth date in “mm/dd/yyyy” format.

#### **Child’s Telephone Number:**

Enter the telephone number to the child’s home.

#### **Child’s Address:**

Enter the address of the child's home.

**Alternate Contact Information**

Which friend or relative is most likely to be able to contact you 6 months from now in case we lose contact with you?"

Confirm the contact information for an alternate contact person who is unlikely to move and the most likely to know the baby's family most recent residence / phone number.

**Question 2a. and 2b.**

Enter name and relationship code of the person being interviewed.

Please specify the primary caretaker's name and relationship to the infant using the relationship codes used in the Network Follow up Program.

**Question 3.**

Type of interview.

Please specify and record whether the interview was administered face to face or via telephone.

**Question 4.**

Location of Interview.

Please specify and record whether the interview was administered at the local center (Option 1) or by the Rochester site (Option 2).

Instructions:

Parents or guardians expressing concerns regarding their child's breathing should be advised to discuss them with the family's primary care physician.

Where the phrase "last contact" is used below, please substitute with the most specific relevant time prompt, e.g. for the 6 month interview, refer to "since NICU discharge"; for the 12 month interview, refer to "over the past 6 months", etc.

Interview begins:

(N.B. The interviewer's script is in italics and enclosed in quotations)

**Scripting:**

*"Some of these questions will be familiar to you. Since we last spoke ( \_\_ ) months ago on ( \_\_ / \_\_ / \_\_ ) we want to learn what changes, if any, there have been to your child's health. We are especially interested in any breathing problems your child may have....."*

**Question 5.**

*"Has the child been with you during the past 6 months?"*

Please enter "Yes" or "No". If child has been with the interviewee less than 6 months, please enter "No".

**Scripting: "Since <our last contact> with you about your child....."**

Please replace the phrase "our last contact", with an interview specific prompt, e.g. "since discharge from the NICU" at the 6 month interview or "since our telephone conversation 6 months ago", for the 12 and 18 month interviews. Equivalent phrases may be used.

**Question 6.**

*"How many times has your child visited a doctor's office?"* |\_\_|\_\_| times

Record the number of times that the baby visited the doctor's office for any reason. If respondent answers "don't know", repeat the question and if he/she still does not know, then insert \* in the blanks to indicate that the data are permanently missing.

**Question 6a.**

*"How many of these times were because of wheezing or breathing problems?"*

Record the number of times that the baby visited the doctor's office with breathing problems as one of the 2 major concerns for the visit. If respondent answers "don't know", repeat the question and if he/she still does not know, then insert \* in the blanks to indicate that the data are permanently missing.

**Scripting: "Since <our last contact> with you about your child....."**

Please replace the phrase "our last contact", with an interview specific prompt, e.g. "since discharge from the NICU" at the 6 month interview or "since our telephone conversation 6 months ago", for the 12 and 18 month interviews. Equivalent phrases may be used.

**Question 7.**

*"How many times has your child visited an Emergency Department (Emergency room)?"*

|\_\_|\_\_| times

Record the number of times that the baby visited the emergency department or emergency room for any reason. If respondent answers "don't know", repeat the question and if he/she still does not know, then insert \* in the blanks to indicate that the data are permanently missing.

**Question 7a.**

*"How many of these times were because of wheezing or breathing problems?"*

Record the number of times that the baby visited emergency services with breathing problems as one of the 2 major concerns for the visit. If respondent answers "don't know", repeat the question and if he/she still does not know, then insert \* in the blanks to indicate that the data are permanently missing.

**Question 8.**

*"How many times has your child stayed in the hospital for 1 or more nights in a row?"*

|\_\_|\_\_| times

Record the number of times the baby was hospitalized for any reason, i.e the number of hospitalizations, not the number of hospitalized days. If respondent answers "don't know", repeat the question and if he/she still does not know, then insert \* in the blanks to indicate that the data are permanently missing.

**Question 8a.**

"How many of these times were because of wheezing or breathing problems?" |\_\_|\_\_|  
times

Record the number of times that the baby was hospitalized with breathing problems as one of the 2 major concerns for the visit. If respondent answers "don't know", repeat the question and if he/she still does not know, then insert \* in the blanks to indicate that the data are permanently missing.

**Script:**

***"The next questions are about your baby's breathing. ...."***

***The first question is about wheezing. By wheezing we mean an expiratory sound (a sound that is made when breathing out, not in) that comes from the chest, sometimes described as whistling or musical."***

**Question 9.**

*"Since <our last contact> with you, has your baby's chest sounded wheezy or whistling?"*

Enter yes if the respondent reports that the baby's chest has sounded wheezy or whistling. The interviewer may repeat the verbal and audio descriptions of wheezing may be repeated to the respondent. If respondent answers "I don't know", interviewer should ask respondent to think back over the time period, repeating the description. If parent is still not sure, record "don't know".

**Question 9a.**

*"Has your baby's breathing sounded like this?" (play audio clip of wheezing).*

This question is intended for all respondents, regardless of whether they reported wheezing in question 9. The audio clip is from a patient with severe, audible wheezing and represents only one of many manifestation of wheezing breathing sounds. If asked, the interviewer may say that this represents just one type of wheezing. We wish to know about all wheezing and therefore we asked two questions.

Record response, "Yes" or "No". If respondent replies "no" or "don't know", interview skips to question 10. If yes, proceed to questions 9b-g.

Those who answered "Yes" to questions 9 or 9a should answer questions 9b-g.

**Question 9b.**

*"Has this occurred with colds?"*

A "cold" is an upper respiratory infection; other phrases for a "cold" include, "head cold", "rhinitis", "runny or water nose" or "sniffles". A cold may be complicated by an otitis media (ear infection).

A "cold" does not include "chest cold", "bronchitis", "pneumonia", or "bronchiolitis".

If the respondent answers “don’t know”, repeat the question and if he/she still does not know, then code the answer as “No”.

**Question 9c.**

*“Has your child’s chest sounded wheezy or whistling apart from colds?”*

Enter “yes” if the baby had wheezy or whistling in the chest at a time when he/she did not have a cold. If the respondent answers “don’t know”, repeat the question and if he/she still does not know, then code the answer as “No”.

**Question 9d.**

*“During what month did your child’s chest first sound wheezy or whistling?”*

\_\_\_\_\_ month \_\_\_\_\_ year

Please record the month and year during which the child’s chest first sounded wheezy or whistling. The respondent may indicate the child’s age at which the child’s chest first sounded wheezy or whistling. The interviewer should record the month and year of the event.

Here the month and year, rather than the age, that the symptoms began is recorded in an effort to avoid confusion regarding chronologic and corrected ages.

The next 4 questions use similar phrases and the same response options. Please emphasize the phrases which are unique in each question (“on average” or “worst two week period”, “daytime” or “nighttime”). If the respondent gives the same response to 5e as 5f, please confirm with the respondent that 5e refers to “on average” and that 5f refers to the “worst two week period”.

**Question 9e1.**

“Since our last contact with you, **on average**, how often has your child’s chest sounded wheezy or whistling during the daytime? *Would you say, never; twice a week or less; more than 2 times a week, but not every day; every day, but not all the time; or everyday, all the time.*”

Record response. Interviewer may repeat the choices or help respondent settle upon the choice.

**Question 9e2.**

“Since our last contact with you, **on average**, how often has your child’s chest sounded wheezy or whistling during the nighttime? *Would you say, never; once every two weeks or less; once a week; two or three times a week; or more than three nights a week/frequently?*”

Record response. Interviewer may repeat the choices or help respondent settle upon the choice.

**Question 9f1.**

“Since our last contact with you, **during the worst 2 week period**, how often has your child’s chest sounded wheezy or whistling during the daytime? *Would you say, never; twice a week or less; more than 2 times a week, but not every day; every day, but not all the time; or everyday, all the time.*”

Record response. Interviewer may repeat the choices or help respondent settle upon the choice.

**Question 9f2.**

"Since our last contact with you, **during the worst 2 week period**, how often has your child's chest sounded wheezy or whistling during the nighttime? *Would you say, never; once every two weeks or less; once a week; two or three times a week; or more than three nights a week/frequently?"*

Record response. Interviewer may repeat the choices or help respondent settle upon the choice.

**Question 9g.**

"*Since our last contact with you, has your child been diagnosed with wheezing by a doctor?"*

Record "Yes" or "No". Physician diagnosed wheezing, wheezy or whistling breath sounds should be recorded as a "Yes" response.

**Question 10.**

"*Since our last contact with you, has your child had a cough for more than 3 days when he/she did not have a cold?"*

Record whether the baby coughs for more than 3 days when otherwise well. Do not include coughing associated with eating, drinking or choking. See question 9 for clarification of phrase "cold". If the respondent answers "don't know", repeat the question and if he/she still does not know, then code the answer as "No".

**Question 10a.**

"*At what time of the day has this cough usually occurred? In the morning; shortly after rising; later in the day; during the night; no relation to time of day?"*

Interviewer should read all responses to the respondent and circle all that apply.

**Question 10b.**

"*Has he/she coughed on most days for as much as 2 to 3 months?"*

Please record "Yes" or "No". If the respondent answers "don't know", repeat the question and if he/she still does not know, then code the answer as "No".

**Question 10c.**

"*During what month did your child first develop the cough?"*

Record month and year that the cough first developed, when the respondent recognized the cough whether or not they view it as a problem. If a range of months is given ask the respondent to pinpoint when the cough first developed. If two months are given (i.e., between January or February) code the first month.

**Question 10d.**

"*Has your child's chest ever sounded wheezy or whistling with episodes of coughing?"*

Record yes if the respondent associates wheezing or whistling breath sounds with the presence of the cough. If the respondent answers “don’t know”, repeat the question and if he/she still does not know, then code the answer as “No”.

**Questions 10e1-10f2.** Questions 10e1-10f2 are completed similarly to questions 9e1-9f2.

**Question 11.**

*“Since our last contact with you, **on average**, how many **days per month** did you have to change your daytime or evening plans because of your child’s breathing problems: Was it...*

*None, we never had to change plans  
More than none but less than 3 days,  
3 to 6 days or  
7 or more days.”*

Please read the choices to the respondent and record their response. The question is designed to determine the number of days that the respondent reports having to change plans because the baby’s breathing is different from baseline. An example of a changed plan includes withholding the baby from a planned daycare or babysitting situation because he / she is wheezing.

This does not include preventive avoidance, such as avoiding social situations or trips because the baby might get sick or may be exposed to another child. The interviewer may assist the respondent in selecting a response by repeating the choices, then having the respondent select a specific answer.

**Question 12.**

*“Since our last contact with you, **during the worst 2 week period**, how many **days** did you have to change your daytime or evening plans because of your child’s breathing problems: Was it...*

*None, we never had to change plans  
More than none but less than 3 days,  
3 to 6 days or  
7 or more days.”*

Interviewer should emphasize the “worst 2 week period”. Record response using criteria similar to those in Question 11.

The next 4 questions relate to respiratory diagnoses that may be associated with wheezing and airway dysfunction, either directly, as secondary symptom or as a condition that may be confused with airway dysfunction.

**Question 13.**

*“Since our last contact with you, has your child had asthma, reactive airways disease or a BPD flare-up diagnosed by a doctor?”*



Record response, either "Yes" or "No". If respondent does not recognize the condition, record "No". If the respondent answers "don't know", repeat the question and if he/she still does not know, then code the answer as "No".

For this question use BPD flare-up, chronic lung disease of prematurity or other terms that may be used at your local center such as BPD exacerbation, chronic lung disease (CLD) flare-up.

**Question 14.**

*"Since our last contact with you, has your child had bronchiolitis, bronchitis, or pneumonia diagnosed by a doctor?"*

Record response, either "Yes" or "No". If respondent does not recognize the condition, record "No". If the respondent answers "don't know", repeat the question and if he/she still does not know, then code the answer as "No".

**Question 15.**

*"Since our last contact with you, has your child had croup diagnosed by a doctor?"*

Record response, either "Yes" or "No". If respondent does not recognize the condition, record "No". If the respondent answers "don't know", repeat the question and if he/she still does not know, then code the answer as "No".

**Script: "The next questions are about your baby's diet....."**

**Question 16.**

*"In the past 6 months, did your baby receive breast milk, either at breast, from a bottle or through a tube?"*

If baby received any breast milk, record "Yes".

If "Yes" to Question 16, answer question 16a and 16b, if "No", skip to Question 17:

**Question 16a.**

*"For how many months did your child receive breast milk? Would you say? ....Less than 1 month, 1-3 months, 4-6 months?"*

Record duration of time that the baby received any breast milk.

**Question 16b.**

*"For how many months did your child receive breast milk for more than half of his/her feedings? Would you say... Less than 1 month, 1-3 months, 4-6 months?"*

Record duration of time that the baby received more than ½ of feedings from breast milk, provided by any route.

A mother who fed her infant breast milk 25% of the time and formula 75% of the time, weaning the baby at 4 months, would answer "yes" to question 16, "4-6 months" to question 16a, and "less than 1 month" to question 16b.

Script: **"The next questions are about smoke exposure....."**

**Question 17.**

*“Which of the following 3 statements best describes the situation regarding smoking in your child’s home?..... Read all options to the interviewee before recording a response: Smoking is allowed in any common room of the home, smoking is limited to part of the house where the child rarely goes, there is no smoking inside at all?”*

**Question 17a.**

If answer to question 17 is “there is no smoking inside at all”, then ask question 17a, “Are there any exceptions to this situation?”

If respondent reports any exceptions, record “Yes”. If no, skip to question 18.

**Question 17b.**

If answer to 17a is “Yes”, then ask question 17b.

“Under what circumstances are the exceptions allowed?”

Record a brief response as free text.

**Question 18.**

*“Which of the following 5 statements best describes the situation regarding smoking in your car?.... Read all options to the interviewee before recording a response: Smoking is usually or always allowed, smoking is sometimes allowed, smoking occurs in the car only when the child is not inside, there is no smoking inside the car”*

Record the response as it applies to the main automobile in which the baby rides. If family does not ride in a car (public transportation only or baby doesn’t leave home), record response #1.

**Question 18a and 18b.** Responses questions to 18a and 18b are completed similarly to questions 17a and 17b.

**Question 19.**

*‘How often has the mother or primary caregiver smoked since your child was born?’*

If speaking with the mother, please substitute “you” for “mother or primary caregiver”. Record response based on occurrence of any smoking activity, regardless of where it takes place. Record “Never” if the mother or primary care giver has never smoked anywhere since the baby was born, record “Daily” if she /he smokes daily in any location, and record “Occasionally” if response is neither “Never” nor “Daily”.

**Question 20.**

*“How many people in the child’s home smoke?”* |\_\_|\_\_| people

Record response based on occurrence of any smoking activity, regardless of where it takes place. The intent of this question is to determine the number of smokers that live in the home, not whether they smoke in the home.

**Script: “The next questions are about your home and your babysitter’s home or day care”**

**Question 21.**

*“Approximately how many hours per week does your child spend at a babysitter’s home or day care?”* |\_\_|\_\_| hrs If 0 skip to question 22.

Record the number of hours that the baby spends outside his/her home, regardless of whether this is in the home of another parent, grandparent, or friend.

**Question 21a.**

If response to question 21 is greater than 0,

*"How frequent is there smoke exposure at the babysitter or daycare?"*

Record response based on occurrence of any smoking activity, regardless of where it takes place. Record never if there is no smoking allowed inside the babysitter or daycare provider's edifice in any location, record daily if smoking occurs inside the edifice daily in any location, and record occasionally if response is neither never nor daily.

**Question 21b.**

*"How many children beside your baby are in the daycare?"*

Record the average number of children less than 12 years of age who inhabited the babysitter or daycare over the past 2 weeks when the baby was present.

**Question 22.**

*"How many children under 12 live in your house?"* [ ] [ ] children (including the baby)

Record number of children who spend more than 7 nights in the home over a two week period. The baby should be included in this number.

**Question 23.**

*"Do you have any pets inside the home?"*

Record "Yes" or "No"

**Question 23a.** If yes record,

*"How many dogs? Cats? Do you have other pets? What kinds? How many?"*

If respondent reports pets, please record the number of dogs and cats separately. Group all other pets together and record total number of pets that are neither a dog nor a cat.

**Script:** *"The last questions involve respiratory treatments that your baby may receive....."*

**Question 24.**

*"Has your child had RSV shots (palivizumab) to prevent Respiratory Syncytial Virus (Synagis, palivizumab, RSV shot)?"*

Record respondent's answer, "Yes", "No" or "Don't know". If respondent does not recognize the treatment, record "Don't Know".

**Question 25.**

*"Has your child had a flu shot?"*

Record respondent's answer, "Yes", "No" or "Don't know". If respondent does not recognize the vaccine, record "Don't Know". If the respondent indicates that the child received a nasal spray immunization, code as "No" and press the F5 key and indicate in the comment field that the child received a nasal spray immunization.

**Question 26.**

*"Since our last contact with you, has your child received oxygen therapy at home?"*

Record respondent's answer, "Yes" or "No". If respondent does not know, the interviewer should prompt further by asking, "does your baby use any oxygen equipment, such as an oxygen tank, at home?"

**Question 26a**

*"Is your child currently on oxygen therapy at home?"*

Record respondent's answer, "Yes" or "No". If respondent does not know, the interviewer should prompt further by asking, "Since our last contact with you, has your baby used any oxygen equipment, such as an oxygen tank, at home?"

**Question 26b – 26d.**

These questions can be answered using the following script.

If response to question 26a is "Yes",

*"What device is used to provide the oxygen?.....Oxygen hood, nasal cannula or ventilator?"*

Record response in checkbox provided.

If response to question 26a is "Yes", the interviewer should ask,

*"What percent oxygen does your baby use?"*

Record response as fraction inspired oxygen (FiO<sub>2</sub>) in the space adjacent to the oxygen delivery device. For example, room air (ambient air) is 21% oxygen, enter as FiO<sub>2</sub> value of 0.21; pure oxygen is 100%, enter as FIO<sub>2</sub> value of 1.0

If response to question 26a is either "nasal cannula" or "oxygen hood", interviewer asks, *"How many liters of oxygen does the baby receive?"*

Record value as liters per minute (1cc is .001liters, 1/8 liter is 0.125 liters, ¼ liter is 0.25 liters, etc.)

**MEDICATIONS**

**Script: "The last two questions involve the medicines your child is taking for breathing problems....."**

**Question 27.**

*"Since our last contact with you, what medicines has your baby taken, including medicines delivered by a nebulizer or breathing machine?"*

For this question, record all respiratory related medications. Record a written response in the table and later, after the interview, record the medication code from the table below. Medications that do not appear on the list are unlikely to be used to treat respiratory conditions in this age group. Do not prompt for each medication in the medication list.

## Chapter 8

### 18-22 Month Questionnaire

#### Introduction

The purpose of this questionnaire is to obtain an **interval** respiratory history and to identify a history of atopy that may increase the likelihood of symptomatic airway dysfunction. Questions are designed to ascertain the frequency and severity of wheezing and cough episodes and to assess the need for outpatient pulmonary care. In addition, risk factors obtained at the 1<sup>st</sup> interview will be confirmed. There are a total of 34 questions, encompassing 27 questions from the 6 month and 12 month questionnaires and 7 questions concerning respiratory infections and allergies.

This interview will be conducted at 18-22 months' corrected age, either by the local NICHD Follow Up Program (Option 1) or long distance from Rochester (Option 2), based on center preference.

#### Instructions for Completing the 18-22 Month Questionnaire (SUPF03)

##### Timing of the Interview:

The target window for this interview is between 18 and 22 months' corrected age. If for any reason the infant is enrolled into the Pulmonary Outcome Study at this time window or becomes available for a Pulmonary Outcomes Interview outside this window, the questionnaire should be administered, collecting an interval history from the time of NICU discharge or the most recent interview, whichever is most recent.

This interview should be administered by a certified study interviewer either by telephone prior to the regularly scheduled 18-22 month NICHD developmental follow-up clinic visit or face to face at the time of the visit.

##### Heading- Infant's Identification

The following information is included in the heading section of all patient specific data forms: Center, Site, Network Number, SUPPORT Follow-up Number, Birth Number and Mother's Initials (**optional**). This information should be completed on each page of the interview in case the completed form pages are separated.

##### Interview Outcome Information

The interview outcome information is located on the cover page of each form after the interview scripting. The outcome information is placed at the beginning of the form to be consistent with the data entry system. If an interview is not conducted, then the data entry person will be able to indicate why without having to scroll through pages of interview questions. Check "Yes" or "No" whether the interview was conducted. If "No", indicate why by checking: 1-Loss of contact, 2-Interviewee refused, 3-Child died, or 4-Other. If "Other", indicate why the interview was not conducted in the space provided. By indicating "Loss of Contact" you have exhausted all means of reaching the family and you do not know how to contact them. If you are still actively trying to reach the family at the end of the open window, then wait to complete the interview outcome information until: 1- the interview is conducted or 2- it is determined that the family is a "loss of contact". Record the initials of the person completing the form.

## 8.1 Conducting the Interview

### 8.1.1 Initiating the interview:

The 18-22 month questionnaire is conducted in the same fashion as for the 6 and 12 month interviews. In addition to the 27 questions included in the 6 and 12 month questionnaires, the 18-22 month questionnaire includes 7 questions about allergies.

**See Chapter 7 of this manual for directions to administer questions 1-27 of the 18-22 month questionnaire. Directions for questions 28-34 begin here.**

**Script: “The next 2 questions regard about respiratory infections.....”**

#### Question 28.

*“During the past year, for how many days has your child been unable to do his/her usual activities because of illnesses such as chest (not head) colds, bronchitis, asthma or pneumonia? 0-3 per year, 4-5 per year, 6-9 per year, more than 9 per year?”*

#### Question 29.

*“During the past year, how many head colds (common colds) has your child had? Would you say...0-3 per year, 4-5 per year, 6-9 per year, more than 9 per year?”*

**Script: “The last questions regard allergies.....”**

#### Question 30.

*“Has your child ever had hay fever or any other condition that makes his/her nose runny, stuffy, or itchy apart from colds?”*

Record response, either “Yes” or “No”. If respondent does not recognize the condition, record “No”. If the respondent answers “don’t know”, repeat the question and if he/she still does not know, then code the answer as “No”.

#### Question 31.

*“Has your child ever had allergies which cause nose, eye or lung problems?”*

Record response, either “Yes” or “No”. If respondent does not recognize the condition, record “No”. If the respondent answers “don’t know”, repeat the question and if he/she still does not know, then code the answer as “No”.

#### Question 32.

*“Has your child ever been allergic to any food?”*

Record response, either “Yes” or “No”. If respondent does not recognize the condition, record “No”. Food allergies refer to reactions such as rashes and swelling, not diarrhea or vomiting. If the respondent answers “don’t know”, repeat the question and if he/she still does not know, then code the answer as “No”.

#### Question 33.

*“Has he/she ever been allergic to any medicine?”*

Record response, either “Yes” or “No”. If respondent does not recognize the condition, record “No”. If the respondent answers “don’t know”, repeat the question and if he/she still does not know, then code the answer as “No”.

**Question 34.**

*"Has your child **ever** had eczema (allergic skin rash)?"*

Record response, either "Yes" or "No". If respondent does not recognize the condition, record "No". If the respondent answers "don't know", repeat the question and if he/she still does not know, then code the answer as "No".

**Question 34a.**

If Question 34 is "Yes",

*"Was this diagnosed by a doctor?"*

Record response, "Yes" or "No"

## **APPENDIX A**

### **List of Acronyms**

BOOST Trial – Benefits of Oxygen Saturation Targeting  
BPD – Bronchopulmonary Dysplasia  
CA – Corrected Age  
CLD – Chronic Lung Disease  
CPAP – Positive pressure applied with a face mask to help keep lungs inflated  
ELBW – Extremely Low Birth Weight Infants  
FEF – Forced Expiratory Flow  
GA – Gestational Age  
GDB – Generic Data Base for the NICHD Neonatal Research Network  
HDMA – House Dust Mite Allergen  
HIPPA – Health Insurance Portability and Accountability Act of 1996  
HSR Group – University of Rochester Health Services Research Group  
IRB – Institutional Review Board  
LBW – Low Birth Weight  
NBW – Normal Birth Weight  
NICHD – The National Institute of Child Health and Human Development  
NICU – Neonatal Intensive Care Unit  
PFT – Pulmonary Function Testing  
RDS – Respiratory Distress Syndrome  
ROP – Retinopathy of Prematurity  
RSV - Respiratory Syncytial Virus  
SUPPORT Trial– The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in  
Extremely Low Birth Weight Infants  
UKOS – The United Kingdom Oscillator Study  
VLBW – Very Low Birth Weight



## **APPENDIX B BREATHING OUTCOMES STUDY FORMS**

- SUPF00      Enrollment Log**
- SUPF01      NICU Discharge-Baseline Interview**
- SUPF02      6 Month Interview and 12 Month Interview**
- SUPF03      18-22 Month Interview**

**The following pages contain the data forms for the Breathing Outcomes Study.**

## APPENDIX C

### Appendix E - Revised 11-17-05 SAMPLE CONSENT FORMS

#### SAMPLE CONSENT FORM FOR PATIENTS ENROLLED IN SUPPORT

**TITLE:** SUPPORT Trial Breathing Outcomes Study of Infants Enrolled in the NICHD Neonatal Research Network SUPPORT Trial

**PRINCIPAL INVESTIGATOR:** Timothy P. Stevens, MD MPH

**CO-PRINCIPAL INVESTIGATOR:** Dale L. Phelps, MD

#### **INTRODUCTION and BACKGROUND:**

This consent form describes a research study and what you may expect if you decide to have your infant participate. You are encouraged to read this consent form carefully and to ask the person who presents it any questions you may have before making your decision whether or not to have your infant participate.

This form describes the known possible risks and benefits in the study. You are completely free to choose whether to participate.

Your infant is invited to be a part of this research project because (s)he is a premature baby who is a member of the National Institutes for Child Health and Human Development (NICHD) Neonatal Research Network SUPPORT Trial. As described in the SUPPORT Trial Consent that was discussed with you previously, the SUPPORT Trial is designed to find out more about treatment with CPAP (positive pressure applied with a face mask to help keep the lungs inflated) and learn the appropriate levels of oxygen saturation (oxygen levels in the blood) in premature babies. The SUPPORT Study will determine the effect of these treatments on your baby's respiratory and visual health prior to discharge from the Neonatal Intensive Care Unit (NICU).

However, 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.

#### **PURPOSE:**

The purpose of Pulmonary 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 delivery at full term.

#### **PROCEDURES:**

You and your infant's participation will begin with an interview before your infant is discharged from the hospital or at the time of your regular follow-up visit with the NICU Outpatient Clinic. 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. 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 visits (((Customize language here based on which option your center chose for administering the questionnaires))) 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. 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 results from your baby's questionnaire will be combined with other infants from around the country. However, your baby's name will not be used.

**NUMBER OF PARTICIPANTS:**

All babies who participate in the SUPPORT Trial will be offered the opportunity to participate in this study. There will be close to 1300 infants enrolled in the SUPPORT Trial. We hope that as many as possible will choose to participate in this study to help determine the long-term effect of the SUPPORT Study treatments.

**RISKS AND DISCOMFORTS:**

You may experience anxiety or psychological discomfort while completing these questionnaires and/or the interviews. You are free to choose not to answer any question for any reason.

**BENEFITS:**

The major benefit to you and your infant is that actual or potential breathing problems experienced by your baby could be identified early.

**CONFIDENTIALITY OF RECORDS AND HIPAA AUTHORIZATION**

While we will make every effort to keep information we learn about you private, this cannot be guaranteed. Other people may need to see the information. While they normally protect the privacy of the information, they may not be required to do so by law. Results of the research may be presented at meetings or in publications, but your name will never be used.

We will use your child's health information to conduct the study, to monitor your child's respiratory status and to determine long term effects on breathing of the SUPPORT Study treatments. Health information is used to report results of research to sponsors and federal regulators. It may be audited to make sure we are following regulations, policies and study plans. If you have never received a copy of the Strong Health HIPAA Notice, please ask the investigator for one. To meet regulations or for reasons related to this research, the study investigator may share a copy of this consent form and records that identify you with the following people: The Department of Health and Human Services, the University of Rochester, the NICHD Neonatal Research Network and organizations (like RTI International) used by NICHD to manage studies.

If you decide to have your child take part, your Authorization for this study will not expire unless you cancel or revoke it. You can always cancel this Authorization by writing to the study investigator. If you cancel your Authorization, your child will be removed from the study. However, standard medical care and any other benefits to which you are otherwise entitled will not be affected. Canceling your Authorization only affects uses and sharing of information after the study investigator gets your written request. Information gathered before then may need to be used and given to others. For example, non-identifying information gathered during your child's initial hospitalization will be sent to the NICHD Neonatal Research Network and to RTI International.

As stated in the section on Voluntary Participation below, you can also refuse to sign this consent/Authorization and not be part of the study. You can also tell us you want to leave the study at any time without canceling the Authorization. By signing this consent form, you give us permission to use and/or share your health information.

**COSTS:**

There is no cost to you to participate in the study.

**CONTACT PERSONS:**

For more information about this research, or if you believe your infant has suffered a research-related injury, please contact Timothy P. Stevens, MD MPH or Dale L. Phelps, MD (Principal Investigators) at (585) 275-2972. You can also reach them, or one of the other attending physicians, by asking the unit secretary in the NICU to page them.

If you have any questions about your rights as a research subject, you may contact the Human Subjects Protection Specialist at the University of Rochester Research Subjects Review Board at Box 315, 601 Elmwood Avenue, Rochester, NY 14642-8315. Telephone: (585) 276-0005, for long-distance you may call toll-free, (877) 449-4441.

**VOLUNTARY PARTICIPATION:**

Taking part in this study is entirely voluntary. You are free not to participate or to withdraw at any time, for whatever reason, without risking loss of present or future care you would otherwise expect to receive. In the event that you do withdraw from this study, the information you have already provided will be kept in a confidential manner.

**SIGNATURES/ DATES:**

I have read (or have had read to me) the contents of this permission form and have been encouraged to ask questions. I have received answers to my questions. I give permission for my child to participate in this study. I will receive a signed copy of this form for my records and future reference.

\_\_\_\_\_  
Study Subject (Print)

Parent/Guardian Signature

Print Name

Date

**PERSON OBTAINING CONSENT**

I have read this form to the parent/guardian of this subject and/or the parent/guardian of this subject has read this form. An explanation of the research was given and questions from the subject's family were solicited and answered to their satisfaction. In my judgment, the parent/guardian has demonstrated comprehension of the information. I will provide the parent/guardian with signed copy of this consent form.

\_\_\_\_\_  
Signature, person conducting  
Informed Consent

\_\_\_\_\_  
Print Name

\_\_\_\_\_  
Date

## **SAMPLE CONSENT FORM FOR FUTURE SUPPORT PATIENTS**

### **Consent to Act as a Research Subject**

#### **The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants**

#### **The SUPPORT Trial of the NICHD Neonatal Research Network**

Neil Finer, MD, his associates, and the National Institutes for Child Health and Human Development (NICHD) Neonatal Research Network are conducting a research study to find out more about treatment with CPAP (positive pressure applied with a face mask to help keep the lungs inflated) and learn the appropriate levels of oxygen saturation (oxygen levels in the blood) in premature babies. You are being asked 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).

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 (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 caused by excessive levels of oxygen.)

**Duration of the Study:** We expect to include about 1300 babies in the study from all the NICHD Neonatal Research Network hospitals over a two-year period.

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.

If you agree to allow your child to be in this study, the following will happen to your child: 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).

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.

We will continue to stay in touch with you and your infant by telephone or in person at one of your visits (((Customize language here based on which option your center chose for administering the questionnaires))) 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 for treatment of breathing problems. We 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.

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 results from your baby's questionnaire will be combined with other infants from around the country. However, your baby's name will not be used.

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 deems this 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.

There may be benefits to your child directly, including a possible decrease in chronic lung disease (need for extra oxygen near discharge) or wheezing or cough in the first 2 years 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.

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 619-543-6560. You may contact the principal investigator Dr. Neil Finer at 619-543-3794

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 or 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.

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 Coordinating Center at RTI International 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.

You may withdraw your child from the study for any reason. In addition, the study doctors may decide to withdraw your child if they feel it is in his/her best interest to do so. You have received a copy of this consent document to keep and the Experimental Subject's Bill of Rights.

You agree to have your child participate.

---

Parent's or legal guardian's signature DATE

---

Relationship of legal guardian to subject DATE

---

Signature of person explaining and getting consent DATE



## APPENDIX D RELATIONSHIP CODES

The following codes are used to identify the primary caretaker.

- 001 - Mother of Child
- 002 - Father of Child
- 011 - Husband, Significant Other (SO)(if different from 002)
- 012 - Wife, Girlfriend (if different from 001)
- 021 - Maternal grandmother
- 022 - Paternal (SO) grandmother
- 031 - Maternal grandfather
- 032 - Paternal (SO) grandfather
- 041 - Maternal aunt
- 042 - Paternal (SO) aunt
- 051 - Maternal uncle
- 052 - Paternal (SO) uncle
- 061 - Brother
- 062 - Step Brother
- 071 - Sister
- 072 - Step Sister
- 081 - Maternal female cousin
- 082 - Paternal (SO) female cousin
- 091 - Maternal male cousin
- 092 - Paternal (SO) male cousin
- 101 - Other maternal relative
- 102 - Other paternal (SO) relative
- 201 - Foster mother
- 202 - Foster father
- 301 - Adoptive mother
- 302 - Adoptive father
- 401 - Other non-relative
- 402 - Social worker/case worker
- 501 - Staff in congregate care
- 502 - Still hospitalized
- 504 - Unknown

## **APPENDIX E**

### **BREATHING BROCHURE**

**The following pages contain the Breathing Brochure.**

## APPENDIX F CONTACT INFORMATION TEMPLATE

All centers (Option 1 and 2 centers) will track their own patient's telephone and contact information for the purpose of administering telephone questionnaires at 6, 12 and 18-22 months.

The following core set of contact information is recommended for all enrolled patients.

For option 2 centers, use template to fax or email patient contact information to the Rochester site.

Network number: \_\_\_\_\_

Patient Name: First \_\_\_\_\_ Last: \_\_\_\_\_

Nickname: *(If relevant)* \_\_\_\_\_

DOB: \_\_\_ / \_\_\_ / \_\_\_\_\_

Gender:     Male   Female

Name of Prior Interview Respondent (Primary Respondent)

### Primary Respondent Contact Information

Name: \_\_\_\_\_

Relationship to patient: \_\_\_\_\_

Mailing address: \_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

Telephone number #1: \_\_\_\_\_

Telephone number #2: \_\_\_\_\_

Email: \_\_\_\_\_

### Secondary (Backup) Caretaker Information

Name: \_\_\_\_\_

Relationship to patient: \_\_\_\_\_

Mailing address: \_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

Telephone number #1: \_\_\_\_\_

Telephone number #2: \_\_\_\_\_

Email: \_\_\_\_\_

NICU Network	<b>SUPPORT TRIAL</b> Breathing Outcomes Study  <b>ENROLLMENT LOG</b>	SUPP00 Rel 1.0 December 12, 2005
Center No: _____	Site: _____	Page 1 of _____

To be filled out for all infants enrolled in the SUPPORT Trial.

Child's Name Last                  First	Date of Birth Month/Day/Year	Mother's Initials (optional)	Birth No*	Network Number	Follow-up Number	Consent Granted			Comments
						1=Yes	2=No	3=Refused	
	__/__/__					1=Yes	2=No	3=Refused	
	__/__/__					1=Yes	2=No	3=Refused	
	__/__/__					1=Yes	2=No	3=Refused	
	__/__/__					1=Yes	2=No	3=Refused	
	__/__/__					1=Yes	2=No	3=Refused	
	__/__/__					1=Yes	2=No	3=Refused	
	__/__/__					1=Yes	2=No	3=Refused	
	__/__/__					1=Yes	2=No	3=Refused	
	__/__/__					1=Yes	2=No	3=Refused	
	__/__/__					1=Yes	2=No	3=Refused	
	__/__/__					1=Yes	2=No	3=Refused	
	__/__/__					1=Yes	2=No	3=Refused	
	__/__/__					1=Yes	2=No	3=Refused	
	__/__/__					1=Yes	2=No	3=Refused	
	__/__/__					1=Yes	2=No	3=Refused	
	__/__/__					1=Yes	2=No	3=Refused	

\*Leave blank for a single birth; Enter 1, 2, etc for multiple birth Initials of person completing this form. \_\_\_\_\_

NICU Network

SUPPORT TRIAL  
Breathing Outcomes Study  
NICU Discharge-Baseline Interview

SUPF01 Rel 1.0  
December 12, 2005

Center: \_\_\_ Site: \_\_\_ Network No. \_\_\_\_\_ Follow-up No. \_\_\_\_\_ Birth No. \_\_\_ Mother's Initials: \_\_\_\_\_ Page 1 of 5

## NICU Discharge-Baseline Interview

This interview should be administered by trained study staff to the parent/guardian. The target window for this interview is prior to NICU discharge or within the first 30 days following NICU discharge. For patients enrolled in the Pulmonary Outcomes Follow up Study after this target window, this interview should be performed at the time of enrollment.

This interview is for:

\_\_\_\_\_  
(Child's name)

All questions pertain only to his/her health.

**N.B.** Parents or guardians expressing concerns regarding their child's breathing should be advised to discuss them with the family's primary care physician.

### Introduction to the Study:

***Premature babies are more likely than full term babies to have breathing problems after discharge from the NICU. The purpose of this study is to see whether or not the treatment your baby received as part of the SUPPORT Study improves your baby's breathing in the 18-22 months following the baby's due date.***

***As part of this study, we will contact you every 6 months or so to ask you questions about your baby's breathing. The questions will be about your baby's breathing symptoms, especially wheezing and coughing, and about your baby's need for medical visits and treatments for breathing problems.***

***Wheezing can mean different sounds to different people. By wheezing we mean an expiratory sound (a sound that is made when breathing out, not in) that comes from the chest, sometimes described as whistling or musical.***

***We have prepared a brochure for you that describes the study and outlines important characteristics of your baby's breathing, especially breathing problems and treatments.***

### Give brochure

***When we call, we'd like you to gather any notes, medications or other information about your baby's breathing. We will ask questions about how often your baby has wheezing or coughing, whether your baby visited a doctor's office, emergency room or was hospitalized for breathing problems, and whether your baby has needed breathing medicines or treatments. If you wish, you may use the brochure to make notes about your baby's breathing.***

***In order to help us understand your baby's breathing and risk for breathing problems at home, we'd like to ask you a few questions about your home and about whether breathing problems run in the family. As with all information we collect, the answers to these questions will be kept confidential.***

### Interview Outcome

Was the interview conducted?  Yes  No

If No why?  Loss of contact  Interviewee refused  Child died  Other SPECIFY \_\_\_\_\_

Initials of person completing this form. \_\_\_\_\_

NICU Network

SUPPORT TRIAL  
Breathing Outcomes Study  
NICU Discharge-Baseline Interview

SUPF01 Rel 1.0  
December 12, 2005

Center: \_\_\_ Site: \_\_\_ Network No. \_\_\_\_\_ Follow-up No. \_\_\_\_\_ Birth No. \_\_\_ Mother's Initials: \_\_\_\_\_ Page 2 of 5

1. Child's Name \_\_\_\_\_  
(first) (last)

2. Today's Date: |\_\_| |\_\_| - |\_\_| |\_\_| - |\_\_| |\_\_| |\_\_| |\_\_|  
mm dd yyyy

3. Child's Sex: 1  Male 2  Female

4. Child's Birthdate: |\_\_| |\_\_| - |\_\_| |\_\_| - |\_\_| |\_\_| |\_\_| |\_\_|  
mm dd yyyy

Enter name and relationship code of the person being interviewed.

5a. Name: \_\_\_\_\_

5b. Relationship Code: |\_\_| |\_\_| |\_\_| |\_\_|

<p>001 - Mother of Child  002 - Father of Child  301 - Adoptive mother  302 - Adoptive father</p> <p>Other: _____  <i>Common codes are listed here. For other relationships, please look up relationship code from Appendix D of the Breathing Outcomes Manual of Operations and enter above.</i></p>
---

6. Type of Interview: 1  Face to Face 2  Telephone

**At this time, we would like a little information about the environment in which your new child will grow up.**

7. First, how many people normally live with you in your home for at least 6 months of the year?

Total household members: |\_\_| |\_\_|

8. After the first few months, will your child be sharing a room with other family members on a regular basis?  
1  Yes 2  No

8a. IF YES: How many other people will sleep in the same room with him/her? |\_\_| |\_\_|

9. How many rooms are there in your house, excluding closets and bathrooms? |\_\_| |\_\_|

10. Do you have any pets inside the home? 1  Yes 2  No Skip to Question 11

If YES, how many.....

10a. check and record number: 1  Dogs in the home? |\_\_| |\_\_|  
2  Cats in the home? |\_\_| |\_\_|  
3  Other pets are in the home? |\_\_| |\_\_| SPECIFY: \_\_\_\_\_

11. Does your home or apartment have air conditioning or some kind of cooling where the baby will sleep at night?

1  Yes 2  No Skip to Question 12

If YES,

11a. Air Conditioning? 1  Yes 2  No  
11b. Evaporative Cooling? 1  Yes 2  No  
(Desert Southwest)  
11c. Other? 1  Yes 2  No If YES, SPECIFY \_\_\_\_\_

12. How is your home heated? (IF MORE THAN ONE, PLEASE CHECK ALL THAT APPLY).

- 1  Steam or hot water (radiator)
- 2  Central gas furnace (furnace)
- 3  Electric
- 4  Wood Stove
- 5  Other SPECIFY: \_\_\_\_\_
- 6  Don't Know

13. What one fuel is used *most* for cooking in your home?

- 1  Electricity
- 2  Gas
- 3  Fuel Oil
- 4  Wood Stove
- 5  Other SPECIFY: \_\_\_\_\_
- 6  Don't Know

**The next questions are about your baby's diet.**

14. Is your child receiving: (READ ALL CHOICES)

- 1  Only breast milk
- 2  Only formula (Skip to Question 15)
- 3  Both breast milk and formula (Skip to Question 15)
- 4  Other SPECIFY: \_\_\_\_\_ (Skip to Question 15)

**If answer to 14 is 1 (only breast milk)**

14a. Will this be supplemented with formula in the first 6 months?

- 1  Yes
- 2  No
- 3  Don't Know

14b. If yes, when will supplements begin? \_\_\_\_\_ months

15. Does the mother (you) plan to work outside the home within the next year?

- 1  Yes
- 2  No
- 3  Don't Know

**The next questions are about smoke exposure.**

16. Which one of the following 3 statements best describes the situation regarding smoking in your child's **home**? Read all options to the interviewee before recording a response.

- 1  Smoking is allowed in any common room of the home
- 2  Smoking is limited to part of the house where the child rarely goes
- 3  There is no smoking inside at all → 16a. Are there any exceptions to this situation?

- 1  Yes
- 2  No (Skip to Question 17)

16b. Under what circumstances are the exceptions allowed? SPECIFY:

\_\_\_\_\_

NICU Network	SUPPORT TRIAL	SUPF01 Rel 1.0
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17. Which one of the following 5 statements best describes the situation regarding smoking in your car? *Read all options to the interviewee before recording a response.*

- 1  Do not have a car
- 2  Smoking is usually or always allowed
- 3  Smoking is sometimes allowed
- 4  Smoking occurs in the car only when the child is not inside
- 5  There is no smoking inside the car → 17a. Are there any exceptions to this situation?  
1  Yes                      2  No (*Skip to Question 18*)

17b. Under what circumstances are the exceptions allowed? SPECIFY:  
\_\_\_\_\_

18. How often has the baby's mother or primary caretaker (you) smoked since your child was born?

- 1  Never                      2  Occasionally                      3  Daily

19. Altogether, how many people who live in the child's home smoke?   people

***In the next section, we'd like to know what breathing and allergy problems run in the family. Administer attached Family History Questionnaire using the following script:***

Mother or guardian:

***We'll start with the baby's mother. How old is the baby's biologic mother? Does she have bronchitis, emphysema, COPD, bronchiectasis, asthma, inhaled allergies, or food allergies?***

***Does the baby's mother have any other chronic respiratory illness?***

***How often does this person smoke in the baby's home?***

Father

***For the baby's biologic father, is he living? How old is he? Does he have bronchitis, emphysema, COPD, bronchiectasis, asthma, inhaled allergies, or food allergies?***

***Does he have any other chronic respiratory illness?***

***How often does he smoke in the baby's home?***

Complete the remainder of the table by collecting the same medical history using the scripting above.

20. Finally, which friend or relative is most likely to be able to contact you 6 months from now in case we lose contact with you?

_____	_____
Name	Relationship
_____	
Address	
_____	
Telephone	
_____	
Cell Phone	
_____	
Email	

***Thank you for your help in providing us with this important information, and for your continued participation in the Breathing Outcomes Study.***



**NICU Discharge-Baseline Interview  
Family History Questionnaire**

	<b>Mother</b>	<b>Father</b>	<b>Maternal Grandmother</b>	<b>Maternal Grandfather</b>	<b>Paternal Grandmother</b>	<b>Paternal Grandfather</b>
1. Relationship to enrolled child:						
2. Living?	1.Yes 2.No 3.DK	1.Yes 2.No 3.DK	1.Yes 2.No 3.DK	1.Yes 2.No 3.DK	1.Yes 2.No 3.DK	1.Yes 2.No 3.DK
3. Age (in years):	_____	_____	_____	_____	_____	_____
4. Does this person have:						
a. COPD	1.Yes 2.No 3.DK	1.Yes 2.No 3.DK	1.Yes 2.No 3.DK	1.Yes 2.No 3.DK	1.Yes 2.No 3.DK	1.Yes 2.No 3.DK
b. Chronic Bronchitis?	1.Yes 2.No 3.DK	1.Yes 2.No 3.DK	1.Yes 2.No 3.DK	1.Yes 2.No 3.DK	1.Yes 2.No 3.DK	1.Yes 2.No 3.DK
c. Emphysema?	1.Yes 2.No 3.DK	1.Yes 2.No 3.DK	1.Yes 2.No 3.DK	1.Yes 2.No 3.DK	1.Yes 2.No 3.DK	1.Yes 2.No 3.DK
d. Bronchiectasis?	1.Yes 2.No 3.DK	1.Yes 2.No 3.DK	1.Yes 2.No 3.DK	1.Yes 2.No 3.DK	1.Yes 2.No 3.DK	1.Yes 2.No 3.DK
e. Asthma?	1.Yes 2.No 3.DK	1.Yes 2.No 3.DK	1.Yes 2.No 3.DK	1.Yes 2.No 3.DK	1.Yes 2.No 3.DK	1.Yes 2.No 3.DK
f. Inhaled Allergies?	1.Yes 2.No 3.DK	1.Yes 2.No 3.DK	1.Yes 2.No 3.DK	1.Yes 2.No 3.DK	1.Yes 2.No 3.DK	1.Yes 2.No 3.DK
g. Food Allergies?	1.Yes 2.No 3.DK	1.Yes 2.No 3.DK	1.Yes 2.No 3.DK	1.Yes 2.No 3.DK	1.Yes 2.No 3.DK	1.Yes 2.No 3.DK
h. Any other chronic respiratory disease? (SPECIFY)	1.Yes 2.No 3.DK _____	1.Yes 2.No 3.DK _____	1.Yes 2.No 3.DK _____	1.Yes 2.No 3.DK _____	1.Yes 2.No 3.DK _____	1.Yes 2.No 3.DK _____
5. How often does this person smoke in the baby's home*?	1. Never 2. Rarely 3. Sometimes 4. Frequently 5. DK	1. Never 2. Rarely 3. Sometimes 4. Frequently 5. DK	1. Never 2. Rarely 3. Sometimes 4. Frequently 5. DK	1. Never 2. Rarely 3. Sometimes 4. Frequently 5. DK	1. Never 2. Rarely 3. Sometimes 4. Frequently 5. DK	1. Never 2. Rarely 3. Sometimes 4. Frequently 5. DK

**\*Never = never; rarely = less than once per month; sometimes = once per month but less than once /week; frequently = once per week or greater; DK = Don't Know**

NICU Network  
 SUPPORT TRIAL  
 Breathing Outcomes Study  
 NICU Discharge-Baseline Interview

Center: \_\_\_\_\_ Site: \_\_\_\_\_ Network No. \_\_\_\_\_ Follow-up No. \_\_\_\_\_ Birth No. \_\_\_\_\_ Mother's Initials \_\_\_\_\_

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	Breathing Outcomes Study				April 17, 2006	
	6 and 12 Month Interview					
Center:	Site:	Network No.	Follow-up No.	Birth No.	Mother's Initials:	Page 1 of 8

## Administered At 6 And 12 Months Corrected Age

This interview should be administered by a trained study interviewer for:

\_\_\_\_\_  
(Child's name)

All questions pertain only to his/her health.

The parent or care giver, who completed the initial interview, should complete this survey and all future surveys. The interviewer will need to ask for that parent (see Manual of Operations).

### Introduction Script:

**When parent or primary care giver is on phone:**

*Hello, my name is <your name>. I am calling from the <NICHD Center>. As you probably remember, when you were in the NICU you enrolled in our study about respiratory health of premature infants. I am calling to ask you some questions about your baby's breathing. It will take about 10-20 minutes to complete. Is this a good time for you?*

*As with all information we collect, the answers to these questions will be kept confidential.*

*Before we begin this interview, it would be helpful if you could gather any notes you have about your baby's breathing as well as any medications your child has been prescribed or has been taking and have them in front of you. As with all information we collect, the answers to these questions will be kept confidential.*

### Interview Outcome

Was the interview conducted?  Yes  No

If No why?  Loss of contact  Interviewee refused  Child died  Other SPECIFY \_\_\_\_\_

Initials of person completing this form. \_\_\_\_\_

Type of Interview  6 Month  12 Month



NICU Network

SUPPORT TRIAL  
Breathing Outcomes Study  
6 and 12 Month Interview

SUPF02 Rel 1.1  
April 17, 2006

Center: \_\_\_\_\_ Site: \_\_\_\_\_ Network No. \_\_\_\_\_ Follow-up No. \_\_\_\_\_ Birth No. \_\_\_\_\_ Mother's Initials: \_\_\_\_\_ Page 3 of 8

3. Type of Interview: 1  Face to Face 2  Telephone

4. Location of Interviewer: 1  Local Center (Option 1) 2  Rochester (Option 2)

**Instructions:**

Parents or guardians expressing concerns regarding their child's breathing should be advised to discuss them with the family's primary care physician.

Where the phrase "last contact" is used below, please substitute with the most specific relevant time prompt, e.g. for the 6 month interview, refer to "since NICU discharge"; for the 12 month interview, refer to "over the past 6 months", etc.

*Interview begins:*

**Some of these questions will be familiar to you. Since we last spoke (\_\_\_\_) months ago on (\_\_\_\_/\_\_\_\_/\_\_\_\_) we want to learn what changes, if any, there have been to your child's health. We are especially interested in any breathing problems your child may have.**

5. Has the child been with you during the past 6 months? 1  Yes 2  No

**Since our last contact with you about your child.....**

6. How many times has your child visited a doctor's office? |\_\_|\_\_| times

6a. How many of these times were because of wheezing or breathing problems? |\_\_|\_\_| times

**Since our last contact with you about your child.....**

7. How many times has your child visited an Emergency Department (Emergency room)? |\_\_|\_\_| times

7a. How many of these times were because of wheezing or breathing problems? |\_\_|\_\_| times

**Since our last contact with you about your child.....**

8. How many times has your child stayed in the hospital for one or more nights in a row? |\_\_|\_\_| times

8a. How many of these times were because of wheezing or breathing problems? |\_\_|\_\_| times

**The next questions are about your baby's breathing.**

**The first question is about wheezing. By wheezing we mean an expiratory sound (a sound that is made when breathing out, not in) that comes from the chest, sometimes described as whistling or musical.**

9. Since our last contact with you, has your baby's chest sounded wheezy or whistling?

- 1  Yes      2  No      3  Don't Know      Ask Question 9a for all responses

9a. "Has your baby's breathing sounded like this?" (play audio clip of wheezing).

- 1  Yes      2  No      3  Don't Know

IF YES TO QUESTION 9 or 9a:

9b. Has this occurred with colds?

- 1  Yes  
2  No  
3  Sometimes

9c. Has your child's chest sounded wheezy or whistling apart from colds?

- 1  Yes  
2  No

9d. During what month did your child's chest first sound wheezy or whistling?

\_\_\_\_ months (enter calendar month, Jan = 01; Feb = 02); \_\_\_\_ Year

9e. Since our last contact with you, **on average**, how often has your child's chest sounded wheezy or whistling during:

**The Daytime? Would you say...(e.1)**

- 1  Never  
2  Twice a week or less  
3  More than two times a week, but not every day  
4  Everyday, but *not* all the time  
5  Everyday, all the time

**The Nighttime? Would you say...(e.2)**

- 1  Never  
2  Once every two weeks or less  
3  Once a week  
4  Two or three times a week  
5  More than three nights a week/Frequently

9f. Since our last contact with you, **during the worst 2 week period**, how often has your child's chest sounded wheezy or whistling during:

**The Daytime? Would you say...(f.1)**

- 1  Never  
2  Twice a week or less  
3  More than two times a week, but not every day  
4  Everyday, but *not* all the time  
5  Everyday, all the time

**The Nighttime? Would you say...(f.2)**

- 1  Never  
2  Once every two weeks or less  
3  Once a week  
4  Two or three times a week  
5  More than three nights a week/Frequently

9g. Since our last contact with you, has your child been diagnosed with wheezing by a doctor?

- 1  Yes  
2  No

**IF YES, BE SURE TO COMPLETE QUESTION 27**

10. Since our last contact with you, has your child had a cough for more than 3 days when he/she did not have a cold?  
1  Yes      2  No *If NO, skip to Question 11*

IF YES TO QUESTION 10

10a. At what time of the day has this cough usually occurred?  
(CHECK ALL THAT APPLY)      1  In the morning, shortly after rising  
2  Later in the day  
3  During the night  
4  No relation to time of day

10b. Has he/she coughed on most days for as much as 2 to 3 months?  
1  Yes  
2  No

10c. During what month and year did your child first develop the cough?  
    |\_|\_| months (enter calendar month, Jan = 01; Feb = 02);      |\_|\_| Year

10d. Has your child's chest ever sounded wheezy or whistling with episodes of coughing?  
1  Yes  
2  No

10e. Since our last contact with you, **on average**, how often has your child had coughing during:  
The Daytime? Would you say... (e.1)      The Nighttime? Would you say... (e.2)

1 <input type="checkbox"/> Never	1 <input type="checkbox"/> Never
2 <input type="checkbox"/> Twice a week or less	2 <input type="checkbox"/> Once every two weeks or less
3 <input type="checkbox"/> More than two times a week, but not every day	3 <input type="checkbox"/> Once a week
4 <input type="checkbox"/> Everyday, but <i>not</i> all the time	4 <input type="checkbox"/> Two or three times a week
5 <input type="checkbox"/> Everyday, all the time	5 <input type="checkbox"/> More than three nights a week/Frequently

10f. Since our last contact with you, **during the worst 2-week period**, how often has your child had coughing?  
The Daytime? Would you say... (f.1)      The Nighttime? Would you say... (f.2)

1 <input type="checkbox"/> Never	1 <input type="checkbox"/> Never
2 <input type="checkbox"/> Twice a week or less	2 <input type="checkbox"/> Once every two weeks or less
3 <input type="checkbox"/> More than two times a week, but not every day	3 <input type="checkbox"/> Once a week
4 <input type="checkbox"/> Everyday, but <i>not</i> all the time	4 <input type="checkbox"/> Two or three times a week
5 <input type="checkbox"/> Everyday, all the time	5 <input type="checkbox"/> More than three nights a week/Frequently

11. Since our last contact with you, **on average**, how many **days per month** did you have to change your daytime or evening plans because of your child's breathing problems:  
1  None, we never had to change plans  
2  More than none but less than 3 days  
3  3-6 days  
4  7 or more days

12. Since our last contact with you, **during the worst 2 week period**, how many **days** did you have to change your daytime or evening plans because of your child's breathing problems:  
1  None, we never had to change plans  
2  More than none but less than 3 days  
3  3-6 days  
4  7 or more days

13. Since our last contact with you, has your child had asthma, reactive airways disease or a BPD\* flare-up diagnosed by a doctor?    1  Yes    2  No  
\*See Manual for explanation

14. Since our last contact with you, has your child had bronchiolitis, bronchitis, or pneumonia diagnosed by a doctor?  
1  Yes 2  No
15. Since our last contact with you, has your child had croup diagnosed by a doctor?  
1  Yes 2  No

**The next questions are about your baby's diet.**

16. Since our last contact with you, did your baby receive breast milk, either at breast, from a bottle or through a tube?  
1  Yes 2  No If NO, skip to Question 17

If yes to Question 16:

- 16a. For how many months did your child receive breast milk feedings?  
Would you say... 1  Less than 1 month  
2  1-3 months  
3  4-6 months
- 16b. For how many months did your child receive breast milk for more than half of his/her feedings?  
Would you say... 1  Less than 1 month  
2  1-3 months  
3  4-6 months

**The next questions are about smoke exposure.**

17. Which one of the following 3 statements best describes the situation regarding smoking in your child's **home**? Read all options to the interviewee before recording a response.
- 1  Smoking is allowed in any common room of the home  
2  Smoking is limited to part of the house where the child rarely goes  
3  There is no smoking inside at all → 17a. Are there any exceptions to this situation?  
1  Yes 2  No (Skip to Question 18)
- 17b. Under what circumstances are the exceptions allowed? SPECIFY:  
\_\_\_\_\_

18. Which one of the following 5 statements best describe the situation regarding smoking in your **car**? Read all options to the interviewee before recording a response.
- 1  Do not have a car  
2  Smoking is usually or always allowed  
3  Smoking is sometimes allowed  
4  Smoking occurs in the car only when the child is not inside  
5  There is no smoking inside the car → 18a. Are there any exceptions to this situation?  
1  Yes 2  No (Skip to Question 19)
- 18b. Under what circumstances are the exceptions allowed? SPECIFY:  
\_\_\_\_\_

19. How often has the **mother or primary care giver** smoked since your child was born?  
1  Never 2  Occasionally 3  Daily

20. How many people in the child's home smoke? |\_\_|\_\_| people

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**The next questions are about your home and your babysitter's home or day care.**

21. Approximately how many hours per week does your child spend at a babysitter's home or day care?

\_\_\_\_ hrs If 0, skip to Question 22

IF 21 is greater than 0:

21a. How frequent is there smoke exposure at the babysitter or daycare?

1  Never    2  Occasionally    3  Daily    4  Don't Know

21b. How many children beside your baby are in the daycare? \_\_\_\_\_ children

22. How many children under 12 live in your house? \_\_\_\_\_ children (including the baby)

23. Do you have any pets inside the home?    1  Yes    2  No    Skip to Question 24

23a. If YES, how many pets are there inside the home?

Check all that apply and record number: 1  Dogs \_\_\_\_\_

2  Cats \_\_\_\_\_

3  Other \_\_\_\_\_ SPECIFY: \_\_\_\_\_

**The last questions involve respiratory treatments that your baby may receive.**

**PROPHYLAXIS**

24. Has your child had RSV shots to prevent Respiratory Syncytial Virus (Synagis, palivizumab, RSV shot)?

1  Yes    2  No    3  Don't Know

25. Has your child had a flu shot?    1  Yes    2  No    3  Don't Know

**OXYGEN**

26. Since our last contact with you, has your child received oxygen therapy at home?

1  Yes    2  No    Skip to Question 27

If yes to Questions 26

26a. Is your child currently on any oxygen therapy at home?

1  Yes    2  No    Skip to Question 27

If yes, indicate Yes or No for each

\*lpm = liters per minute

26b. Oxygen cannula    1  Yes    2  No    FiO2 \_\_\_\_\_    lpm\* \_\_\_\_\_

26c. Oxygen hood    1  Yes    2  No    FiO2 \_\_\_\_\_    lpm\* \_\_\_\_\_

26d. Ventilator    1  Yes    2  No    FiO2 \_\_\_\_\_    lpm\* \_\_\_\_\_



NICU Network	<b>SUPPORT TRIAL</b> <b>Breathing Outcomes Study</b> <b>6 and 12 Month Interview</b>	<b>SUPF02 Rel 1.1</b> <b>April 17, 2006</b>
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**MEDICATIONS** (Enter responses in table. Do not prompt for each medication in the Medication Code List below.)

**The last two questions involve the medicines your child is taking for breathing problems.**

27. Since our last contact with you, what medicines has your baby taken, including medicines delivered by a nebulizer or breathing machine at home?	27a.  Code	27b. Does he/she take that medicine everyday, sometimes or only when sick? (repeat for each medication)
1		1 <input type="checkbox"/> Everyday    2 <input type="checkbox"/> Sometimes    3 <input type="checkbox"/> Only when Sick
2		1 <input type="checkbox"/> Everyday    2 <input type="checkbox"/> Sometimes    3 <input type="checkbox"/> Only when Sick
3		1 <input type="checkbox"/> Everyday    2 <input type="checkbox"/> Sometimes    3 <input type="checkbox"/> Only when Sick
4		1 <input type="checkbox"/> Everyday    2 <input type="checkbox"/> Sometimes    3 <input type="checkbox"/> Only when Sick
5		1 <input type="checkbox"/> Everyday    2 <input type="checkbox"/> Sometimes    3 <input type="checkbox"/> Only when Sick
6		1 <input type="checkbox"/> Everyday    2 <input type="checkbox"/> Sometimes    3 <input type="checkbox"/> Only when Sick
7		1 <input type="checkbox"/> Everyday    2 <input type="checkbox"/> Sometimes    3 <input type="checkbox"/> Only when Sick

**Medication Code List:**

<p><i>Rescue medicines:</i></p> <ul style="list-style-type: none"> <li>1 Albuterol</li> <li>2 Proventil</li> <li>3 Serevent</li> <li>4 Ventolin</li> <li>5 Volmax</li> <li>6 Xopenex</li> </ul> <p><i>Other Inhaled medications:</i></p> <ul style="list-style-type: none"> <li>7 Cromolyn (Intal)</li> <li>8 Nedocromil (Tilade)</li> </ul> <p><i>Inhaled steroids:</i></p> <ul style="list-style-type: none"> <li>9 Advair</li> <li>10 Aerobid</li> <li>11 Azmacort</li> <li>12 Beclovent</li> <li>13 Flovent</li> <li>14 Vanceril</li> <li>15 Pulmicort</li> </ul>	<p><i>Systemic steroids:</i></p> <ul style="list-style-type: none"> <li>16 Decadron</li> <li>17 Prednisone</li> <li>18 Prednisolone</li> </ul> <p><i>Leukotriene blocker:</i></p> <ul style="list-style-type: none"> <li>19 Accolate</li> <li>20 Singulair</li> </ul> <p><i>Methylxanthines:</i></p> <ul style="list-style-type: none"> <li>21 Theophylline</li> </ul> <p><i>Diuretic medications:</i></p> <ul style="list-style-type: none"> <li>22 Diuril</li> <li>23 Lasix</li> <li>24 Aldactizide</li> <li>25 Aldactone</li> </ul> <p><i>Miscellaneous / Non-specific</i></p> <ul style="list-style-type: none"> <li>26 Nebulizer</li> <li>27 Other _____</li> </ul>
---	--

**Thank you for your cooperation in providing us with this important information, and for your continued participation in the Breathing Outcomes Study.**

NICU Network

SUPPORT TRIAL  
Breathing Outcomes Study  
18-22 Month Interview

SUPF03 Rel 1.1  
April 10, 2007

Center: \_\_\_\_\_ Site: \_\_\_\_\_ Network No. \_\_\_\_\_ Follow-up No. \_\_\_\_\_ Birth No. \_\_\_\_\_ Mother's Initials: \_\_\_\_\_ Page 1 of 10

## Administered At 18-22 Months Corrected Age

This interview should be administered by a trained study interviewer. The target window for this interview is between 18-22 months' corrected age.

\_\_\_\_\_  
(Child's name)

All questions pertain only to his/her health.

### Introduction Script:

When parent or primary care giver is on phone:

*Hello, my name is <your name>. I am calling from the <NICHD Center>. As you probably remember, when you were in the NICU you enrolled in our study about respiratory health of premature infants. I am calling to ask you some questions about your baby's breathing. It will take about 10-20 minutes to complete. Is this a good time for you?*

*As with all information we collect, the answers to these questions will be kept confidential.*

*Before we begin this interview, it would be helpful if you could gather any notes you have about your baby's breathing as well as any medications your child has been prescribed or has been taking and have them in front of you.*

### Interview Outcome

Was the interview conducted? 1• Yes 2• No

If No why? 1• Loss of contact 2• Interviewee refused 3• Child died 4• Other SPECIFY \_\_\_\_\_

Initials of person completing this form. \_\_\_\_\_



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Center: _____	Site: _____	Network No. _____	Follow-up No. _____	Birth No. _____	Mother's Initials: _____	Page 3 of 10

Enter name and relationship code of the person being interviewed\*:

2a. Name: \_\_\_\_\_ 2b. Relationship Code: [ ] [ ] [ ] [ ]

001 - Mother of Child 002 - Father of Child 301 - Adoptive mother 302 - Adoptive father  Other: _____ <i>Common codes are listed here for other relationships, please look up relationship code from Appendix D of the Breathing Outcomes Manual of Operations and enter above.</i>
---

3. Type of Interview: 1• Face to Face 2• Telephone

4. Location of Interviewer: 1• Local Center (Option 1) 2• Rochester (Option 2)

Instructions:

Parents or guardians expressing concerns regarding their child's breathing should be advised to discuss them with the family's primary care physician.

Where the phrase "last contact" is used below, please substitute with the most specific relevant time prompt, e.g. for the 18-22 month interview, refer to "over the past 6 months", etc.

*Interview begins:*

**Some of these questions will be familiar to you. Since we last spoke (\_\_\_) months ago on (\_\_\_/\_\_\_/\_\_\_) we want to learn what changes, if any, there have been to your child's health. We are especially interested in any breathing problems your child may have.**

5. Has the child been with you over the past 6 months? 1• Yes 2• No

**Since our last contact with you about your child...**

6. How many times has your child visited a doctor's office? [ ] [ ] times

6a. How many of these times were because of wheezing or breathing problems? [ ] [ ] times

**Since our last contact with you about your child...**

7. How many times has your child visited an Emergency Department (Emergency room)? [ ] [ ] times

7a. How many of these times were because of wheezing or breathing problems? [ ] [ ] times

**Since our last contact with you about your child...**

8. How many times has your child stayed in the hospital one or more nights in a row? [ ] [ ] times

8a. How many of these times were because of wheezing or breathing problems? [ ] [ ] times

**The next questions are about your baby's breathing.**

**The first question is about wheezing. By wheezing we mean an expiratory sound (a sound that is made when breathing out, not in) that comes from the chest, sometimes described as whistling or musical.**

9. Since our last contact with you, has your baby's chest sounded wheezy or whistling?

- 1• Yes      2• No      3• Don't Know      *Ask Question 9a for all responses*

9a. "Has your baby's breathing sounded like this?" (**play audio clip of wheezing**).

- 1• Yes      2• No      3• Don't Know

IF YES TO QUESTION 9 or 9a:

9b. Has this occurred with colds?

- 1• Yes  
2• No  
3• Sometimes

9c. Has your child's chest sounded wheezy or whistling apart from colds?

- 1• Yes  
2• No

9d. During what month and year did your child's chest first sound wheezy or whistling?

\_\_\_\_|\_\_\_\_| months (enter calendar month, Jan = 01; Feb = 02);      \_\_\_\_|\_\_\_\_| Year

9e. Since our last contact with you, **on average**, how often has your child's chest sounded wheezy or whistling during:

**The Daytime? Would you say...(e.1)**

- 1  Never  
2  Twice a week or less  
3  More than two times a week, but not every day  
4  Everyday, but *not* all the time  
5  Everyday, all the time

**The Nighttime? Would you say...(e.2)**

- 1  Never  
2  Once every two weeks or less  
3  Once a week  
4  Two or three times a week  
5  More than three nights a week/Frequently

9f. Since our last contact with you, **during the worst 2 week period**, how often has your child's chest sounded wheezy or whistling during:

**The Daytime? Would you say...(f.1)**

- 1  Never  
2  Twice a week or less  
3  More than two times a week, but not every day  
4  Everyday, but *not* all the time  
5  Everyday, all the time

**The Nighttime? Would you say...(f.2)**

- 1  Never  
2  Once every two weeks or less  
3  Once a week  
4  Two or three times a week  
5  More than three nights a week/Frequently

9g. Since our last contact with you, has your been diagnosed with wheezing by a doctor?

- 1• Yes  
2• No

10. Since our last contact with you, has your child had a cough for more than 3 days when he/she did not have a cold?

- 1• Yes      2• No      Skip to Question 11

IF YES TO QUESTION 10

10a. At what time of the day has this cough usually occurred?  
(CHECK ALL THAT APPLY)

- 1• In the morning, shortly after rising
- 2• Later in the day
- 3• During the night
- 4• No relation to time of day

10b. Has he/she coughed on most days for as much as 2 to 3 months?

- 1• Yes
- 2• No

10c. During what month and year did your child first develop the cough?

    |\_|\_| months (enter calendar month, Jan = 01; Feb = 02);      |\_|\_| Year

10d. Has your child's chest ever sounded wheezy or whistling with episodes of coughing?

- 1• Yes
- 2• No

10e. Since our last contact with you, **on average**, how often has your child had coughing during:

<u><b>The Daytime? Would you say... (e.1)</b></u>	<u><b>The Nighttime? Would you say...(e.2)</b></u>
1 <input type="checkbox"/> Never	1 <input type="checkbox"/> Never
2 <input type="checkbox"/> Twice a week or less	2 <input type="checkbox"/> Once every two weeks or less
3 <input type="checkbox"/> More than two times a week, but not every day	3 <input type="checkbox"/> Once a week
4 <input type="checkbox"/> Everyday, but <i>not</i> all the time	4 <input type="checkbox"/> Two or three times a week
5 <input type="checkbox"/> Everyday, all the time	5 <input type="checkbox"/> More than three nights a week/Frequently

10f. Since our last contact with you, **during the worst 2-week period**, how often has your child had coughing?

<u><b>The Daytime? Would you say... (f.1)</b></u>	<u><b>The Nighttime? Would you say...(f.2)</b></u>
1 <input type="checkbox"/> Never	1 <input type="checkbox"/> Never
2 <input type="checkbox"/> Twice a week or less	2 <input type="checkbox"/> Once every two weeks or less
3 <input type="checkbox"/> More than two times a week, but not every day	3 <input type="checkbox"/> Once a week
4 <input type="checkbox"/> Everyday, but <i>not</i> all the time	4 <input type="checkbox"/> Two or three nights a week
5 <input type="checkbox"/> Everyday, all the time	5 <input type="checkbox"/> More than three nights a week/Frequently

11. Since our last contact with you, **on average**, how many **days per month** did you have to change your daytime or evening plans because of your child's breathing problems:

- 1  None, we never had to change plans
- 2  More than none but less than 3 days
- 3  3-6 days
- 4  7 or more days

12. Since our last contact with you, **during the worst 2 week period**, how many **days** did you have to change your daytime or evening plans because of your child's breathing problems:

- 1  None, we never had to change plans
- 2  More than none but less than 3 days
- 3  3-6 days
- 4  7 or more days

13. Since our last contact with you, has your child had asthma, reactive airways disease or a BPD\* flare-up diagnosed by a doctor?    1• Yes    2• No

\*See Manual for explanation

NICU Network

SUPPORT TRIAL  
Breathing Outcomes Study  
18-22 Month Interview

SUPF03 Rel 1.1  
April 10, 2007

Center: \_\_\_\_\_ Site: \_\_\_\_\_ Network No. \_\_\_\_\_ Follow-up No. \_\_\_\_\_ Birth No. \_\_\_\_\_ Mother's Initials: \_\_\_\_\_ Page 6 of 10

14. Since our last contact with you, has your child had bronchiolitis, bronchitis, or pneumonia diagnosed by a doctor?  
1• Yes 2• No
15. Since our last contact with you, has your child had croup diagnosed by a doctor?  
1• Yes 2• No

**The next question are about your baby's diet.**

16. Since our last contact with you, did your baby receive mother's breast milk, either at breast, from a bottle or through a tube?  
1• Yes 2• No *If NO, skip to Question 17*

If yes to Question 16:

16a. For how many months did your child receive breast milk feedings?

- Would you say... 1• Less than 1 month  
2• 1-3 months  
3• 4-6 months

16b. For how many months did your child receive breast milk for more than half of his/her feedings?

- Would you say... 1• Less than 1 month  
2• 1-3 months  
3• 4-6 months

**The next questions are about smoke exposure.**

17. Which one of the following 3 statements best describes the situation regarding smoking in your child's **home**? *Read all options to the interviewee before recording a response.*

- 1  Smoking is allowed in any common room of the home  
2  Smoking is limited to part of the house where the child rarely goes  
3  There is no smoking inside at all → 17a. Are there any exceptions to this situation?

1• Yes 2• No (*Skip to Question 18*)

17b. Under what circumstances are the exceptions allowed? SPECIFY:  
\_\_\_\_\_

18. Which one of the following 5 statements best describes the situation regarding smoking in your **car**? *Read all options to the interviewee before recording a response.*

- 1  Do not have a car  
2  Smoking is usually or always allowed  
3  Smoking is sometimes allowed  
4  Smoking occurs in the car only when the child is not inside  
5  There is no smoking inside the car → 18a. Are there any exceptions to this situation?

1• Yes 2• No (*Skip to Question 19*)

18b. Under what circumstances are the exceptions allowed? SPECIFY:  
\_\_\_\_\_

19. How often has the **mother or primary care giver** smoked since your child was born?

1• Never 2• Occasionally 3• Daily

20. How many people in the child's home smoke?    people

**The next questions are about your home and your babysitter's home or day care.**

21. Approximately how many hours per week does your child spend at a babysitter's home or day care?

\_\_\_\_ hrs If 0 skip to question 22

IF 21 is greater than 0: \_\_\_\_\_

21a. How frequent is there smoke exposure at the babysitter or daycare?

1• Never 2• Occasionally 3• Daily 4• Don't Know

21b. How many children beside your baby are in the daycare? \_\_\_\_\_ children

22. How many children under 12 live in your house? \_\_\_\_\_ children

23. Do you have any pets inside the home? 1• Yes 2• No Skip to Question 24

23a. If YES, how many pets are there inside the home?

Check all that apply and record number: 1• Dogs \_\_\_\_\_

2• Cats \_\_\_\_\_

3• Other \_\_\_\_\_ SPECIFY: \_\_\_\_\_

**The last questions involve respiratory treatments that your baby may receive.**

**PROPHYLAXIS**

24. Has your child had RSV shots to prevent Respiratory Syncytial Virus (Synagis, palivizumab RSV, shot)?

1• Yes 2• No 3• Don't Know

25. Has your child had a flu shot? 1• Yes 2• No 3• Don't Know

**OXYGEN**

26. Since our last contact with you, has your child received oxygen therapy at home?

1• Yes 2• No Skip to Question 27

If yes to Questions 26 \_\_\_\_\_

26a. Is your child currently on any oxygen therapy at home?

1• Yes 2• No Skip to Question 27

If yes, indicate Yes or No for each

\*lpm = liters per minute

26b. Oxygen cannula 1• Yes 2• No FiO2 \_\_\_\_\_ lpm\* \_\_\_\_\_

26c. Oxygen hood 1• Yes 2• No FiO2 \_\_\_\_\_ lpm\* \_\_\_\_\_

26d. Ventilator 1• Yes 2• No FiO2 \_\_\_\_\_ lpm\* \_\_\_\_\_



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**MEDICATIONS** (Enter responses in table. Do not prompt for each medication in the Medication Code List below.)

The next questions involve the medicines your child is taking for breathing problems.

27. Since our last contact with your, what medicines has your baby taken, including medicines taken by a nebulizer or breathing machine at home?	27a.  Code	27b.  Does he/she take that medicine everyday, sometimes or only when sick? (repeat for each medication)
1		1 <input type="checkbox"/> Everyday    2 <input type="checkbox"/> Sometimes    3 <input type="checkbox"/> Only when Sick
2		1 <input type="checkbox"/> Everyday    2 <input type="checkbox"/> Sometimes    3 <input type="checkbox"/> Only when Sick
3		1 <input type="checkbox"/> Everyday    2 <input type="checkbox"/> Sometimes    3 <input type="checkbox"/> Only when Sick
4		1 <input type="checkbox"/> Everyday    2 <input type="checkbox"/> Sometimes    3 <input type="checkbox"/> Only when Sick
5		1 <input type="checkbox"/> Everyday    2 <input type="checkbox"/> Sometimes    3 <input type="checkbox"/> Only when Sick
6		1 <input type="checkbox"/> Everyday    2 <input type="checkbox"/> Sometimes    3 <input type="checkbox"/> Only when Sick
7		1 <input type="checkbox"/> Everyday    2 <input type="checkbox"/> Sometimes    3 <input type="checkbox"/> Only when Sick

Medication Code List:

<p><i>Rescue medicines:</i></p> <ul style="list-style-type: none"><li>1 Albuterol</li><li>2 Proventil</li><li>3 Serevent</li><li>4 Ventolin</li><li>5 Volmax</li><li>6 Xopenex</li></ul> <p><i>Other Inhaled medications:</i></p> <ul style="list-style-type: none"><li>7 Cromolyn (Intal)</li><li>8 Nedocromil (Tilade)</li></ul> <p><i>Inhaled steroids:</i></p> <ul style="list-style-type: none"><li>9 Advair</li><li>10 Aerobid</li><li>11 Azmacort</li><li>12 Beclovent</li><li>13 Flovent</li><li>14 Vancericil</li><li>15 Pulmicort</li></ul>	<p><i>Systemic steroids:</i></p> <ul style="list-style-type: none"><li>16 Decadron</li><li>17 Prednisone</li><li>18 Prednisolone</li></ul> <p><i>Leukotriene blocker:</i></p> <ul style="list-style-type: none"><li>19 Accolate</li><li>20 Singulair</li></ul> <p><i>Methylxanthines:</i></p> <ul style="list-style-type: none"><li>21 Theophylline</li></ul> <p><i>Diuretic medications:</i></p> <ul style="list-style-type: none"><li>22 Diuril</li><li>23 Lasix</li><li>24 Aldactizide</li><li>25 Aldactone</li></ul> <p>Miscellaneous / Non-specific</p> <ul style="list-style-type: none"><li>26 Nebulizer</li><li>27 Other _____</li></ul>
---	--

**The next 2 questions are about respiratory infections.....**

28. **During the past year**, for how many days has your child been unable to do his/her usual activities because of illnesses such as chest (not head) colds, bronchitis, asthma or pneumonia?

- 0-3 per year
- 4-5 per year
- 6-9 per year
- more than 9 per year

29. **During the past year**, how many head colds (common colds) has your child had? Would you say...

- 0-3 per year
- 4-5 per year
- 6-9 per year
- more than 9 per year

**The last questions are about allergies.**

30. Has your child **ever** had hay fever or any other condition that makes his/her nose runny, stuffy, or itchy **apart** from colds?                    1 • Yes                    2 • No

31. Has your child **ever** had allergies which cause nose, eye or lung problems?

- 1 • Yes                    2 • No

32. Has your child **ever** been allergic to any food?

- 1 • Yes                    2 • No

NICU Network

**SUPPORT TRIAL**  
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33. Has he/she **ever** been allergic to any medicine?

1• Yes      2• No

34. Has your child **ever** had eczema (allergic skin rash)?

1• Yes      2• No *(End of Interview)*

34a. Was eczema diagnosed by a doctor?

1• Yes      2• No

***End of Interview***

**THANK YOU FOR YOUR COOPERATION**

NICU Network

SUPPORT TRIAL  
Breathing Outcomes Study  
NICU Discharge-Baseline Interview

SUPP01S Rel 1.0  
February 17, 2006

Center: \_\_\_ Site: \_\_\_ Network No. \_\_\_\_\_ Follow-up No. \_\_\_\_\_ Birth No. \_\_\_ Mother's Initials: \_\_\_\_\_ Page 1 of 5

## Entrevista inicial para dada de alta de NICU

[Newborn Intensive Care Unit-Unidad de Cuidados Intensivos para Recién Nacidos]

Esta entrevista debe ser suministrada al padre/ madre/ representante por personal entrenado. El momento indicado para esta entrevista es antes de la dada de alta de la NICU o en los primeros 30 días después de la dada de alta. Para los pacientes registrados en el Estudio de Seguimiento de Resultados Pulmonares [Pulmonary Outcome Follow up Study] después de este tiempo, esta entrevista debe hacerse al momento de registrarse.

Esta entrevista es para:

\_\_\_\_\_  
(Nombre del niño(a))

Todas las preguntas son acerca de la salud del niño(a).

Nota: A los padres o representantes que estén preocupados por la respiración de su niño(a) se les debe recomendar que lo discutan con el médico principal de la familia.

### Introducción al estudio:

Los bebés prematuros tienen más posibilidades de tener problemas respiratorios después de la dada de alta de la NICU que los bebés de término completo. El propósito de este estudio es ver si el tratamiento que su bebé recibió como parte del Estudio de Apoyo [SUPPORT Study] mejora la respiración de su bebé en los 18 a 22 meses siguientes a la fecha probable de nacimiento.

Como parte de este estudio, lo contactaremos cada 6 meses, más o menos, para hacerle preguntas sobre la respiración de su bebé. Las preguntas serán acerca de los síntomas respiratorios de su bebé, especialmente resuello [respiración difícil y ruidosa] y tos, y acerca de las necesidades de su bebé de visitas médicas y tratamientos para los problemas respiratorios.

El resuello puede significar diferentes sonidos para distintas personas. Por resuello queremos decir un sonido de expiración (un sonido que se hace cuando se respira hacia fuera, no hacia dentro) que procede del pecho, algunas veces descrito como silbante o musical.

Le hemos preparado un folleto que describe el estudio y enfatiza características importantes de la respiración de su bebé, especialmente los problemas de la respiración y los tratamientos.

### Entregar folleto.

Cuando llamemos, nos gustaría que tuviera a mano todas las notas, medicamentos o cualquier otra información acerca de la respiración de su bebé. Le haremos preguntas acerca de qué tan frecuentemente su bebé resuela o tose, si su bebé ha visitado el consultorio médico, la sala de emergencias o ha sido hospitalizado por problemas respiratorios, y si su bebé ha requerido medicamentos o tratamientos para su respiración. Si lo desea, puede usar el folleto para tomar notas acerca de la respiración de su bebé.

Para poder ayudarnos a entender la respiración de su bebé y el riesgo de problemas respiratorios en la casa, nos gustaría hacerle algunas preguntas acerca de su casa y acerca de si hay problemas respiratorios en la familia. Como toda la información que recopilamos, las respuestas a estas preguntas se mantendrán en forma confidencial.

### Interview Outcome

Was the interview conducted? 1  Yes 2  No

If No why? 1  Loss of contact 2  Interviewee refused 3  Child died 4  Other SPECIFY \_\_\_\_\_

Initials of person completing this form. \_\_\_\_\_

NICU Network

SUPPORT TRIAL  
Breathing Outcomes Study

SUPF01S Rel 1.0  
February 17, 2006

NICU Discharge-Baseline Interview

Center: \_\_\_ Site: \_\_\_ Network No. \_\_\_ Follow-up No. \_\_\_ Birth No. \_\_\_ Mother's Initials: \_\_\_ Page 2 of 5

1. Nombre del niño(a) \_\_\_\_\_ 2. Fecha de hoy |\_\_|\_|-|\_\_|\_|-|\_\_|\_|\_|\_|\_|  
(Nombre) (Apellido) mes día año

3. Sexo del niño(a) 1  Masculino 2  Femenino

4. Fecha de nacimiento del niño(a): |\_\_|\_|-|\_\_|\_|-|\_\_|\_|\_|\_|\_|  
mes día año

Coloque el nombre y el código de relación de la persona entrevistada.

5a. Nombre: \_\_\_\_\_ 5b. Código de relación\*: |\_\_|\_|\_|

001 – Madre del niño(a)  
002 – Padre del niño(a)  
301 – Madre adoptiva  
302 – Padre adoptivo

Otro: \_\_\_\_\_

*\*Los códigos comunes están listados aquí. Para otras relaciones, por favor busque los códigos de relaciones en el apéndice D del Manual de Operaciones de Resultados Respiratorios.*

6. Tipo de entrevista: 1  Persona a persona 2  Telefónica

**Ahora nos gustaría tener información acerca del ambiente en el que su niño(a) crecerá.**

7. Primero, ¿cuántas personas normalmente viven con usted en su casa por lo menos 6 meses del año?  
Número total: |\_\_|\_|\_|

8. Después de los primeros meses, ¿su niño(a) estará compartiendo regularmente una habitación con otros miembros de la familia?

1  Sí 2  No

8a. Si la respuesta es sí: ¿Cuántas personas dormirán en la misma habitación con él /ella? |\_\_|\_|\_|

9. ¿Cuántas habitaciones hay en su casa, excluyendo clóset y baños? |\_\_|\_|\_|

10. ¿Tiene animales dentro de la casa? 1  Sí 2  No *Vaya a la pregunta 11*

Si la respuesta es sí: ¿Cuántos?

10a. Marque y registre la cantidad: 1  Perros en la casa? |\_\_|\_|\_|

2  Gatos en la casa? |\_\_|\_|\_|

3  Otros animales en la casa? |\_\_|\_|\_| ESPECIFIQUE: \_\_\_\_\_

11. ¿Su casa o apartamento tiene aire acondicionado o algún tipo de ventilación? 1  Sí 2  No *Vaya a la pregunta 12*

Si la respuesta es sí,

11a. ¿Aire acondicionado? 1  Sí 2  No

11b. ¿Enfriamiento por evaporación? 1  Sí 2  No

(Desierto del Suroeste)

11c. ¿Otro? 1  Sí 2  No SI LA RESPUESTA ES SÍ, ESPECIFIQUE: \_\_\_\_\_

NICU Network

SUPPORT TRIAL  
Breathing Outcomes Study

SUPF01S Rel 1.0  
February 17, 2006

NICU Discharge-Baseline Interview

Center: \_\_\_ Site: \_\_\_ Network No. \_\_\_\_\_ Follow-up No. \_\_\_\_\_ Birth No. \_\_\_ Mother's Initials: \_\_\_\_\_ Page 3 of 5

12. ¿Qué tipo de calefacción hay en su casa? (Si es más de uno, por favor marque todos los que hay)

- 1  Vapor o agua caliente (radiador)
- 2  Calentador central a gas (calefacción)
- 3  Eléctrica
- 4  Estufa de leña
- 5  Otro, ESPECIFIQUE: \_\_\_\_\_
- 6  No sabe

13. ¿Cuál combustible es utilizado mayormente para cocinar en su casa?

- 1  Electricidad
- 2  Gas
- 3  Gas oil
- 4  Cocina de leña
- 5  Otro, ESPECIFIQUE: \_\_\_\_\_
- 6  No sabe

**Las siguientes preguntas son acerca de la dieta de su bebé:**

14. Su bebé está tomando: (LEA TODAS LAS OPCIONES)

- 1  Sólo leche materna
- 2  Sólo preparado para biberón (*Vaya a la pregunta 15*)
- 3  Ambos, leche materna y preparado para biberón (*Vaya a la pregunta 15*)
- 4  Otro, ESPECIFIQUE: \_\_\_\_\_ (*Vaya a la pregunta 15*)

**Si la respuesta a la 14 es 1 (Sólo leche materna)**

14a. ¿Le complementará con fórmula en los primeros 6 meses?

- 1  Sí
- 2  No
- 3  No sabe

14b. Si la respuesta es sí, ¿Cuándo empezará el complemento? A los \_\_\_\_|\_\_\_\_| meses

15. ¿La madre (usted) planifica trabajar fuera del hogar en el próximo año?

- 1  Sí
- 2  No
- 3  No sabe

**Las siguientes preguntas son acerca de la exposición a humo (de cigarrros, cigarrillos, etc.)**

16. ¿Cuál de las siguientes afirmaciones representa mejor la situación en cuanto a fumar en la **casa** de su niño(a)?

Lea todas las opciones al entrevistado antes de registrar su respuesta.

- 1  Se permite fumar en cualquier habitación general de la casa.
- 2  Se permite fumar sólo en una parte de la casa a donde el niño(a) generalmente no va.
- 3  No se permite fumar dentro de la casa → 16a. ¿Hay excepciones a esta situación?

- 1  Sí
- 2  No (*Vaya a la pregunta 17*)

16b. ¿Ante cuáles circunstancias se admiten las excepciones? ESPECIFIQUE:

\_\_\_\_\_

NICU Discharge-Baseline Interview

Center: \_\_\_ Site: \_\_\_ Network No. \_\_\_\_\_ Follow-up No. \_\_\_\_\_ Birth No. \_\_\_ Mother's Initials: \_\_\_ Page 4 of 5

17. ¿Cuál de las siguientes afirmaciones representa mejor la situación en cuanto a fumar en su **automóvil**? Lea todas las opciones al entrevistado antes de registrar su respuesta.

- 1  No tiene automóvil
- 2  Usualmente o siempre se permite fumar.
- 3  Se permite fumar a veces.
- 4  Se permite fumar en el automóvil sólo cuando el niño(a) no está presente.
- 5  No se fuma dentro del automóvil → 17a. ¿Hay excepciones a esta situación?

1  Sí 2  No (Vaya a la pregunta 18)

17b. ¿Ante cuáles circunstancias se admiten las excepciones? **ESPECIFIQUE:**

18. ¿Qué tan frecuentemente ha fumado la madre o el cuidador(a) principal (usted) del niño(a) desde que él /ella nació?

- 1  Nunca 2  Ocasionalmente 3  Diariamente

19. En total, ¿Cuántas personas que viven en la casa del niño(a) fuman? |\_\_|\_\_| personas

**En la siguiente sección nos gustaría saber qué problemas de alergias y respiración se presentan en la familia. Suministre el Cuestionario de Historia Familiar anexo, utilizando el siguiente diálogo:**

Madre o cuidador(a)

**Empezaremos con la madre del bebé. ¿Qué edad tiene la madre biológica del bebé? ¿Ella sufre de bronquitis, enfisema, COPD (enfermedades pulmonares obstructivas crónicas), bronquiectasia, asma, alergias por inhalación, o alergias a comidas?**

**¿Tiene alguna otra enfermedad respiratoria crónica la madre del bebé?**

**¿Qué tan frecuentemente fuma esta persona en la casa del bebé?**

Padre.

**¿El padre biológico del bebé está vivo? ¿Qué edad tiene? ¿Sufre él de bronquitis, enfisema, COPD, bronquiectasia, asma, alergias por inhalación, o alergias a comidas?**

**¿Tiene alguna otra enfermedad respiratoria crónica?**

**¿Qué tan frecuentemente fuma él en la casa del bebé?**

Complete el resto de la tabla recabando la misma historia médica usando el diálogo anterior.

20. Finalmente ¿Cuál familiar o amigo(a) tiene más probabilidades de mantener contacto con usted en estos 6 meses en caso de que perdamos contacto con usted?

Nombre _____	Relación _____
Dirección _____	
Teléfono _____	
Celular _____	
E mail _____	

**Gracias por su ayuda en proporcionarnos esta importante información y por su participación continua en el Estudio de Resultados Respiratorios.**

**Entrevista inicial para dada de alta de NICU**

1. Relación con el niño(a) inscrito:	<b>Madre</b>	<b>Padre</b>	<b>Abuela Materna</b>	<b>Abuelo Materno</b>	<b>Abuela Paterna</b>	<b>Abuelo Paterno</b>
2. ¿Vive?	1.Sí 2.No 3.NS	1.Sí 2.No 3.NS	1.Sí 2.No 3.NS	1.Sí 2.No 3.NS	1.Sí 2.No 3.NS	1.Sí 2.No 3.NS
3. Edad (en años)	_____	_____	_____	_____	_____	_____
4. Esta persona tiene:						
a. COPD	1.Sí 2.No 3.NS	1.Sí 2.No 3.NS	1.Sí 2.No 3.NS	1.Sí 2.No 3.NS	1.Sí 2.No 3.NS	1.Sí 2.No 3.NS
b. ¿Bronquitis crónica?	1.Sí 2.No 3.NS	1.Sí 2.No 3.NS	1.Sí 2.No 3.NS	1.Sí 2.No 3.NS	1.Sí 2.No 3.NS	1.Sí 2.No 3.NS
c. ¿Enfisema?	1.Sí 2.No 3.NS	1.Sí 2.No 3.NS	1.Sí 2.No 3.NS	1.Sí 2.No 3.NS	1.Sí 2.No 3.NS	1.Sí 2.No 3.NS
d. ¿Bronquiectasia?	1.Sí 2.No 3.NS	1.Sí 2.No 3.NS	1.Sí 2.No 3.NS	1.Sí 2.No 3.NS	1.Sí 2.No 3.NS	1.Sí 2.No 3.NS
e. ¿Asma?	1.Sí 2.No 3.NS	1.Sí 2.No 3.NS	1.Sí 2.No 3.NS	1.Sí 2.No 3.NS	1.Sí 2.No 3.NS	1.Sí 2.No 3.NS
f. ¿Alergia por inhalación?	1.Sí 2.No 3.NS	1.Sí 2.No 3.NS	1.Sí 2.No 3.NS	1.Sí 2.No 3.NS	1.Sí 2.No 3.NS	1.Sí 2.No 3.NS
g. ¿Alergias a comida?	1.Sí 2.No 3.NS	1.Sí 2.No 3.NS	1.Sí 2.No 3.NS	1.Sí 2.No 3.NS	1.Sí 2.No 3.NS	1.Sí 2.No 3.NS
h. ¿Alguna otra enfermedad crónica respiratoria? (ESPECIFIQUE)	1.Sí 2.No 3.NS _____ _____	1.Sí 2.No 3.NS _____ _____	1.Sí 2.No 3.NS _____ _____	1.Sí 2.No 3.NS _____ _____	1.Sí 2.No 3.NS _____ _____	1.Sí 2.No 3.NS _____ _____
5. ¿Qué tan frecuentemente fuma esta persona en la casa del bebé*?	1. Nunca 2. Rara vez 3. Algunas veces 4. Frecuentemente 5. NS	1. Nunca 2. Rara vez 3. Algunas veces 4. Frecuentemente 5. NS	1. Nunca 2. Rara vez 3. Algunas veces 4. Frecuentemente 5. NS	1. Nunca 2. Rara vez 3. Algunas veces 4. Frecuentemente 5. NS	1. Nunca 2. Rara vez 3. Algunas veces 4. Frecuentemente 5. NS	1. Nunca 2. Rara vez 3. Algunas veces 4. Frecuentemente 5. NS

\* Nunca = Nunca; rara vez = menos de una vez al mes; Algunas veces = una vez al mes pero menos de una vez por semana; Frecuentemente = una vez por semana o más; NS = No Sabe

NICU Network  
 SUPPORT TRIAL  
 Breathing Outcomes Study  
 NICU Discharge- Baseline Interview  
 Center: \_\_\_\_\_ Site: \_\_\_\_\_ Network No. \_\_\_\_\_ Follow-up No. \_\_\_\_\_ Birth No. \_\_\_\_\_ Mother's Initials: \_\_\_\_\_ Page 5 of 5  
 SUPP01S Rel 1.0  
 February 17, 2006



NICU Network

SUPPORT TRIAL  
Breathing Outcomes Study  
6 and 12 Month Interview

SUPF02S Rel 1.1  
April 17, 2006

Center: \_\_\_ Site: \_\_\_ Network No. \_\_\_ Follow-up No. \_\_\_ Birth No. \_\_\_ Mother's Initials: \_\_\_ Page 1 of 8

## Para suministrar a los 6 y 12 meses de edad corregida

Esta entrevista debe ser suministrada por un entrevistador entrenado en este estudio para:

\_\_\_\_\_  
(Nombre del niño(a))

Todas las preguntas son acerca de la salud del niño(a).

El padre o cuidador, quien completó la entrevista inicial, debe completar esta y todos las entrevistas siguientes. El entrevistador deberá pedir a esa persona. (Ver el manual de Operaciones)

### Diálogo de introducción:

**Cuando el padre o cuidador principal esté al teléfono:**

**Hola, mi nombre es <su nombre>. Estoy llamando del < centro NICHD>. Probablemente se acuerde que cuando estuvo en la NICU se inscribió en el estudio acerca de la salud respiratoria de bebés prematuros. Lo(a) estoy llamando para hacerle algunas preguntas acerca de la respiración de su bebé. Tomará unos 10 a 20 minutos para completar. ¿Tiene tiempo en este momento?**

**Al igual que con toda la información que obtenemos, las respuestas a estas preguntas se mantendrán confidenciales.**

**Antes de empezar esta entrevista, sería de ayuda si pudiera tener a mano cualquier información que posea acerca de la respiración de su bebé, así como los medicamentos que se le han recetado a su niño(a) o que él /ella ha estado tomando. Al igual que con toda la información que recopilamos, las respuestas a estas preguntas se mantendrán confidenciales.**

### Interview Outcome

Was the interview conducted? 1  Yes 2  No

If No why? 1  Loss of contact 2  Interviewee refused 3  Child died 4  Other SPECIFY \_\_\_\_\_

Initials of person completing this form. \_\_\_ \_\_\_

Type of Interview 1  6 Month 2  12 Month

NICU Network

SUPPORT TRIAL  
Breathing Outcomes Study  
6 and 12 Month Interview

SUPF02S Rel 1.1  
April 17, 2006

Center: \_\_\_\_\_ Site: \_\_\_\_\_ Network No. \_\_\_\_\_ Follow-up No. \_\_\_\_\_ Birth No. \_\_\_\_\_ Mother's Initials: \_\_\_\_\_ Page 2 of 8

1. FECHA DE HOY: |\_\_| |\_\_| - |\_\_| |\_\_| - |\_\_| |\_\_| |\_\_| |\_\_|  
mes día año

POR FAVOR CONFIRME LA INFORMACIÓN PERSONAL Y HAGA LAS CORRECCIONES NECESARIAS.

Nombre del niño(a): \_\_\_\_\_  
(Nombre) (Apellido)

Fecha de nacimiento del niño(a): |\_\_| |\_\_| - |\_\_| |\_\_| - |\_\_| |\_\_| |\_\_| |\_\_|  
mes día año

Número telefónico: \_\_\_\_\_ - \_\_\_\_\_ - \_\_\_\_\_

Dirección  
\_\_\_\_\_  
\_\_\_\_\_

¿Cuál amigo(a) o familiar tiene más probabilidades de poder contactarlo dentro de 6 meses en caso de que perdamos contacto con usted?

\_\_\_\_\_  
Nombre Relación

\_\_\_\_\_  
Dirección

\_\_\_\_\_  
Teléfono

\_\_\_\_\_  
Teléfono Celular

\_\_\_\_\_  
Email

Coloque el nombre y el código de relación de la persona que está siendo entrevistada:

2a. Nombre: \_\_\_\_\_ 2b. Código de Relación\*: |\_\_| |\_\_| |\_\_|

- 001 – Madre del niño(a)
  - 002 – Padre del niño(a)
  - 301 – Madre adoptiva del niño(a)
  - 302 – Padre adoptivo del niño(a)
- Otro: \_\_\_\_\_
- \*Los códigos comunes están listados aquí. Para otras relaciones, por favor busque los códigos de relaciones en el apéndice D del Manual de Operaciones de Resultados Respiratorios.*



Las siguientes preguntas son acerca de la respiración de su bebé.

La primera pregunta es acerca de resuello. Por resuello queremos decir un sonido de la exhalación (un sonido que se hace cuando se respira hacia fuera, no hacia dentro) que viene del pecho, algunas veces descrito como silbante o musical.

9. Desde nuestro último contacto, ¿el pecho de su bebé ha sonado como un resuello o silbante?

- 1  Sí      2  No      3  No sabe    Haga la pregunta 9a para cualquier respuesta

9a. ¿La respiración de su bebé ha sonado así? (Ponga la grabación del resuello)

- 1  Sí      2  No      3  No sabe

Si la respuesta a la pregunta 9 o 9a es **afirmativa**:

9b. ¿Esto ha ocurrido con resfríos?

- 1  Sí  
2  No  
3  Algunas veces

9c. ¿El pecho de su bebé ha sonado como un resuello o silbante aunque no tenga resfriado?

- 1  Sí  
2  No

9d. ¿En qué mes el pecho de su bebé empezó a sonar como un resuello o silbante?

\_\_\_\_ Mes (Anote el mes, enero = 01, febrero = 02); \_\_\_\_ Año

9e. Desde nuestro último contacto, **en promedio**, ¿cuántas veces ha sonado como un resuello o silbante el pecho de su bebé durante:

**el día? Usted diría que...(e.1)**

- 1  Nunca  
2  Dos veces a la semana o menos  
3  Más de dos veces a la semana pero no todos los días  
4  Todos los días, pero no todo el tiempo  
5  Todos los días, todo el tiempo.

**la noche? Usted diría que...(e.2)**

- 1  Nunca  
2  Una vez cada dos semanas o menos  
3  Una vez a la semana.  
4  Dos o tres veces a la semana  
5  Más de tres noches a la semana / Frecuentemente

9f. Desde nuestro último contacto con usted, **durante el peor periodo de 2 semanas**, ¿qué tan frecuentemente ha sonado como un resuello o silbante el pecho de su bebé durante:

**el día? Usted diría que...(e.1)**

- 1  Nunca  
2  Dos veces a la semana o menos  
3  Más de dos veces a la semana pero no todos los días  
4  Todos los días, pero no todo el tiempo  
5  Todos los días, todo el tiempo.

**la noche? Usted diría que...(e.2)**

- 1  Nunca  
2  Una vez cada dos semanas o menos  
3  Una vez a la semana.  
4  Dos o tres veces a la semana  
5  Más de tres noches a la semana / Frecuentemente

9g. Desde nuestro último contacto con usted, ¿ha sido su niño diagnosticado con resuello por un doctor?

- 1  Sí  
2  No

**SI LA RESPUESTA ES AFIRMATIVA, ASEGÚRESE DE COMPLETAR LA PREGUNTA 27**

10. Desde nuestro último contacto con usted, ¿su niño(a) ha tenido tos por más de 3 días aun cuando no estaba resfriado?  Sí  No *Si la respuesta es negativa, vaya a la pregunta 11*

**Si la respuesta a la pregunta 10 es afirmativa**

10a. ¿A qué hora del día ha ocurrido esta tos generalmente?

(MARQUE TODAS LAS APLICABLES)

- 1 En la mañana, poco después de despertarse  
 2 Más tarde en el día  
 3 Durante la noche  
 4 No tiene relación a la hora del día

10b. ¿Ha tosido la mayoría de los días por tanto como 2 o 3 meses?  Sí  No

10c. ¿Durante qué mes y año empezó a toser su bebé?

\_\_\_\_ Mes (Anote el mes, enero = 01, febrero = 02); \_\_\_\_ Año

10d. ¿El pecho de su bebé ha sonado con resuello o silbante durante los ataques de tos?  Sí  No

10e. Desde nuestro último contacto, **en promedio**, ¿cuántas veces ha tenido tos su bebé durante:

**el día? Usted diría que...(e.1)**

**la noche? Usted diría que...(e.2)**

- 1 Nunca  
 2 Dos veces a la semana o menos  
 3 Más de dos veces a la semana pero no todos los días  
 4 Todos los días, pero no todo el tiempo  
 5 Todos los días, todo el tiempo.

- 1 Nunca  
 2 Una vez cada dos semanas o menos  
 3 Una vez a la semana.  
 4 Dos o tres veces a la semana  
 5 Más de tres noches a la semana / Frecuentemente

10f. Desde nuestro último contacto con usted, durante el peor periodo de 2 semanas, ¿qué tan frecuentemente ha tenido tos su bebé?

**el día? Usted diría que...(e.1)**

**la noche? Usted diría que...(e.2)**

- 1 Nunca  
 2 Dos veces a la semana o menos  
 3 Más de dos veces a la semana pero no todos los días  
 4 Todos los días, pero no todo el tiempo  
 5 Todos los días, todo el tiempo.

- 1 Nunca  
 2 Una vez cada dos semanas o menos  
 3 Una vez a la semana.  
 4 Dos o tres veces a la semana  
 5 Más de tres noches a la semana / Frecuentemente

11. Desde nuestro último contacto con usted, **en promedio**, ¿cuántos **días por mes** tuvo que cambiar sus planes de día o de noche por los problemas de respiración de su bebé?:

- 1 Nunca, no tuvimos que cambiar los planes.  
 2 Uno o más, pero menos de 3 días  
 3 3 a 6 días  
 4 7 días o más

12. Desde nuestro último contacto con usted, **durante el peor periodo de 2 semanas**, ¿cuántos **días** tuvo que cambiar sus planes de día o de noche por los problemas de respiración de su bebé?:

- 1 Nunca, no tuvimos que cambiar los planes.  
 2 Uno o más, pero menos de 3 días  
 3 3 a 6 días  
 4 7 días o más

13. Desde nuestro último contacto con usted, ¿su niño(a) ha tenido asma, enfermedad respiratoria reactiva o un ataque de EBP<sub>1</sub>\* diagnosticado por un médico?  Sí  No \*Ver Manual para explicación <sub>1</sub>Enfermedad Bronquio Pulmonar

NICU Network	SUPPORT TRIAL Breathing Outcomes Study 6 and 12 Month Interview	SUPF02S Rel 1.1 April 17, 2006				
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14. Desde nuestro último contacto con usted, ¿su niño(a) ha tenido bronquiolitis, bronquitis o neumonía diagnosticado por un médico?

1  Sí 2  No

15. Desde nuestro último contacto con usted, ¿su niño ha tenido crup diagnosticado por un médico?

1  Sí 2  No

**Las siguientes preguntas son acerca de la dieta de su bebé.**

16. Desde nuestro último contacto con usted, ¿su bebé tomó leche materna bien sea del pecho, de un biberón o a través de un tubo?

1  Sí 2  No Si la respuesta es negativa, vaya a la pregunta 17

Si la respuesta a la pregunta 16 es afirmativa:

16a. ¿Por cuántos meses recibió su bebé alimentación de leche materna?

Diría usted que... 1  Menos de 1 mes  
2  1 a 3 meses  
3  4 a 6 meses

16b. ¿Por cuántos meses tomó su bebé leche materna por la mitad o más de su alimentación?

Diría usted que... 1  Menos de 1 mes  
2  1 a 3 meses  
3  4 a 6 meses

**Las siguientes preguntas son acerca de la exposición de su bebé al humo.**

17. ¿Cuál de las siguientes 3 afirmaciones describe mejor la situación en cuanto a fumar en la **casa** de su bebé? Lea todas las opciones al entrevistado antes de escribir su respuesta.

- 1  Se permite fumar en cualquier habitación de la casa  
2  Se permite fumar en parte de la casa donde el niño rara vez está  
3  No se permite fumar dentro → 17a. ¿Hay alguna excepción a esta situación?

1  Sí 2  No (Vaya a la pregunta 18)

17b. ¿Bajo qué circunstancias se permiten las excepciones? ESPECIFIQUE:

\_\_\_\_\_

18. ¿Cuál de las siguientes 5 afirmaciones describe mejor la situación en cuanto a fumar en su **automóvil**? Lea todas las opciones al entrevistado antes de escribir su respuesta.

- 1  No tiene automóvil  
2  Se permite fumar siempre o usualmente.  
3  Se permite fumar a veces  
4  Se permite fumar en el automóvil sólo cuando el niño(a) no está en él.  
5  No se permite fumar dentro del automóvil → 18a. ¿Hay alguna excepción a esta situación?

1  Sí 2  No (Vaya a la pregunta 19)

18b. ¿Bajo qué circunstancias se permiten las excepciones? ESPECIFIQUE:

\_\_\_\_\_

19. ¿Qué tan frecuentemente ha fumado **la madre o cuidador primario** del niño(a) desde que nació el bebé?

1  Nunca 2  Ocasionalmente 3  Diariamente

20. ¿Cuántas personas fuman en la casa del niño(a)? \_\_\_\_\_ Personas

**Las siguientes preguntas son acerca de su casa o el hogar del cuidador o de cuidado diario.**

21. ¿Aproximadamente cuántas horas semanales pasa su niño(a) en la casa del cuidador o de cuidado diario?  
\_\_\_\_ Horas Si son 0, vaya a la pregunta 22

Si la respuesta a la 21 es mayor de 0:

21a. ¿Qué tan frecuente es la exposición al humo en el hogar del cuidador o de cuidado diario?

1  Nunca 2  Ocasionalmente 3  Diariamente 4  No sabe

21b. ¿Cuántos niños además del suyo están en el hogar de cuidado diario? \_\_\_\_\_ Niños

22. ¿Cuántos niños menores de 12 años viven en su casa? \_\_\_\_\_ Niños

23. ¿Tiene animales dentro de la casa? 1  Sí 2  No Vaya a la pregunta 24

23a. Si la respuesta es afirmativa, ¿cuántos animales hay dentro de la casa?

Marque todos los que hayan y anote la cantidad:

1  Perros \_\_\_\_\_

2  Gatos \_\_\_\_\_

3  Otro \_\_\_\_\_ ESPECIFIQUE: \_\_\_\_\_

**Las últimas preguntas son acerca de tratamientos respiratorios que su bebe pueda estar recibiendo.**

**PROFILAXIS**

24. ¿Ha recibido su bebé la inyección RSV contra el virus respiratorio sincitial (Synagis, palivizumab o RSV)?

1  Sí 2  No 3  No sabe

25. ¿Su niño ha tenido la vacuna antigripal? 1  Sí 2  No 3  No sabe

**OXÍGENO**

26. Desde nuestro ultimo contacto con usted, ¿su niño ha recibido oxígeno terapia en la casa?

1  Sí 2  No Vaya a la pregunta 27

Si la respuesta a la pregunta 26 es afirmativa

26a. ¿Su niño recibe actualmente alguna oxígeno terapia en la casa?

1  Sí 2  No Vaya a la pregunta 27

Si la respuesta es sí, indique para cada una de las siguientes

\*lpm = litros por minuto

26b. Cánula de oxígeno 1  Sí 2  No FiO2 \_\_\_\_\_ lpm\* \_\_\_\_\_

26c. Tienda de oxígeno 1  Sí 2  No FiO2 \_\_\_\_\_ lpm\* \_\_\_\_\_

26d. Ventilador para respiración 1  Sí 2  No FiO2 \_\_\_\_\_ lpm\* \_\_\_\_\_

NICU Network	<b>SUPPORT TRIAL</b> <b>Breathing Outcomes Study</b> <b>6 and 12 Month Interview</b>	<b>SUPF02S Rel 1.1</b> <b>April 17, 2006</b>
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**MEDICAMENTOS** (Anote la respuesta en la tabla. No mencione ningún medicamento de la Lista de Códigos de Medicamentos más adelante.)

**Las últimas dos preguntas son acerca de los medicamentos que su niño(a) está tomando para los problemas respiratorios.**

27. Desde nuestro último contacto con usted, ¿Qué medicamentos ha tomado su bebé, incluyendo las medicinas suministradas con nebulizador o máquina respiratoria en la casa?	27a.  Código	27b.  ¿Él /ella toma este medicamento todos los días, algunas veces o sólo cuando está enfermo(a)? (repita para cada medicamento)
1		1 <input type="checkbox"/> Todos los días    2 <input type="checkbox"/> A veces    3 <input type="checkbox"/> Sólo cuando enfermo
2		1 <input type="checkbox"/> Todos los días    2 <input type="checkbox"/> A veces    3 <input type="checkbox"/> Sólo cuando enfermo
3		1 <input type="checkbox"/> Todos los días    2 <input type="checkbox"/> A veces    3 <input type="checkbox"/> Sólo cuando enfermo
4		1 <input type="checkbox"/> Todos los días    2 <input type="checkbox"/> A veces    3 <input type="checkbox"/> Sólo cuando enfermo
5		1 <input type="checkbox"/> Todos los días    2 <input type="checkbox"/> A veces    3 <input type="checkbox"/> Sólo cuando enfermo
6		1 <input type="checkbox"/> Todos los días    2 <input type="checkbox"/> A veces    3 <input type="checkbox"/> Sólo cuando enfermo
7		1 <input type="checkbox"/> Todos los días    2 <input type="checkbox"/> A veces    3 <input type="checkbox"/> Sólo cuando enfermo

Lista de Código de Medicamentos:

<b>Medicamentos de Rescate:</b> 1. Albuterol 2. Proventil 3. Serevent 4. Ventolin 5. Volmax 6. Xopenex  <b>Otros medicamentos inhalados:</b> 7. Cromolyn (Intal) 8. Nedocromil (Tilade)  <b>Esteroides inhalados:</b> 9. Advair 10. Aerobid 11. Azmacort 12. Beclovent 13. Flovent 14. Vanceril 15. Pulmicort	<b>Esteroides sistémicos:</b> 16. Decadron 17. Prednisone 18. Prednisolone  <b>Bloqueadores de leucotrienos:</b> 19. Accolate 20. Singulair  <b>Metilxantinas:</b> 21. Theophylline  <b>Medicamentos diuréticos:</b> 22. Diuril 23. Lasix 24. Aldactizide 25. Aldactone  <b>Misceláneos / No específicos:</b> 26. Nebulizador 27. Otro _____
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**Gracias por su cooperación al proporcionarnos esta importante información, y por su continua participación en el Estudio de Resultados Respiratorios.**



NICU Network

SUPPORT TRIAL  
Breathing Outcomes Study  
18-22 Month Interview

SUPF03S Rel 1.1  
April 10, 2007

Center: \_\_\_ Site: \_\_\_ Network No. \_\_\_\_\_ Follow-up No. \_\_\_\_\_ Birth No. \_\_\_ Mother's Initials: \_\_\_\_\_ Page 1 of 10

## Suministrada entre los 18 y 22 meses de edad corregida

Esta entrevista debe ser suministrada por un entrevistador entrenado en este estudio. El momento para esta entrevista es entre los 18 y 22 meses de edad corregida.

\_\_\_\_\_  
(Nombre del niño(a))

Todas las preguntas son acerca de la salud del niño(a).

### Diálogo de introducción:

Cuando el padre o cuidador principal esté al teléfono:

Hola, mi nombre es <su nombre>. Estoy llamando del < centro NICHD>. Probablemente se acuerde que cuando estuvo en la NICU se inscribió en el estudio acerca de la salud respiratoria de bebés prematuros. Lo(a) estoy llamando para hacerle algunas preguntas acerca de la respiración de su bebé. Tomará unos 10 a 20 minutos para completar. ¿Tiene tiempo en este momento?

Al igual que con toda la información que obtenemos, las respuestas a estas preguntas se mantendrán confidenciales.

Antes de empezar esta entrevista, sería de ayuda si pudiera tener a mano cualquier información que posea acerca de la respiración de su bebé así como los medicamentos que se le han recetado a su niño(a) o que él /ella ha estado tomando.

### Interview Outcome

Was the interview conducted? 1• Yes 2• No

If No why? 1• Loss of contact 2• Interviewee refused 3• Child died 4• Other SPECIFY \_\_\_\_\_

Initials of person completing this form. \_\_\_\_\_





Las siguientes preguntas son acerca de la respiración de su bebé.

La primera pregunta es acerca de resuello. Por resuello queremos decir un sonido de la expiración (un sonido que se hace cuando se respira hacia fuera, no hacia dentro) que viene del pecho, algunas veces descrito como silbante o musical.

9. Desde nuestro último contacto, ¿el pecho de su bebé ha sonado con resuello o silbante?

- 1• Sí      2• No      3• No sabe *Haga la pregunta 9a para cualquier respuesta*

9a. ¿La respiración de su bebé ha sonado así? (Ponga la grabación del resuello)

- 1• Sí      2• No      3• No sabe

Si la respuesta a la pregunta 9 o 9a es afirmativa:

9b. ¿Esto ha ocurrido con resfríos?

- 1• Sí  
2• No  
3• Algunas veces

9c. ¿El pecho de su bebé ha sonado con resuello o silbante aunque no tenga resfriado?

- 1• Sí  
2• No

9d. ¿En qué mes el pecho de su bebé empezó a sonar con resuello o silbante?

\_\_\_\_ Mes (Anote el mes, enero = 01, febrero = 02); \_\_\_\_ Año

9e. Desde nuestro último contacto, **en promedio**, ¿cuántas veces ha sonado con resuello o silbante el pecho de su bebé durante:

**el día? Usted diría que...(e.1)**

- 1  Nunca  
2  Dos veces a la semana o menos  
3  Más de dos veces a la semana pero no todos los días  
4  Todos los días, pero no todo el tiempo  
5  Todos los días, todo el tiempo.

**la noche? Usted diría que...(e.2)**

- 1  Nunca  
2  Una vez cada dos semanas o menos  
3  Una vez a la semana.  
4  Dos o tres veces a la semana  
5  Más de tres noches a la semana / Frecuentemente

9f. Desde nuestro último contacto con usted, **durante el peor periodo de 2 semanas**, ¿qué tan frecuentemente ha sonado con resuello o silbante el pecho de su bebé durante:

**el día? Usted diría que...(e.1)**

- 1  Nunca  
2  Dos veces a la semana o menos  
3  Más de dos veces a la semana pero no todos los días  
4  Todos los días, pero no todo el tiempo  
5  Todos los días, todo el tiempo.

**la noche? Usted diría que...(e.2)**

- 1  Nunca  
2  Una vez cada dos semanas o menos  
3  Una vez a la semana.  
4  Dos o tres veces a la semana  
5  Más de tres noches a la semana / Frecuentemente

9g. Desde nuestro último contacto con usted, ¿ha sido su niño diagnosticado con resuello por un doctor?

- 1• Sí  
2• No

10. Desde nuestro último contacto con usted, ¿su niño(a) ha tenido tos por más de 3 días aun cuando no estaba resfriado? 1• Sí 2• No *Vaya a la pregunta 11*

Si la respuesta a la pregunta 10 es **afirmativa**

10a. ¿A qué hora del día ha ocurrido esta tos generalmente?

(Marque todas las aplicables)

- 1• En la mañana, poco después de despertarse
- 2• Más tarde en el día
- 3• Durante la noche
- 4• No tiene relación a la hora del día

10b. ¿Ha tosido la mayoría de los días por tanto como 2 o 3 meses? 1• Sí

2• No

10c. ¿Durante qué mes y año empezó a toser su bebé?

\_\_\_\_ Mes (Anote el mes, enero = 01, febrero = 02); \_\_\_\_ Año

10d. ¿El pecho de su bebé ha sonado con resuello o silbante durante los ataques de tos? 1• Sí

2• No

10e. Desde nuestro último contacto, **en promedio**, ¿cuántas veces ha tenido tos su bebé durante:

**el día? Usted diría que...(e.1)**

**la noche? Usted diría que...(e.2)**

1 Nunca

1 Nunca

2 Dos veces a la semana o menos

2 Una vez cada dos semanas o menos

3 Más de dos veces a la semana pero no todos los días

3 Una vez a la semana.

4 Todos los días, pero no todo el tiempo

4 Dos o tres veces a la semana

5 Todos los días, todo el tiempo.

5 Más de tres noches a la semana /  
Frecuentemente

10f. Desde nuestro último contacto con usted, **durante el peor periodo de 2 semanas**, ¿qué tan frecuentemente ha tenido tos su bebé?

**el día? Usted diría que...(e.1)**

**la noche? Usted diría que...(e.2)**

1 Nunca

1 Nunca

2 Dos veces a la semana o menos

2 Una vez cada dos semanas o menos

3 Más de dos veces a la semana pero no todos los días

3 Una vez a la semana.

4 Todos los días, pero no todo el tiempo

4 Dos o tres veces a la semana

5 Todos los días, todo el tiempo.

5 Más de tres noches a la semana /  
Frecuentemente

11. Desde nuestro último contacto con usted, **en promedio**, cuántos **días por mes** tuvo que cambiar sus planes de día o de noche por los problemas de respiración de su bebé:

1 Nunca, no tuvimos que cambiar los planes.

2 Uno o más, pero menos de 3 días

3 3 a 6 días

4 7 días o más

12. Desde nuestro último contacto con usted, **durante el peor periodo de 2 semanas**, cuántos **días** tuvo que cambiar sus planes de día o de noche por los problemas de respiración de su bebé:

1 Nunca, no tuvimos que cambiar los planes.

2 Uno o más, pero menos de 3 días

3 3 a 6 días

4 7 días o más

13. Desde nuestro último contacto con usted, ¿su niño(a) ha tenido asma, enfermedad respiratoria reactiva o un ataque de EBP<sub>1</sub>\* diagnosticado por un médico? 1• Sí 2• No \**Ver Manual para explicación* ,Enfermedad Bronquio Pulmonar

NICU Network

SUPPORT TRIAL  
Breathing Outcomes Study  
18-22 Month Interview

SUPF03S Rel 1.1  
April 10, 2007

Center: \_\_\_ Site: \_\_\_ Network No. \_\_\_\_\_ Follow-up No. \_\_\_\_\_ Birth No. \_\_\_ Mother's Initials: \_\_\_\_\_ Page 6 of 10

14. Desde nuestro último contacto con usted, ¿su niño(a) ha tenido bronquiolitis, bronquitis o neumonía diagnosticado por un médico?

- 1• Sí 2• No

15. Desde nuestro último contacto con usted, ¿su niño ha tenido crup diagnosticado por un médico?

- 1• Sí 2• No

**Las siguientes preguntas son acerca de la dieta de su bebé.**

16. Desde nuestro último contacto con usted, ¿su bebé tomó leche materna bien sea del pecho, de un biberón o a través de un tubo?

- 1• Sí 2• No *Si la respuesta es negativa, vaya a la pregunta 17*

Si la respuesta a la pregunta 16 es afirmativa:

16a. ¿Por cuántos meses recibió su bebé alimentación de leche materna?

- Diría usted que... 1• Menos de 1 mes  
2• 1 a 3 meses  
3• 4 a 6 meses

16b. ¿Por cuántos meses tomó su bebé leche materna por la mitad o más de su alimentación?

- Diría usted que... 1• Menos de 1 mes  
2• 1 a 3 meses  
3• 4 a 6 meses

**Las siguientes preguntas son acerca de la exposición de su bebé a humo.**

17. ¿Cuál de las siguientes 3 afirmaciones describe mejor la situación en cuanto a fumar en la **casa** de su bebé? Lea todas las opciones al entrevistado antes de escribir su respuesta.

- 1  Se permite fumar en cualquier habitación de la casa  
2  Se permite fumar en parte de la casa donde el niño rara vez está  
3  No se permite fumar dentro → 17a. ¿Hay alguna excepción a esta situación?

- 1• Sí 2• No (*Vaya a la pregunta 18*)

17b. ¿Bajo qué circunstancias se permiten las excepciones? ESPECIFIQUE:

\_\_\_\_\_

18. ¿Cuál de las siguientes 5 afirmaciones describe mejor la situación en cuanto a fumar en su **automóvil**? Lea todas las opciones al entrevistado antes de escribir su respuesta.

- 1  No tiene automóvil  
2  Se permite fumar siempre o usualmente.  
3  Se permite fumar a veces  
4  Se permite fumar en el automóvil sólo cuando el niño(a) no está en él.  
5  No se permite fumar dentro del automóvil → 18a. ¿Hay alguna excepción a esta situación?

- 1• Sí 2• No (*Vaya a la pregunta 19*)

18b. ¿Bajo qué circunstancias se permiten las excepciones? ESPECIFIQUE:

\_\_\_\_\_

19. ¿Qué tan frecuentemente ha fumado **la madre o cuidador primario** del niño(a) desde que nació el bebé?

- 1• Nunca 2• Ocasionalmente 3• Diariamente

20. ¿Cuántas personas fuman en la casa del niño(a)? [ ] [ ] [ ] Personas

**Las siguientes preguntas son acerca de su casa o el hogar del cuidador o de cuidado diario.**

21. ¿Aproximadamente cuántas horas semanales pasa su niño(a) en la casa del cuidador o de cuidado diario?  
[ ] [ ] Horas Si son 0, vaya a la pregunta 22

Si la respuesta a la 21 es mayor de 0:

21a. ¿Qué tan frecuente es la exposición al humo en el hogar del cuidador o de cuidado diario?  
1• Nunca 2• Ocasionalmente 3• Diariamente 4• No sabe

21b. ¿Cuántos niños además del suyo están en el hogar de cuidado diario? [ ] [ ] [ ] Niños

22. ¿Cuántos niños menores de 12 años viven en su casa? [ ] [ ] Niños

23. ¿Tiene animales dentro de la casa? 1• Sí 2• No Vaya a la pregunta 24

23a. Si la respuesta es afirmativa, ¿cuántos animales hay dentro de la casa?

Marque todos los que hayan y anote la cantidad:

1• Perros [ ] [ ]

2• Gatos [ ] [ ]

3• Otro [ ] [ ] ESPECIFIQUE: \_\_\_\_\_

Las últimas preguntas son acerca de tratamientos respiratorios que su bebe pueda estar recibiendo.

**PROFILAXIS**

24. ¿Ha recibido su bebé la inyección RSV contra el virus respiratorio sincitial (Synagis, palivizumab o RSV)?

1• Sí 2• No 3• No sabe

25. ¿Su niño ha tenido la vacuna antigripal? 1• Sí 2• No 3• No sabe

**OXÍGENO**

26. Desde nuestro ultimo contacto con usted, ¿su niño ha recibido oxigenoterapia en la casa?

1• Sí 2• No Vaya a la pregunta 27

Si la respuesta a la pregunta 26 es afirmativa

26a. ¿Su niño recibe actualmente alguna oxigenoterapia en la casa?

1• Sí 2• No Vaya a la pregunta 27

Si la respuesta es sí, indique para cada una de las siguientes \*lpm = litros por minuto

26b. Cánula de oxígeno 1• Sí 2• No FiO2 \_\_\_\_\_ lpm\* \_\_\_\_\_

26c. Tienda de oxígeno 1• Sí 2• No FiO2 \_\_\_\_\_ lpm\* \_\_\_\_\_

26d. Ventilador para respiración 1• Sí 2• No FiO2 \_\_\_\_\_ lpm\* \_\_\_\_\_

NICU Network

**SUPPORT TRIAL  
Breathing Outcomes Study  
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**SUPF03S Rel 1.1  
April 10, 2007**

Center: \_\_\_\_\_ Site: \_\_\_\_\_ Network No. \_\_\_\_\_ Follow-up No. \_\_\_\_\_ Birth No. \_\_\_\_\_ Mother's Initials: \_\_\_\_\_ Page 8 of 10

**MEDICAMENTOS** (Anoté la respuesta en la tabla. No mencione ningún medicamento de la Lista de Códigos de Medicamentos más adelante.)

**Las siguientes preguntas son acerca de los medicamentos que su niño(a) está tomando para los problemas respiratorios.**

27. Desde nuestro último contacto con usted, ¿Qué medicamentos ha tomado su bebé, incluyendo las medicinas suministradas con nebulizador o máquina respiratoria en la casa?	27a.  Código	27b.  ¿Él /ella toma este medicamento todos los días, algunas veces o sólo cuando está enfermo(a)? (repita para cada medicamento)
1		1 <input type="checkbox"/> Todos los días 2 <input type="checkbox"/> A veces 3 <input type="checkbox"/> Sólo cuando enfermo
2		1 <input type="checkbox"/> Todos los días 2 <input type="checkbox"/> A veces 3 <input type="checkbox"/> Sólo cuando enfermo
3		1 <input type="checkbox"/> Todos los días 2 <input type="checkbox"/> A veces 3 <input type="checkbox"/> Sólo cuando enfermo
4		1 <input type="checkbox"/> Todos los días 2 <input type="checkbox"/> A veces 3 <input type="checkbox"/> Sólo cuando enfermo
5		1 <input type="checkbox"/> Todos los días 2 <input type="checkbox"/> A veces 3 <input type="checkbox"/> Sólo cuando enfermo
6		1 <input type="checkbox"/> Todos los días 2 <input type="checkbox"/> A veces 3 <input type="checkbox"/> Sólo cuando enfermo
7		1 <input type="checkbox"/> Todos los días 2 <input type="checkbox"/> A veces 3 <input type="checkbox"/> Sólo cuando enfermo



Lista de Código de Medicamentos:

<p>Medicamentos de Rescate:</p> <ol style="list-style-type: none"><li>1. Albuterol</li><li>2. Proventil</li><li>3. Serevent</li><li>4. Ventolin</li><li>5. Volmax</li><li>6. Xopenex</li></ol> <p>Otros medicamentos inhalados:</p> <ol style="list-style-type: none"><li>7. Cromolyn (Intal)</li><li>8. Nedocromil (Tilade)</li></ol> <p>Esteroides inhalados:</p> <ol style="list-style-type: none"><li>9. Advair</li><li>10. Aerobid</li><li>11. Azmacort</li><li>12. Beclovent</li><li>13. Flovent</li><li>14. Vanceril</li><li>15. Pulmicort</li></ol>	<p>Esteroides sistémicos:</p> <ol style="list-style-type: none"><li>16. Decadron</li><li>17. Prednisone</li><li>18. Prednisolone</li></ol> <p>Bloqueadores de leucotrienos:</p> <ol style="list-style-type: none"><li>19. Accolate</li><li>20. Singulair</li></ol> <p>Metilxantinas:</p> <ol style="list-style-type: none"><li>21. Theophylline</li></ol> <p>Medicamentos diuréticos:</p> <ol style="list-style-type: none"><li>22. Diuril</li><li>23. Lasix</li><li>24. Aldactizide</li><li>25. Aldactone</li></ol> <p>Misceláneos / No específicos:</p> <ol style="list-style-type: none"><li>26. Nebulizador</li><li>27. Otro _____</li></ol>
---	--

Las siguientes 2 preguntas son acerca de infecciones respiratorias .....

28. **Durante este año pasado**, ¿por cuántos días ha estado su niño imposibilitado de hacer sus actividades debido a enfermedades como resfriados del pecho (no de la cabeza), bronquitis, asma o neumonía?

- 1  0 a 3 por año
- 2  4 a 5 por año
- 3  6 a 9 por año
- 4  más de 9 por año

29. **Durante este año pasado**, ¿cuántos resfriados comunes ha tenido su niño(a)? Diría usted que...

- 1  0 a 3 por año
- 2  4 a 5 por año
- 3  6 a 9 por año
- 4  más de 9 por año

Las últimas preguntas son acerca de alergias.

30. ¿**Alguna vez** ha tenido su niño fiebre del heno o alguna otra condición que hace que tenga la nariz mucosa (aguada), tapada, o con picazón **aparte** de los resfriados?

- 1  Sí
- 2  No

31. ¿**Alguna vez** ha tenido su niño alergias que le causen problemas de la nariz, ojos o pulmones?

- 1  Sí
- 2  No

32. ¿**Alguna vez** ha sido su niño alérgico a algún alimento?

- 1  Sí
- 2  No

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33. ¿**Alguna vez** él / ella ha sido alérgico a algún medicamento?

1• Sí      2• No

34. ¿**Alguna vez** ha tenido su niño eczema (salpullido alérgico)?

1• Sí      2• No (*Fin de la entrevista*)

34a. ¿El eczema fue diagnosticado por un médico?

1• Sí      2• No

***Fin de la entrevista***

***GRACIAS POR SU COOPERACIÓN***

**From:** [Bock, Robert \(NIH/NICHD\) \[E\]](#)  
**To:** [Wally Carlo, M.D.](#); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [wacarlo@uab.edu](mailto:wacarlo@uab.edu); [Finer, Neil](#)  
**Cc:** [McGrath, John \(NIH/NICHD\) \[E\]](#)  
**Subject:** RE: May 12 Conference call  
**Date:** Wednesday, May 12, 2010 1:01:34 PM

---

John McGrath is set to make the introductions. I've called in and am on hold.

---

**From:** Wally Carlo, M.D. [[WCarlo@peds.uab.edu](mailto:WCarlo@peds.uab.edu)]  
**Sent:** Tuesday, May 11, 2010 1:26 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]; [wacarlo@uab.edu](mailto:wacarlo@uab.edu); Finer, Neil  
**Cc:** McGrath, John (NIH/NICHD) [E]  
**Subject:** RE: May 12 Conference call

Yes, I can be on the call at 12:45 Eastern.

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: 205 266 (b)

**From:** Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]  
**Sent:** Tuesday, May 11, 2010 12:16 PM  
**To:** Bock, Robert (NIH/NICHD) [E]; [wacarlo@uab.edu](mailto:wacarlo@uab.edu); 'Finer, Neil'  
**Cc:** McGrath, John (NIH/NICHD) [E]  
**Subject:** RE: May 12 Conference call  
**Importance:** High

Hi  
Reminder for tomorrow's call –  
If possible can you join at 12:45 PM ET? (9:45 AM PT) –  
Let me know  
Thanks for all your help!!  
Rose

---

**From:** Bock, Robert (NIH/NICHD) [E]  
**Sent:** Wednesday, April 28, 2010 2:40 PM  
**To:** [wacarlo@uab.edu](mailto:wacarlo@uab.edu); 'Finer, Neil'  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** May 12 Conference call

Hello all. I just wanted to take a minute or so to go over our plan for the media briefing on May 12th.

Either I or someone from my office will make will make a very brief statement, something like “Thank you for joining our media availability at the National Institutes of Health. Researchers with the Neonatal Research Network will describe the results of a large clinical trial on oxygen and preterm infants. With us today are Dr. Rosemary Higgins, Program Scientist for the NICHD Neonatal Research Network, and two researchers with the network, Dr.

Waldemar Carlo and Dr. Neil Finer. “

Then, I propose that Rose speak for about five minutes, explaining the need for the studies and their design.

After which, either I or Rose will introduce Dr. Carlo, who will speak for five minutes and describe his study and its findings, and then we will introduce Dr. Finer, who will talk for five minutes about his study and its findings.

After everyone is finished speaking, we'll invite calls from press in attendance.

Please let me know if you have any comments, questions or concerns.

Thanks.  
Bob

From: Higgins, Rosemary (NIH/NICHHD) [E]  
Sent: Friday, April 23, 2010 4:07 PM  
To: wacarlo@uab.edu; 'Finer, Neil'; Martinez, Fernando  
Cc: Bock, Robert (NIH/NICHHD) [E]  
Subject: Conference call for SUPPORT discussion - May 12 1 PM ET

Confirmation #: 35225550

Dear SONDRADIETZ,

Your conference reservation is confirmed. Thank you for choosing Conference America.

KERIN REEVES

Conference Leader:

SANDA PECINA

Organization:

ACADEMY FOR EDUCATIONAL DEVELOP

Conference Date:

05/12/2010 Wednesday

Conference Time:

1:00PM Eastern Time

Dial in Number:

1-800-351 (b) USA

Passcode:

(b) (6)

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network  
Pregnancy and Perinatology Branch  
Center for Developmental Biology and Perinatal Medicine  
Eunice Kennedy Shriver National Institute of Child Health and Human Development  
National Institutes of Health  
6100 Executive Blvd., Room 4B03  
MSC 7510  
Bethesda, MD 20892  
For overnight delivery use Rockville, MD 20852  
301-496-5575  
301-496-3790 (FAX)  
higginsr@mail.nih.gov

**From:** Bock, Robert (NIH/NICHD) [E]  
**To:** Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; wacarlo@uab.edu; Finer, Neil  
**Cc:** McGrath, John (NIH/NICHD) [E]  
**Subject:** RE: May 12 Conference call  
**Date:** Wednesday, May 12, 2010 10:04:20 AM

---

Thanks, all. Marianne Miller and John McGrath will join you on the call this afternoon. I'm out of the office, checking in remotely. If something comes up, please call me on my cell at 240-472-(b)

---

From: Wally Carlo, M.D. [WCarlo@ped.s.uab.edu]  
Sent: Tuesday, May 11, 2010 1:26 PM  
To: Higgins, Rosemary (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]; wacarlo@uab.edu; Finer, Neil  
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To: Bock, Robert (NIH/NICHD) [E]; wacarlo@uab.edu; 'Finer, Neil'  
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Subject: RE: May 12 Conference call  
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To: wacarlo@uab.edu; 'Finer, Neil'  
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Bob

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Sent: Friday, April 23, 2010 4:07 PM  
To: wacarlo@uab.edu; 'Finer, Neil'; Martinez, Fernando  
Cc: Bock, Robert (NIH/NICHD) [E]  
Subject: Conference call for SUPPORT discussion - May 12 1 PM ET

Confirmation #: 35225550

Dear SONDRA DIETZ,

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KERIN REEVES

Conference Leader:

SANDA PECINA

Organization:

ACADEMY FOR EDUCATIONAL DEVELOP

Conference Date:

05/12/2010 Wednesday

Conference Time:

1:00PM Eastern Time

Dial in Number:

1-800-351-(b) USA

Passcode:

(b) (6)

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network  
Pregnancy and Perinatology Branch  
Center for Developmental Biology and Perinatal Medicine  
Eunice Kennedy Shriver National Institute of Child Health and Human Development  
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6100 Executive Blvd., Room 4B03  
MSC 7510  
Bethesda, MD 20892  
For overnight delivery use Rockville, MD 20852  
301-496-5575  
301-496-3790 (FAX)  
higginsr@mail.nih.gov



**From:** [Wally Carlo, M.D.](mailto:Wally_Carlo_M.D.)  
**To:** [Duara, Shahnaz; nfiner@ucsd.edu](mailto:Duara_Shahnaz; nfiner@ucsd.edu)  
**Cc:** [Higgins, Rosemary \(NIH/NICHD\) \[F\]](mailto:Higgins_Rosemary_(NIH/NICHD)_F)  
**Subject:** RE: New SUPPORT Form  
**Date:** Thursday, May 12, 2005 6:12:07 AM

---

I think it is ok. wally

---

**From:** Duara, Shahnaz [<mailto:SDuara@med.miami.edu>]  
**Sent:** Wednesday, May 11, 2005 3:33 PM  
**To:** [nfiner@ucsd.edu](mailto:nfiner@ucsd.edu); Wally Carlo, M.D.  
**Cc:** Higgins, Rosemary (NIH/NICHD)  
**Subject:** FW: New SUPPORT Form

Hi Neil and Wally,

Ruth had a question regrading the 24 hour dump vis-a-vis the pilot. Are you OK with Wade's suggestion that she do the dump at the end of te week and let Scott separate out Day 1 info?

Shahnaz

-----Original Message-----

**From:** Everett, Ruth [<mailto:REverett@med.miami.edu>]  
**Sent:** Wednesday, May 11, 2005 3:46 PM  
**To:** Duara, Shahnaz  
**Subject:** FW: New SUPPORT Form

Here is the original e-mail I sent Wade.

-----Original Message-----

**From:** Wade Rich [<mailto:wrich@ucsd.edu>]  
**Sent:** Wednesday, May 11, 2005 8:55 AM  
**To:** Everett, Ruth  
**Subject:** RE: New SUPPORT Form

Violations I can live with. The SAEs on the other hand...

---

**From:** Everett, Ruth [<mailto:REverett@med.miami.edu>]  
**Sent:** Wednesday, May 11, 2005 6:48 AM  
**To:** [wrich@ucsd.edu](mailto:wrich@ucsd.edu)  
**Subject:** RE: New SUPPORT Form

So far so good! Lets just see how the 14 days go by without any violations.

-----Original Message-----

**From:** Wade Rich [<mailto:wrich@ucsd.edu>]  
**Sent:** Wednesday, May 11, 2005 8:46 AM  
**To:** Everett, Ruth  
**Cc:** [nfiner@ucsd.edu](mailto:nfiner@ucsd.edu)  
**Subject:** RE: New SUPPORT Form

Ruth,

I am not at all clear about the pilot plan. Scott can always pull of that 24 hours, but if it were me I would save that data to a file, not erase your data, and then just continue until your regular

download day. Congrats on your enrollment ! Did everything go OK?  
Wade

---

**From:** Everett, Ruth [mailto:REverett@med.miami.edu]  
**Sent:** Wednesday, May 11, 2005 6:37 AM  
**To:** wrich@ucsd.edu  
**Subject:** RE: New SUPPORT Form

Hello Wade, how did you read my mind? I was just thinking about you because we are up and running, and have enrolled 1 baby, consented 3 and one refused. So what I wanted to know is regarding the down load, because I am part of the oxygenation pilot should I down load day one and send it to Scott, or just hold off and down load this baby once a month or every two weeks. However initially I think I am going to down load every week. When you get a chance let me know what you think.

-----Original Message-----

**From:** Wade Rich [mailto:wrich@ucsd.edu]  
**Sent:** Tuesday, May 10, 2005 4:38 PM  
**To:** ahensman@wihri.org; mball@leland.stanford.edu; grisbyca@email.uc.edu; ellen\_hale@oz.ped.emory.edu; gaynelle.hensley@utsouthwestern.edu; 'Mcdavid, Georgia E'; auten002@mc.duke.edu; linda\_reubens@urmc.rochester.edu; lucmille@iupui.edu; mcollins@peds.uab.edu; Nancy.Miller@utsouthwestern.edu; 'Nancy Newman'; npeters@wfubmc.edu; monica.konstantino@yale.edu; ae5357@wayne.edu; rbridge@ucsd.edu; risa.demetrio@sharp.com; kathy.arnell@sharp.com; Everett, Ruth; brenda.H.Morris@uth.tmc.edu; cotte010@mc.duke.edu; crosen@mednet.swmed.edu; vanmeurs@leland.stanford.edu; kurt.schibler@cchmc.org; alaptook@wihri.org; Jobea0@chmcc.org; bpointindex@iupui.edu; edward.donovan@chmcc.org; jlemons@iupui.edu; moshea@wfubmc.edu; sshankar@med.wayne.edu; Duara, Shahnaz; susie.buchter@oz.ped.emory.edu; wcarlo@peds.uab.edu; mcw3@cwru.edu; Vineet.bhandari@yale.edu; vivek.Narendran@cchmc.org; Walid.Salhab@utsouthwestern.edu; (b) (6) 'Lenora Jackson'; 'Estelle Fischer'; Mike Danyleiko (Mike Danyleiko); wrich@ucsd.edu; nfiner@ucsd.edu; higginsr@mail.nih.gov; 'Das, Abhik'; 'Poole, W. Kenneth'; Schaefer, Scott E.; 'Petrie, Carolyn'  
**Subject:** FW: New SUPPORT Form

Fellow coordinator folks,

It was my intent that you guys give some feedback on the best way to do the supplemental data collection form (Supp11)

before it became anything official. Now that Betty has sent you all a copy, please look at it and think about the best way

to gather this data. As I will be away, please forward your comments to Angelita Hensman who will collate them and help

us come up with a best plan for the form.

Thank you.

Wade

Wade Rich, RRT-NPS

Clinical Research Administrator

Division of Neonatology

UCSD Medical Center

200 W Arbor Dr

San Diego, CA 92103-8774

619-543-5375

pgr 290-(b)

---

**From:** Hastings, Betty J. [mailto:bkh@rti.org]

**Sent:** Friday, May 06, 2005 6:15 AM

**To:** ahensman@wihri.org; mball@leland.stanford.edu; grisbyca@email.uc.edu; ellen\_hale@oz.ped.emory.edu; gaynelle.hensley@utsouthwestern.edu; Georgia E McDavid; auten002@mc.duke.edu; linda\_reubens@urmc.rochester.edu; lucmille@iupui.edu; mcollins@peds.uab.edu; Nancy.Miller@utsouthwestern.edu; Nancy Newman; npeters@wfubmc.edu; monica.konstantino@yale.edu; ae5357@wayne.edu; rbridge@ucsd.edu; risa.demetrio@sharp.com; kathy.arnell@sharp.com; Reverett@med.miami.edu; brenda.H.Morris@uth.tmc.edu; cotte010@mc.duke.edu; crosen@mednet.swmed.edu; vanmeurs@leland.stanford.edu; kurt.schibler@cchmc.org; alaptook@wihri.org; Jobea0@chmcc.org; bpointindex@iupui.edu; edward.donovan@chmcc.org; jlemons@iupui.edu; moshea@wfubmc.edu; sshankar@med.wayne.edu; sduara@miami.edu; susie.buchter@oz.ped.emory.edu; wcarlo@peds.uab.edu; mcow3@cwru.edu; Vineet.bhandari@yale.edu; vivek.Narendran@cchmc.org; Walid.Salhab@utsouthwestern.edu; (b) (6) Lenora Jackson; Estelle E. Fischer; Holly Mincey; Jody Shively; Kate Bridges, MD

**Cc:** wrich@ucsd.edu; nfiner@ucsd.edu; higginsr@mail.nih.gov; Das, Abhik; Poole, W. Kenneth; Petrie, Carolyn; Schaefer, Scott E.; Auman, Jeanette O.

**Subject:** New SUPPORT Form

Attached is a Technical Memo, new SUPPORT study form(SUPP11) and corresponding MOP Chapter 16 for this form. This form is intended to be completed if an infant is on support after day 14.

Please let us know if you have questions about this material.

Thanks.

Betty <<SUP02.doc>> <<SUPP11 5-5-05 .doc>> <<Chapter 16.doc>>

**Betty Hastings**

RTI International

Statistic Research Division

P.O. Box 12194

Research Triangle Park, NC 27709-2194

Telephone: (919) 485-7740

Fax: (919) 485-7762

[bkh@rti.org](mailto:bkh@rti.org)

**From:** Archer, Stephanie (NIH/NICHD) [E]  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Request for breathing outcomes forms and manual  
**Date:** Tuesday, May 11, 2010 9:19:39 AM

---

We have 14 yeses for this now. I assume you are a yes also, right (that would make 15)?

-----Original Message-----

From: Higgins, Rosemary (NIH/NICHD) [E]  
Sent: Tuesday, May 11, 2010 8:28 AM  
To: Archer, Stephanie (NIH/NICHD) [E]  
Subject: FW: Request for breathing outcomes forms and manual

-----Original Message-----

From: Pablo Sanchez [<mailto:Pablo.Sanchez@UTSouthwestern.edu>]  
Sent: Monday, May 10, 2010 11:25 PM  
To: Higgins, Rosemary (NIH/NICHD) [E]  
Subject: Re: Request for breathing outcomes forms and manual

I suppose yes, but why does everyone want our forms and manuals??----pablo

>>> "Higgins, Rosemary (NIH/NICHD) [E]" <[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)> 5/10/10 3:36 PM >>>

Hi

The prematurity and respiratory outcomes program (PROP) which is sponsored by NHLBI has asked for the breathing outcomes forms and manual. Please send me a yes/no vote by May 17 to share these items with this newly formed group of investigators.

The PROP Network includes:

Alan Jobe (Cincinnati)  
Judy Aschner (Vanderbilt)  
Aaron Hamvas (Washington Univ)  
Roberta Kellar (UCSF)  
Gloria Pryhuber (Rochester)  
Barbara Schmidt (Penn) - Coordinating center

Rose

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network  
Pregnancy and Perinatology Branch  
Center for Developmental Biology and Perinatal Medicine  
Eunice Kennedy Shriver National Institute of Child Health and Human Development  
National Institutes of Health  
6100 Executive Blvd., Room 4B03  
MSC 7510  
Bethesda, MD 20892  
For overnight delivery use Rockville, MD 20852  
301-496-5575  
301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

## **Higgins, Rosemary (NIH/NICHD) [E]**

---

**From:** Finer, Neil <nfiner@ucsd.edu>  
**Sent:** Monday, May 10, 2010 6:30 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; 'Wally Carlo, M.D.'  
**Subject:** RE: Pulse Oximetry- Outcomes from High vs Low Targets.ppt

Hi Rose

On your graph – I would include the DR-CPAP study as it was pre-requisite to SUPPORT

Where do I go to upload the slides??

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:** Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]  
**Sent:** Monday, May 10, 2010 12:25 PM  
**To:** 'Wally Carlo, M.D.'; Finer, Neil  
**Subject:** RE: Pulse Oximetry- Outcomes from High vs Low Targets.ppt

Here is the introduction set of slides that I will give (probably 4 -5 minutes max)

Rose

---

**From:** Wally Carlo, M.D. [<mailto:WCarlo@peds.uab.edu>]  
**Sent:** Monday, May 10, 2010 3:19 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; [nfiner@ucsd.edu](mailto:nfiner@ucsd.edu)  
**Subject:** FW: Pulse Oximetry- Outcomes from High vs Low Targets.ppt

Hi Rose and Neil:

I have moved three slides from the back to the talk as we will have 15 min for the talk (as I recall).

Neil:

They want us to submit the power point presentation by tomorrow. Just wanted to remind 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: 205 266 (b)

---

**From:** Cassandra Hudson  
**Sent:** Monday, May 10, 2010 2:07 PM  
**To:** Wally Carlo, M.D.  
**Subject:** Pulse Oximetry- Outcomes from High vs Low Targets.ppt

## **Higgins, Rosemary (NIH/NICHD) [E]**

---

**From:** Finer, Neil <nfiner@ucsd.edu>  
**Sent:** Monday, May 10, 2010 6:21 PM  
**To:** Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Pulse Oximetry- Outcomes from High vs Low Targets.ppt  
**Attachments:** SUPPORT Final rev PAS-ATS May10final ATS.ppt

I arrive at 6:15  
Would you guys like to meet with me or just the 2 of you??  
Let me know  
I have added some comparative slides for COIN, VON and Rojas  
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:** Wally Carlo, M.D. [<mailto:WCarlo@peds.uab.edu>]  
**Sent:** Monday, May 10, 2010 12:59 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil  
**Subject:** RE: Pulse Oximetry- Outcomes from High vs Low Targets.ppt

Sure. I get in around noon so I can meet you whenever you want.

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: 205 266 (b)

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]  
**Sent:** Monday, May 10, 2010 2:55 PM  
**To:** Wally Carlo, M.D.; [nfiner@ucsd.edu](mailto:nfiner@ucsd.edu)  
**Subject:** RE: Pulse Oximetry- Outcomes from High vs Low Targets.ppt

Stephanie is updating one for me.

Also, I get to New Orleans around 630 PM on Saturday – do you want to have dinner or a snack??  
Rose

---

**From:** Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]  
**Sent:** Monday, May 10, 2010 3:52 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu  
**Subject:** RE: Pulse Oximetry- Outcomes from High vs Low Targets.ppt

I have an older version. I will look for it

Wally Carlo, M.D.  
Edwin M. Dixon Professor of Pediatrics  
University of Alabama at Birmingham  
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---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Monday, May 10, 2010 2:47 PM  
**To:** Wally Carlo, M.D.; nfiner@ucsd.edu  
**Subject:** RE: Pulse Oximetry- Outcomes from High vs Low Targets.ppt

Let me see if I can get one together

Rose

---

**From:** Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]  
**Sent:** Monday, May 10, 2010 3:43 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu  
**Subject:** RE: Pulse Oximetry- Outcomes from High vs Low Targets.ppt

The slides will be very helpful so others not aware of the NRN get a feeling how we are structured.

Do you want to address the efficiency we have by showing a cross sectional slides of trials and years so the audience realize we do multiple trials at the same time?

Wally Carlo, M.D.  
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---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Monday, May 10, 2010 2:25 PM  
**To:** Wally Carlo, M.D.; nfiner@ucsd.edu  
**Subject:** RE: Pulse Oximetry- Outcomes from High vs Low Targets.ppt

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Rose

---

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**Sent:** Monday, May 10, 2010 3:19 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu  
**Subject:** FW: Pulse Oximetry- Outcomes from High vs Low Targets.ppt

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Neil:

They want us to submit the power point presentation by tomorrow. Just wanted to remind you.

wally

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Cell: 205 266 (b)

---

**From:** Cassandra Hudson  
**Sent:** Monday, May 10, 2010 2:07 PM  
**To:** Wally Carlo, M.D.  
**Subject:** Pulse Oximetry- Outcomes from High vs Low Targets.ppt

**From:** Avroy Fanaroff  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** Re: Request for breathing outcomes forms and manual  
**Date:** Monday, May 10, 2010 6:19:26 PM

---

fine to share

Av

On Mon, May 10, 2010 at 4:36 PM, Higgins, Rosemary (NIH/NICHD) [E]  
<higginsr@mail.nih.gov> wrote:

> Hi

>

> The prematurity and respiratory outcomes program (PROP) which is sponsored  
> by NHLBI has asked for the breathing outcomes forms and manual. Please send  
> me a yes/no vote by May 17 to share these items with this newly formed group  
> of investigators.

>

>

>

> The PROP Network includes:

> Alan Jobe (Cincinnati)

>

> Judy Aschner (Vanderbilt)

>

> Aaron Hamvas (Washington Univ)

> Roberta Kellar (UCSF)

>

> Gloria Pryhuber (Rochester)

>

> Barbara Schmidt (Penn) – Coordinating center

>

>

>

> Rose

>

>

>

> Rosemary D. Higgins, MD

>

> Program Scientist for the Neonatal Research Network

>

> Pregnancy and Perinatology Branch

>

> Center for Developmental Biology and Perinatal Medicine

>

> Eunice Kennedy Shriver National Institute of Child Health and Human

> Development

>

> National Institutes of Health

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> 6100 Executive Blvd., Room 4B03

>

> MSC 7510

>

> Bethesda, MD 20892

- >
- > For overnight delivery use Rockville, MD 20852
- >
- > 301-496-5575
- >
- > 301-496-3790 (FAX)
- >
- > [higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)
- >
- >

--

Avroy A. Fanaroff, M.D.  
Eliza Henry Barnes Professor of Neonatology  
Rainbow Babies & Children's Hospital  
Professor of Pediatrics  
Case Western Reserve University School of Medicine  
11100 Euclid Avenue  
Cleveland, Ohio 44106  
(216) 844-3387  
[aaf2@case.edu](mailto:aaf2@case.edu)

**From:** [Ronald N. Goldberg](mailto:Ronald.N.Goldberg@mc.duke.edu)  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](mailto:Higgins.Rosemary@nih.gov)  
**Subject:** Re: Request for breathing outcomes forms and manual  
**Date:** Monday, May 10, 2010 5:02:24 PM

---

yes

Ronald N. Goldberg, M.D.  
Shaad-McBryde Professor of Pediatrics  
Chief, Neonatal-Perinatal Medicine  
Box 2739  
Duke University Medical Center  
Durham, NC 27710  
Phone: 919-681-6037  
Fax: 919-681-6065  
email: [goldb008@mc.duke.edu](mailto:goldb008@mc.duke.edu)

"Higgins, Rosemary (NIH/NICHD) [E]"  
<[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)>

05/10/2010 04:36 PM

To " (Luc.Brion@UTSouthwestern.edu)"  
<[Luc.Brion@UTSouthwestern.edu](mailto:Luc.Brion@UTSouthwestern.edu)>, " (rohls@unm.edu)"  
<[rohls@unm.edu](mailto:rohls@unm.edu)>, "aaf2@po.cwru.edu" <[aaf2@po.cwru.edu](mailto:aaf2@po.cwru.edu)>, Abhik Das <[adas@rti.org](mailto:adas@rti.org)>, "alaptook@WHR1.org" <[alaptook@WHR1.org](mailto:alaptook@WHR1.org)>, "Ambal (ambal@uab.edu)" <[ambal@uab.edu](mailto:ambal@uab.edu)>, "Brad Yoder (Bradley.yoder@hsc.utah.edu)" <[Bradley.yoder@hsc.utah.edu](mailto:Bradley.yoder@hsc.utah.edu)>, Brenda Poindexter <[bpindex@iupui.edu](mailto:bpindex@iupui.edu)>, "Carlo Waldemar (E-mail)" <[wcarlo@peds.uab.edu](mailto:wcarlo@peds.uab.edu)>, "cotte010@mc.duke.edu" <[cotte010@mc.duke.edu](mailto:cotte010@mc.duke.edu)>, Dennis Wallace <[dwallace@rti.org](mailto:dwallace@rti.org)>, Ed Bell <[Edward-bell@uiowa.edu](mailto:Edward-bell@uiowa.edu)>, Ed Donovan <[edward.donovan@cchmc.org](mailto:edward.donovan@cchmc.org)>, "Ehrenkranz Richard (E-mail)" <[richard.ehrenkranz@yale.edu](mailto:richard.ehrenkranz@yale.edu)>, "Ivan Frantz (ifrantz@tuftsmedicalcenter.org)" <[ifrantz@tuftsmedicalcenter.org](mailto:ifrantz@tuftsmedicalcenter.org)>, "Kennedy, Kathleen A" <[Kathleen.A.Kennedy@uth.tmc.edu](mailto:Kathleen.A.Kennedy@uth.tmc.edu)>, Kristi Watterberg <[kwatterberg@salud.unm.edu](mailto:kwatterberg@salud.unm.edu)>, "Kurt Schibler [kurt.schibler@cchmc.org]" <[kurt.schibler@cchmc.org](mailto:kurt.schibler@cchmc.org)>, Matthew Bizzarro <[matthew.bizzarro@yale.edu](mailto:matthew.bizzarro@yale.edu)>, Michelle Walsh <[mcw3@po.cwru.edu](mailto:mcw3@po.cwru.edu)>, Mickey Caplan <[mcaplan@northshore.org](mailto:mcaplan@northshore.org)>, "Oh William (E-mail)" <[william\\_oh@brown.edu](mailto:william_oh@brown.edu)>, Pablo Sanchez <[Pablo.Sanchez@UTSouthwestern.edu](mailto:Pablo.Sanchez@UTSouthwestern.edu)>, "Poole Kenneth (E-mail)" <[poo@rti.org](mailto:poo@rti.org)>, Roger Faix <[Roger.Faix@hsc.utah.edu](mailto:Roger.Faix@hsc.utah.edu)>, Ronald GOldberg <[goldb008@mc.duke.edu](mailto:goldb008@mc.duke.edu)>, Seetha Shankaran <[sshankar@med.wayne.edu](mailto:sshankar@med.wayne.edu)>, "Stevenson David (E-mail)" <[dstevenson@stanford.edu](mailto:dstevenson@stanford.edu)>, "Stoll Barbara (E-mail)" <[barbara\\_stoll@oz.ped.emory.edu](mailto:barbara_stoll@oz.ped.emory.edu)>, "Tyson Jon (E-mail)" <[Jon.E.Tyson@uth.tmc.edu](mailto:Jon.E.Tyson@uth.tmc.edu)>, "VanMeurs, Krisa" <[vanmeurs@leland.stanford.edu](mailto:vanmeurs@leland.stanford.edu)>

cc "Archer, Stephanie (NIH/NICHD) [E]" <[archerst@mail.nih.gov](mailto:archerst@mail.nih.gov)>, "Stevens, Timothy" <[Timothy\\_Stevens@URMC.Rochester.edu](mailto:Timothy_Stevens@URMC.Rochester.edu)>

Subject Request for breathing outcomes forms and manual

Hi

The prematurity and respiratory outcomes program (PROP) which is sponsored by NHLBI has asked for the breathing outcomes forms and manual. Please send me a yes/no vote by May 17 to share these items with this newly formed group of investigators.

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Rose

Rosemary D. Higgins, MD  
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301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

**From:** Archer, Stephanie (NIH/NICHD) [E]  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** Re: Pulse Oximetry- Outcomes from High vs Low Targets.ppt  
**Date:** Monday, May 10, 2010 4:49:01 PM

---

Should I add Vitamin E and Optimizing Cooling? If so, what start dates?

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Archer, Stephanie (NIH/NICHD) [E]  
**Sent:** Mon May 10 16:27:34 2010  
**Subject:** RE: Pulse Oximetry- Outcomes from High vs Low Targets.ppt

Yes, that's the one

---

**From:** Archer, Stephanie (NIH/NICHD) [E]  
**Sent:** Monday, May 10, 2010 4:27 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** Re: Pulse Oximetry- Outcomes from High vs Low Targets.ppt

You mean the one with the horizontal bars on a timeline? I have it and can update it.

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Archer, Stephanie (NIH/NICHD) [E]  
**Sent:** Mon May 10 15:49:09 2010  
**Subject:** FW: Pulse Oximetry- Outcomes from High vs Low Targets.ppt

Stephanie

Do you have updated slides on the overlapping trials that the NRN has done? We did this for the council report a few years ago.

I am introducing the network and the SUPPORT Trial on Sunday at ATS. Wally thinks it would be good to include in my ATS talk (attached). Please send it to me if you have it.

Thanks  
Rose

---

**From:** Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]  
**Sent:** Monday, May 10, 2010 3:43 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu  
**Subject:** RE: Pulse Oximetry- Outcomes from High vs Low Targets.ppt

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**Sent:** Monday, May 10, 2010 2:25 PM  
**To:** Wally Carlo, M.D.; nfiner@ucsd.edu  
**Subject:** RE: Pulse Oximetry- Outcomes from High vs Low Targets.ppt

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Rose

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**Sent:** Monday, May 10, 2010 3:19 PM  
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wally

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1700 6th Avenue South  
176F Suite 9380R  
Birmingham, AL 35233-7335  
Phone: 205 934 4680  
FAX: 205 934 3100  
Cell: 205 266 (b)

---

**From:** Cassandra Hudson  
**Sent:** Monday, May 10, 2010 2:07 PM

This document is provided for reference purposes only. Persons with disabilities having difficulty accessing information in this document should e-mail NICHD FOIA Office at NICHDFOIARequest@mail.nih.gov for assistance.

**To:** Wally Carlo, M.D.

**Subject:** Pulse Oximetry- Outcomes from High vs Low Targets.ppt



**From:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**To:** [Archer, Stephanie \(NIH/NICHD\) \[E\]](#)  
**Subject:** RE: Pulse Oximetry- Outcomes from High vs Low Targets.ppt  
**Date:** Monday, May 10, 2010 4:50:00 PM

---

NO

This is for this weekend, so not yet started

Thanks  
Rose

---

**From:** Archer, Stephanie (NIH/NICHD) [E]  
**Sent:** Monday, May 10, 2010 4:49 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** Re: Pulse Oximetry- Outcomes from High vs Low Targets.ppt

Should I add Vitamin E and Optimizing Cooling? If so, what start dates?

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Archer, Stephanie (NIH/NICHD) [E]  
**Sent:** Mon May 10 16:27:34 2010  
**Subject:** RE: Pulse Oximetry- Outcomes from High vs Low Targets.ppt

Yes, that's the one

---

**From:** Archer, Stephanie (NIH/NICHD) [E]  
**Sent:** Monday, May 10, 2010 4:27 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** Re: Pulse Oximetry- Outcomes from High vs Low Targets.ppt

You mean the one with the horizontal bars on a timeline? I have it and can update it.

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Archer, Stephanie (NIH/NICHD) [E]  
**Sent:** Mon May 10 15:49:09 2010  
**Subject:** FW: Pulse Oximetry- Outcomes from High vs Low Targets.ppt

Stephanie

Do you have updated slides on the overlapping trials that the NRN has done? We did this for the council report a few years ago.

I am introducing the network and the SUPPORT Trial on Sunday at ATS. Wally thinks it would be good to include in my ATS talk (attached). Please send it to me if you have it.

Thanks  
Rose

---

**From:** Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]  
**Sent:** Monday, May 10, 2010 3:43 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu  
**Subject:** RE: Pulse Oximetry- Outcomes from High vs Low Targets.ppt

The slides will be very helpful so others not aware of the NRN get a feeling how we are structured.

Do you want to address the efficiency we have by showing a cross sectional slides of trials and years so the audience realize we do multiple trials at the same time?

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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**Sent:** Monday, May 10, 2010 2:25 PM  
**To:** Wally Carlo, M.D.; nfiner@ucsd.edu  
**Subject:** RE: Pulse Oximetry- Outcomes from High vs Low Targets.ppt

Here is the introduction set of slides that I will give (probably 4 -5 minutes max)

Rose

---

**From:** Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]  
**Sent:** Monday, May 10, 2010 3:19 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu  
**Subject:** FW: Pulse Oximetry- Outcomes from High vs Low Targets.ppt

Hi Rose and Neil:

I have moved three slides from the back to the talk as we will have .15 min for the talk (as I recall).

Neil:

They want us to submit the power point presentation by tomorrow. Just wanted to remind you.

wally

Wally Carlo, M.D.  
Edwin M. Dixon Professor of Pediatrics

University of Alabama at Birmingham  
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**To:** [Archer, Stephanie \(NIH/NICHD\) \[E\]](#)  
**Subject:** FW: Pulse Oximetry- Outcomes from High vs Low Targets.ppt  
**Date:** Monday, May 10, 2010 3:49:00 PM  
**Attachments:** [SUPPORT TRAIL OVERVIEW FOR ATS.ppt](#)  
**Importance:** High

---

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wally

Wally Carlo, M.D.  
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University of Alabama at Birmingham  
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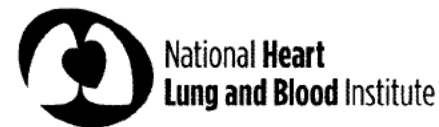
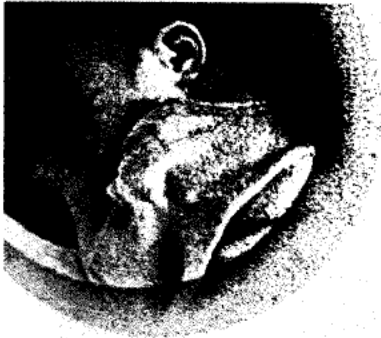
---

**From:** Cassandra Hudson  
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NICHD

# SUPPORT TRIAL

## NICHD Neonatal Research Network



# NICHD NRN Mission

The Neonatal Research Network is designed to conduct studies to investigate the safety and efficacy of treatment and management strategies to care for newborn infants.



# Origins of Neonatal Research Network (NRN)

- Neonatal management, especially for high-risk term and preterm infants, has often adopted practices without objective evaluation
- NICHD established the Neonatal Research Network in 1986 to address the need for well-designed clinical trials in Neonatal Medicine





# NICHD NRN Aims

- Identify priority issues for research in the promotion of infant health and prevention of disease
- Evaluate interventions for efficacy, safety, and cost-effectiveness, including:
  - Translational research
  - Genetics
  - New technologies



# Background NRN

- Collaborative participation on common protocols
- Cooperative agreements
- Competitively peer-reviewed
  - Open competition
  - Content of grant, concept proposal, depth of faculty and institution
  - Priority score
  - Diversity in population



# Neonatal Practice 2003-2004

- Trend towards more use of CPAP
- Trend towards use of lower oxygen saturation targets

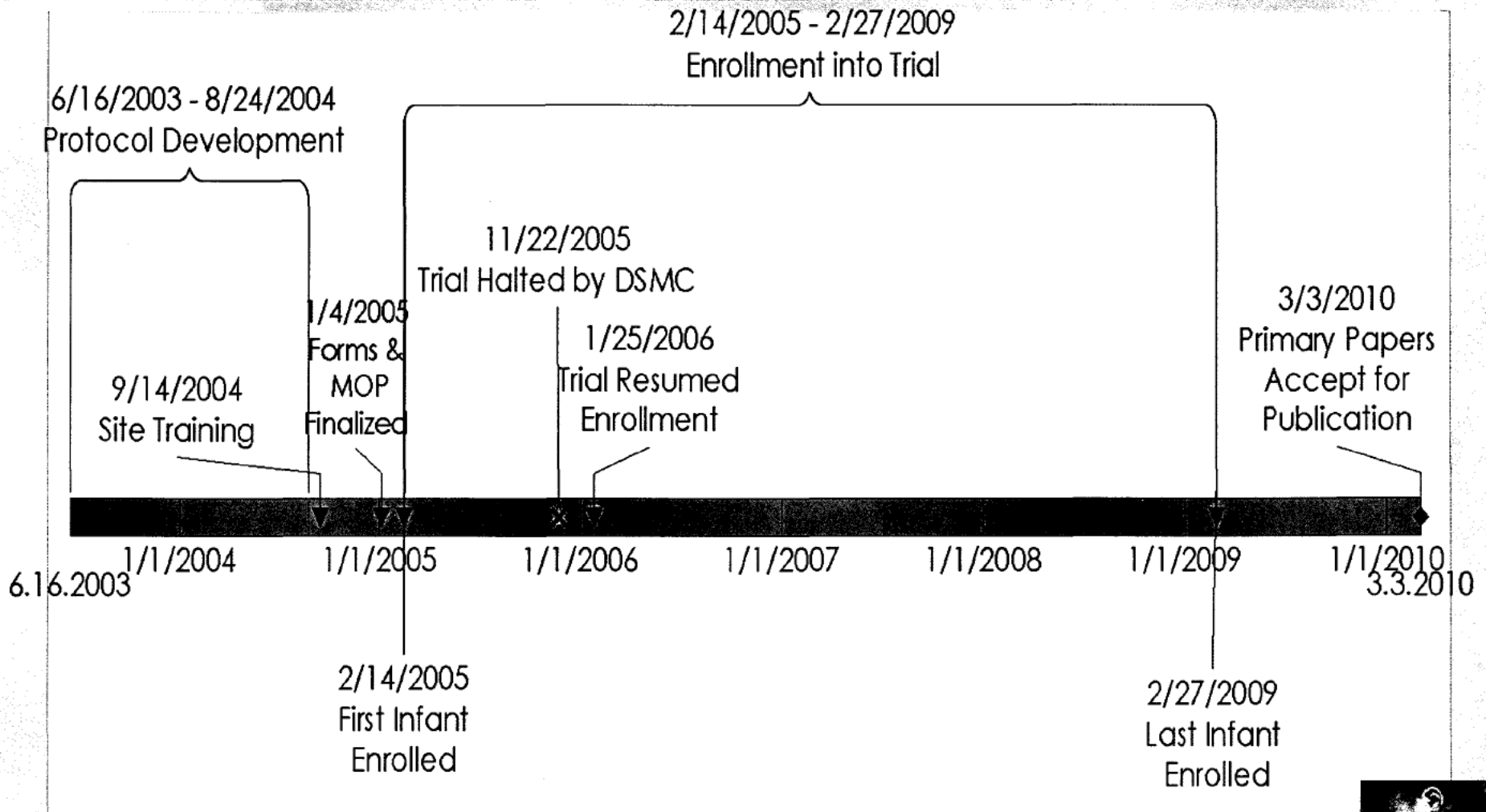


# SUPPORT RESEARCH QUESTIONS

- Where do we target saturations for optimal outcome?
  - Low 90's
  - Mid-high 80's
- What's better?
  - Early Surfactant
  - CPAP

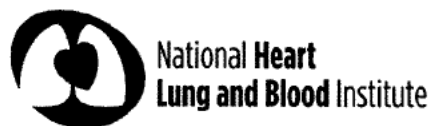


# SUPPORT TIMELINE



# NICHD Neonatal Research Network SUPPORT Trial Centers (2004-2009)

- Brown University
- Case Western Reserve University
- Duke University
- Emory University
- Indiana University
- Research Triangle Institute
- Stanford University
- Tufts Medical Center
- University of Alabama – Birmingham
- University of Cincinnati
- University of California – San Diego
- 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
- Wayne State University
- Wake Forest University
- Yale University



NICHD



**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Blaisdell, Carol (NIH/NHLBI) [E]  
**Subject:** RE: support breathing outcomes  
**Date:** Monday, May 10, 2010 1:50:00 PM

---

Can you give me a call when you have a minute??  
301-435-7909

I have tried twice to leave you a message and have not gotten your voicemail

Rose

---

**From:** Blaisdell, Carol (NIH/NHLBI) [E]  
**Sent:** Monday, May 10, 2010 10:55 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: support breathing outcomes

Yes, that would be great.

Carol

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Monday, May 10, 2010 10:55 AM  
**To:** Blaisdell, Carol (NIH/NHLBI) [E]  
**Subject:** RE: support breathing outcomes

This needs Steering Committee approval – would you like me to send it for a vote?

Thanks

Rose

---

**From:** Blaisdell, Carol (NIH/NHLBI) [E]  
**Sent:** Monday, May 10, 2010 10:52 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** support breathing outcomes

Dear Rose,

Hope you enjoyed PAS and had a little time to explore Vancouver (you had a busy schedule ☺).

Our prematurity and respiratory outcomes program (PROP) was just awarded (start 5/1).

Alan Jobe is one of the PIs, and would like to make use of the breathing outcomes surveys that were developed for PROP. We are having a meeting of the pulmonology co-Is and PIs (neonatologists) at ATS and I would like to distribute some of the SUPPORT breathing outcome CRFs as a starting point for discussions on developing tools to assess respiratory disease risk/phenotyping in NICU grads.

Attached are the ones Alan and I were thinking of distributing, but wanted your input on what can and cannot be shared. The MOP is something that looks like I should NOT distribute.

How was the feedback at PAS about SUPPORT?

Thanks, Carol

**Carol J. Blaisdell, M.D.**  
**Medical Officer**  
**Lung Developmental Biology and**  
**Pediatric Pulmonary Diseases**  
**Division of Lung Diseases, NHLBI/NIH**  
**(301) 435-0222 phone**



## Higgins, Rosemary (NIH/NICHD) [E]

---

**From:** Finer, Neil <nfiner@ucsd.edu>  
**Sent:** Thursday, May 06, 2010 1:48 PM  
**To:** Gantz, Marie  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]; WCarlo@peds.uab.edu; Rich, Wade; Das, Abhik  
**Subject:** Re: PDF of your article

Thanks Marie

The definition of bpd is made clear in the methods and again on the table I think they already noted the figure issue and were changing both

Neil  
Sent from my iPhone

On May 6, 2010, at 10:26 AM, "Gantz, Marie" <[mgantz@rti.org](mailto:mgantz@rti.org)> wrote:

> Neil,  
>  
> I've read the proofs and these are my comments.  
>  
> In the abstract, shouldn't the primary outcome be described as death  
> or requirement for supplemental oxygen or positive pressure support  
> at 36 weeks (with an attempt at withdrawal...) Positive pressure supp  
> ort is not mentioned in the abstract, although it is in the Outcomes  
> section on page 3.  
>  
> In the box at the top of page 4 describing Figure 1 it states that the  
> numbers "exclude pregnant women who were screened but hose babies  
> were not subsequently born at a study center between 24 weeks 0 days  
> and 27 weeks 6 days of gestation." It is more accurate to say that  
> the numbers exclude babies who were not enrolled in the GDB; they  
> include infants enrolled in the GDB who were born outside of the SUP  
> PORT GA window.  
>  
> WALLY: The comment above also applies to Figure 1 in your paper.  
> Sorry I didn't catch that before.  
>  
> NEIL: I have to get off the internet and I did not have a chance to  
> check all of the numbers in the appendix tables, but please check them  
> against the attached version of the tables (these are the last  
> versions I sent you).  
>  
> I will not have internet access for the rest of the day. Hope this is  
> the last of it!  
>  
> 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: Thursday, May 06, 2010 11:48 AM  
> To: 'higginsr@mail.nih.gov'; 'WCarlo@peds.uab.edu'; Rich, Wade; Das,  
> Abhik; Gantz, Marie  
> Subject: FW: PDF of your article  
>  
> FYI  
>  
> From: Nejm Article [<mailto:nejmarticle@mms.org>]  
> Sent: Thursday, May 06, 2010 5:06 AM  
> To: Finer, Neil  
> Subject: PDF of your article  
>  
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> <T2 Other Outcomes - 23NOV09.doc>  
> <T1 Patient Description - 17NOV09.doc> <Cause of Death - 09NOV09.doc>

## Higgins, Rosemary (NIH/NICHD) [E]

---

**From:** Finer, Neil <nfiner@ucsd.edu>  
**Sent:** Thursday, May 06, 2010 1:44 PM  
**To:** Wally Carlo, M.D.  
**Cc:** Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; WCarlo@peds.uab.edu; Rich, Wade; Das, Abhik  
**Subject:** Re: PDF of your article

I agree with Wally  
Neil

Sent from my iPhone

On May 6, 2010, at 10:40 AM, "Wally Carlo, M.D." <WCarlo@peds.uab.edu> wrote:

> Marie.

>

> I think we should not introduce the GDB at this stage. I think the  
> statement is reasonable and sufficient to clarify to readers who got  
> enrolled. It is a technical clarification that may not be needed.  
> What do others think?

>

> Wally

>

> -----Original Message-----

> From: Gantz, Marie <mgantz@rti.org>

> Sent: Thursday, May 06, 2010 1:25 PM

> To: Finer, Neil <nfiner@ucsd.edu>; higginsr@mail.nih.gov

> <higginsr@mail.nih.gov

> >; WCarlo@peds.uab.edu <WCarlo@peds.uab.edu>; Rich, Wade

> ><wrich@ucsd.edu ; Das, Abhik <adas@rti.org>

> Subject: RE: PDF of your article

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> Neil,

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> I've read the proofs and these are my comments.

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>  
>  
> Marie

>  
>  
>  
>  
>  
>  
>  
> Marie Gantz, Ph.D.

>  
> Research Statistician

>  
> RTI International

>  
> [mgantz@rti.org](mailto:mgantz@rti.org)

>  
> 828-254-6255

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> \_\_\_\_\_  
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> From: Finer, Neil [<mailto:nfiner@ucsd.edu>]

> Sent: Thursday, May 06, 2010 11:48 AM

> To: 'higginsr@mail.nih.gov'; 'WCarlo@peds.uab.edu'; Rich, Wade; Das,

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**From:** [Bock, Robert \(NIH/NICHD\) \[E\]](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Cc:** [Spong, Catherine \(NIH/NICHD\) \[E\]](#)  
**Subject:** RE: May 16 NHLBI lunch session at ATS  
**Date:** Thursday, May 06, 2010 1:08:54 PM

---

If you trust him not to share the material with the press and break the embargo, I don't see any problem with it.

Cathy, what do you think?

-----Original Message-----

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Thursday, May 06, 2010 1:06 PM  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Cc:** Spong, Catherine (NIH/NICHD) [E]  
**Subject:** Re: May 16 NHLBI lunch session at ATS

John Kinsella, the discussant

----- Original Message -----

**From:** Bock, Robert (NIH/NICHD) [E]  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Spong, Catherine (NIH/NICHD) [E]  
**Sent:** Thu May 06 13:00:50 2010  
**Subject:** RE: May 16 NHLBI lunch session at ATS

Shared with who?

-----Original Message-----

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Thursday, May 06, 2010 1:00 PM  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Cc:** Spong, Catherine (NIH/NICHD) [E]  
**Subject:** May 16 NHLBI lunch session at ATS

Bob

Both Neil Finer and Wally Carlo are presenting the SUPPORT study at ATS. There are two discussants, Dr. Rose Viscardi and Dr. John Kinsella. Rose attended the SUPPORT sessions at PAS. Unfortunately, John had any emergency and could not attend. Can the slides for the talks be shared in advance of the meeting (say perhaps late next week, just prior to the on-line release) on Friday?

Thanks

Rose

**From:** [Hogan, Sharon](#)  
**To:** [Archer, Stephanie \(NIH/NICHD\) \[E\]](#); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); ["wcarlo@peds.uab.edu"](mailto:wcarlo@peds.uab.edu)  
**Cc:** [Moskowitz, Deborah](#)  
**Subject:** RE: Your page proofs in the NEJM  
**Date:** Thursday, May 06, 2010 12:13:19 PM

---

Hi, Wally,

Please confirm that these changes (to the Appendix) apply to your article only and not to Dr. Finer's article. We have made the author line consistent in both articles.

Thanks,

Sharon

Sharon Cloud Hogan  
Manuscript Editor  
The New England Journal of Medicine  
10 Shattuck St.  
Boston, MA 02115-6094  
phone: 617-487-6564, 781-740-4482, or 1-800-445-8080  
fax: 617-739-9864  
[shogan@nejm.org](mailto:shogan@nejm.org)

-----Original Message-----

From: Archer, Stephanie (NIH/NICHD) [E] [<mailto:archerst@mail.nih.gov>]  
Sent: Thursday, May 06, 2010 11:07 AM  
To: Higgins, Rosemary (NIH/NICHD) [E]; ["wcarlo@peds.uab.edu"](mailto:wcarlo@peds.uab.edu)  
Subject: RE: Your page proofs in the NEJM

Hi Wally,

Attached is a Word file with changes to make to the Acknowledgements Section.

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)

-----Original Message-----

From: Higgins, Rosemary (NIH/NICHD) [E]  
Sent: Thursday, May 06, 2010 11:03 AM  
To: ["wcarlo@peds.uab.edu"](mailto:wcarlo@peds.uab.edu); Archer, Stephanie (NIH/NICHD) [E]  
Subject: URGENT:Re: Your page proofs in the NEJM

Stephanie

Can you assist Wally?? We need the boilerplate changes within the next hour.



Thanks  
Rose

----- Original Message -----

From: Wally Carlo, M.D. <WCarlo@peds.uab.edu>  
To: Higgins, Rosemary (NIH/NICHD) [E]  
Sent: Thu May 06 11:00:17 2010  
Subject: RE: Your page proofs in the NEJM

ok

Wally

-----Original Message-----

From: Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov>  
Sent: Thursday, May 06, 2010 10:52 AM  
To: 'adas@rti.org' <adas@rti.org>; 'wcarlo@peds.uab.edu' <wcarlo@peds.uab.edu>; 'mgantz@rti.org' <mgantz@rti.org>  
Subject: Re: Your page proofs in the NEJM

SUPPORT study group or subcommittee on behalf or EKS NICHD NRN

Thanks  
Rose

----- Original Message -----

From: Das, Abhik <adas@rti.org>  
To: Wally Carlo, M.D. <WCarlo@peds.uab.edu>; Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie <mgantz@rti.org>  
Sent: Thu May 06 09:49:41 2010  
Subject: RE: Your page proofs in the NEJM

Wally:

I quickly looked at this, and it looks like they have made the changes we asked for. One question about the authorship -- should it be NICHD NRN and SUPPORT Study Group, or SUPPORT Study Group on behalf of the NICHD NRN? Also, the footnote for authorship on the 1st page mentions some 'writing committee', that I don't think ever existed (at least, formally!). Perhaps they can simply write here: "The authors and their affiliations are listed in the Appendix. Address reprint requests to Dr. Wally Carlo at ..."

Thanks

Abhik

-----Original Message-----

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]  
Sent: Wednesday, May 05, 2010 7:03 PM  
To: Rosemary (NIH/NICHD) Higgins; Gantz, Marie; Das, Abhik  
Subject: FW: Your page proofs in the NEJM  
Importance: High

Wally

This document is provided for reference purposes only. Persons with disabilities having difficulty accessing information in this document should e-mail NICHD FOIA Office at [NICHDFOIARequest@mail.nih.gov](mailto:NICHDFOIARequest@mail.nih.gov) for assistance.

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**From:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**To:** [Bock, Robert \(NIH/NICHD\) \[E\]](#)  
**Cc:** [Spong, Catherine \(NIH/NICHD\) \[E\]](#)  
**Subject:** SUPPORT close to final NEJM papers  
**Date:** Thursday, May 06, 2010 12:07:00 PM  
**Attachments:** [1carl\\_0a\\_OLF\[1\].pdf](#)  
[2fine\\_0a\\_OLF.pdf](#)

---

Bob

Here are the "close to final" SUPPORT papers. I have asked both authors to list the group as SUPPORT Study on behalf of the Eunice Kennedy Shriver NICHD Neonatal Research Network. I also was told last night (a the dinner for the Resuscitation Workshop that I and Raju are attending) that there is most certainly an editorial. Colin Morley told me he wrote it (and that NEJM re-wrote it). NEJM has not told us this yet. I am not sure if this editorial will be in the on-line release on 5/16.

Let me know if you need anything else from me. I am leaving Vancouver tonight and will get home tomorrow, but am taking the remainder of the day off. You can reach me on my B or cell if you need to talk to me I am set with your edits for the press teleconference to occur on 5/12.

Thanks for all your help

Rose

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "wcarlo@peds.uab.edu"  
**Subject:** Re: URGENT:Re: Your page proofs in the NEJM  
**Date:** Thursday, May 06, 2010 11:15:00 AM

---

Are you all set now??

----- Original Message -----

From: Wally Carlo, M.D. <WCarlo@peds.uab.edu>  
To: Higgins, Rosemary (NIH/NICHD) [E]  
Sent: Thu May 06 11:13:45 2010  
Subject: RE: URGENT:Re: Your page proofs in the NEJM

Thanks.

Wally

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Sent: Thursday, May 06, 2010 11:03 AM  
To: 'wcarlo@peds.uab.edu' <wcarlo@peds.uab.edu>; Archer, Stephanie (NIH/NICHD) [E] <archerst@mail.nih.gov>  
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To: Wally Carlo, M.D. <WCarlo@peds.uab.edu>; Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie

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Sent: Thu May 06 09:49:41 2010

Subject: RE: Your page proofs in the NEJM

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Thanks

Abhik

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From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]

Sent: Wednesday, May 05, 2010 7:03 PM

To: Rosemary (NIH/NICHD) Higgins; Gantz, Marie; Das, Abhik

Subject: FW: Your page proofs in the NEJM

Importance: High

Wally

**From:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**To:** [Archer, Stephanie \(NIH/NICHD\) \[E\]](#)  
**Subject:** Re: Protocol Review | SUPPORT ROP  
**Date:** Thursday, May 06, 2010 10:55:33 AM

---

I looked at this protocol and there are significant issues -over 200 kids have expired. We have already followed up over 75 percent of the survivors. We have not introduced the genomics idea to the parents. I am not so sure this has appropriate feasibility.

Rose

---

**From:** Archer, Stephanie (NIH/NICHD) [E]  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Thu May 06 10:44:14 2010  
**Subject:** RE: Protocol Review | SUPPORT ROP

I talked to John and he is willing to review the protocol.

Since the GPN meeting a few weeks ago, John did get new information from the GPN specimen analysis center at UPenn. They changed their extraction protocol from the Oragene tubes and may be getting higher yields now. We don't have the complete data back yet. Not sure if, for instance, the lower yield samples were from earlier preemies vs. term babies.

This might not impact Mike's study if he's gathering saliva from SUPPORT toddlers/young children vs. babies. I'm assuming that Mike intends to collect these samples at the SUPPORT MRI 6-7 Year FU? This wasn't specifically stated in the protocol, but he's too late for most of the 18-22 months FUs.

Mike's budget looks pretty good, except no indirects, of course. I didn't see a line item for purchase of the Oragene tubes. These tubes do expire after a while (I'd have to check on how long they are good for), so sites/RTI might have to make multiple purchases of the tubes.

One thing that UPenn is going to do for GPN is to run the samples through PCR analysis first to see if each sample is worth putting on a SNP chip - so we don't waste money on expensive chips for nothing.

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Thursday, May 06, 2010 1:32 AM  
**To:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: Protocol Review | SUPPORT ROP

thanks for the info - is this publicly available?? if not, it may present some issues - perhaps we could ask Uma or John to review the study (then they could potentially comment "on the record"). Can you ask Uma or JOHN is this is publicly available?

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](mailto:higginsr@mail.nih.gov)

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**From:** Archer, Stephanie (NIH/NICHD) [E]  
**Sent:** Wednesday, May 05, 2010 3:21 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** Protocol Review | SUPPORT ROP

FYI, Mike's protocol is proposing to use Oragene tubes to collect buccal swabs. Uma has heard from questions about using this in neonates and getting reliable yields for DNA analysis. GPN has some preliminary tests on saliva vs. cord blood samples and gotten some mixed results. We're going to try going back to the tubes that didn't replicate well and extract the entire tube, rather than a portion of it, for analysis to see if that improves.

These were on neonates. Not sure what the extended genomics community is finding for toddlers/young children, but might be worth asking.

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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:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Wednesday, May 05, 2010 12:15 PM  
**To:** 'Brenda Poindexter'; Robin E.' Webb  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; Das, Abhik; kristin zaterka  
**Subject:** FW: concept and protocol

Robin-  
Can you set up a protocol review call?  
Brenda – can you assign reviewers?

Thanks  
Rose  
Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network

---

**From:** Michael Cotten [mailto:cotte010@mc.duke.edu]  
**Sent:** Saturday, May 01, 2010 5:45 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** 'goldb008@mc.duke.edu'; John  
**Subject:** Re: concept and protocol

Hi Rose...

here's the protocol submission for the SUPPORT secondary to test for associations between genetic variants in angiogenesis and oxygen response pathway genes and ROP, w/ assessment of interactions with the oxygen sat target.

thanks

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: 919-681-6024  
fax: 919-681-6065  
email: cotte010@mc.duke.edu

"Higgins, Rosemary (NIH/NICHD) [E]"  
<higginsr@mail.nih.gov>  
05/01/2010 09:14 AM

To "cotte010@mc.duke.edu" <cotte010@mc.duke.edu>  
cc "goldb008@mc.duke.edu" <goldb008@mc.duke.edu>  
Subject Re: concept and protocol

Mike

We are currently tracking the neuroimaging cohort (approx 560). There is a protocol to follow the breathing outcomes infants, but this requires revisions and needs to go back to protocol review. This also would exclude the deaths from the study (slightly over 200).

Hope this helps  
Rose

---

**From:** Michael Cotten <cotte010@mc.duke.edu>  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Sat May 01 01:55:41 2010  
**Subject:** Re: concept and protocol

Hi Rose..in finalizing the SUPPORT secondary to submit, I've come to realize that the follow up is complete for the study kids....except maybe about 100 still missing....per the montly report....is there longer term followup in the works for the SUPPORT cohort?

I've asked John Dagle whether or not they are sending out buccal swabs to homes for samples from



kids and if they've had success...otherwise..w/o further followup for the SUPPORT kids, I don't think we'll be able to do the oxygen-genomics proposal....

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: 919-681-6024  
fax: 919-681-6065  
email: cotte010@mc.duke.edu

"Higgins, Rosemary (NIH/NICHD) [E]"  
<higginsr@mail.nih.gov>  
04/05/2010 04:18 PM

To "Michael Cotten" <cotte010@mc.duke.edu>  
cc "Archer, Stephanie (NIH/NICHD) [E]" <archerst@mail.nih.gov>, "Ron Goldberg  
(goldb008@mc.duke.edu)" <goldb008@mc.duke.edu>  
Subject concept and protocol

Mike

We have the following concept you presented which is overdue for a protocol submission. If we do not receive a protocol by May 1, we will remove this from the pending list:

SUPPORT DNA collection for ROP risk

We also have the following protocol which is overdue for a protocol resubmission. IF we do not receive a revision by June 1, we will remove it from the list:

Prospective DNA Repository

Thanks

Rose

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network  
Pregnancy and Perinatology Branch  
Center for Developmental Biology and Perinatal Medicine  
Eunice Kennedy Shriver National Institute of Child Health and Human Development  
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**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "wcarlo@peds.uab.edu"; "adas@rti.org"; "mgantz@rti.org"  
**Subject:** Re: Your page proofs in the NEJM  
**Date:** Thursday, May 06, 2010 10:49:09 AM

---

Wally

We should be called the Eunice Kennedy Shriver NICHD Neonatal Research Network.

Also, Stephanie said they did not make all of the requested changes in the boilerplate. I will have her create on on word document for teh additions and send it.

Thanks

Rose

----- Original Message -----

From: Wally Carlo, M.D. <WCarlo@peds.uab.edu>  
To: Das, Abhik <adas@rti.org>; Wally Carlo, M.D. <WCarlo@peds.uab.edu>; Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie <mgantz@rti.org>  
Sent: Thu May 06 10:46:29 2010  
Subject: RE: Your page proofs in the NEJM

I alreadyasked the to take out the writing committee. The wording is similar to what you suggest.

I actually like the NRN first as that is our main group and what will persist. . It was their idea.

Wally

-----Original Message-----

From: Das, Abhik <adas@rti.org>  
Sent: Thursday, May 06, 2010 9:49 AM  
To: Wally Carlo, M.D. <WCarlo@peds.uab.edu>; Rosemary (NIH/NICHD) Higgins <higginsr@mail.nih.gov>; Gantz, Marie <mgantz@rti.org>  
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Importance: High

Wally

**From:** Archer, Stephanie (NIH/NICHD) [E]  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Oximtrex galleys  
**Date:** Thursday, May 06, 2010 10:20:51 AM  
**Attachments:** Carlo\_SUPPORT\_galleys\_2010-05-05\_swa.pdf

---

The authors are in the correct order, but they did not make all of the requested changes on the boilerplate. See attached with red balloons for changes.

---

Stephanie Wilson Archer  
The Eunice Kennedy Shriver  
National Institute of Child Health and Human Development  
Pregnancy & Perinatology Branch  
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Rockville, MD 20852

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**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Thursday, May 06, 2010 1:41 AM  
**To:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** Oximtrex galleys  
**Importance:** High

Stephanie

Here are Wally's galleys- can you make sure the authors are in the appropriate order and that the correct individuals are listed in the boilerplate?

Please do this first on THURSDAY and send it back to me.

Also, I will not be in the office until Monday now. I am taking a leave day on Friday.

Rose  
Rosemary D. Higgins, MD  
Program Scientist for the *Eunice Kennedy Shriver* NICHD Neonatal Research Network  
Pregnancy and Perinatology Branch  
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**From:** Archer, Stephanie (NIH/NICHD) [E]  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Protocol Review | SUPPORT ROP  
**Date:** Thursday, May 06, 2010 9:17:08 AM

---

GPN's analysis isn't available publicly yet, but the question of quality between saliva and blood samples is "out there" in the community. Uma came across it in another conference - someone in Australia, I believe, completed study recruitment collecting neonatal saliva then couldn't use it because of quality issues. That's why GPN decided to do a small sample analysis to see how usable our samples are going to be.

I'll talk to John and Uma today.

---

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C. Michael Cotten MD MHS  
Associate Professor of Pediatrics  
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301-496-3790 (FAX)  
higginsr@mail.nih.gov

## **Higgins, Rosemary (NIH/NICHD) [E]**

---

**From:** Finer, Neil <nfiner@ucsd.edu>  
**Sent:** Wednesday, May 05, 2010 7:24 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** Fwd: NEJM article

FYI  
Neil

Sent from my iPhone

Begin forwarded message:

From: "Moskowitz, Deborah" <dmoskowitz@nejm.org<mailto:dmoskowitz@nejm.org>>  
Date: May 5, 2010 3:36:48 PM PDT  
To: "Finer, Neil" <nfiner@ucsd.edu<mailto:nfiner@ucsd.edu>>  
Subject: RE: NEJM article

Group on the first page – there was just no room for all the authors. They're now listed in the Appendix.

I've asked Layout to resend the page proofs to you. You should receive them in the morning – please let me know if you do not.

--Debbie

From: Finer, Neil [<mailto:nfiner@ucsd.edu>]  
Sent: Wednesday, May 05, 2010 6:09 PM  
To: Moskowitz, Deborah  
Cc: 'higginsr@mail.nih.gov<<mailto:higginsr@mail.nih.gov>>'  
Subject: RE: NEJM article

Hi Debbie  
I don't seem to have any galley's  
What was the decision about authors – group vs individuals etc??  
Thanks again  
Neil

From: Moskowitz, Deborah [<mailto:dmoskowitz@nejm.org>]  
Sent: Wednesday, May 05, 2010 2:40 PM  
To: Finer, Neil  
Subject: RE: NEJM article

Thanks so much! I believe you should have received page proofs of your article on Friday, April 30. Did you not receive them?

From: Finer, Neil [<mailto:nfiner@ucsd.edu>]  
Sent: Wednesday, May 05, 2010 5:21 PM  
To: Moskowitz, Deborah; 'WCarlo@peds.uab.edu<<mailto:WCarlo@peds.uab.edu>>'  
Cc: 'higginsr@mail.nih.gov<<mailto:higginsr@mail.nih.gov>>'; Rich, Wade

Subject: RE: NEJM article

Hi Debbie

1. For simplicity – leave out airway
2. You are correct – please make the same as the Carlo Paper
3. You are correct with the (b) (4)

Many thanks

I did not receive another version of the galleys There was no attachment with your email Be well Neil

From: Moskowitz, Deborah [mailto:dmoskowitz@nejm.org]  
Sent: Wednesday, May 05, 2010 11:53 AM  
To: Finer, Neil  
Subject: NEJM article  
Importance: High

Hi, Dr. Finer,

I have a few questions concerning your NEJM article:

(b) (4)

Did the page proofs look OK to you? Let me know if you have any further changes.

Thanks!  
--Debbie

Deborah K. Moskowitz  
Senior Manuscript Editor  
The New England Journal of Medicine  
<mailto:dmoskowitz@nejm.org>dmoskowitz@nejm.org<mailto:dmoskowitz@nejm.org>  
tel: 617-487-6509

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**From:** Das, Abhik  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** FW: concept and protocol  
**Date:** Wednesday, May 05, 2010 2:37:56 PM

---

I probably don't remember, but did we discuss this in the SUPPORT subcommittee?

Thanks  
Abhik

Abhik Das  
Senior Research Statistician  
RTI International

-----Original Message-----

From: Poindexter, Brenda B [mailto:[bpoindex@iupui.edu](mailto:bpoindex@iupui.edu)]  
Sent: Wednesday, May 05, 2010 02:05 PM Eastern Standard Time  
To: richard.ehrenkranz@yale.edu; kwatterberg@salud.unm.edu; ifrantz@tuftsmedicalcenter.org; jon.e.tyson@uth.tmc.edu; kurt.schibler@cchmc.org; Roger.Faix@hsc.utah.edu; Wallace, Dennis; Das, Abhik  
Cc: 'Higgins, Rosemary (NIH/NICHD) [E]'; Webb, Robin E.; Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin  
Subject: FW: concept and protocol

Protocol Review Subcommittee-

Robin will be setting up a call to discuss the attached protocol - depending on availability we could even consider trying to meet in DC during the upcoming meeting. Kurt, given your genomics expertise I'd like to ask you to review this one (promise you'll get a break next time-I know you just reviewed the other SUPPORT secondary as well) and would also like to ask Ivan to review. Let me know if either of you have any conflicts. Thanks, Brenda

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)]  
Sent: Wednesday, May 05, 2010 12:15 PM  
To: Poindexter, Brenda B; Robin E.' Webb  
Cc: Archer, Stephanie (NIH/NICHD) [E]; Das, Abhik; kristin zaterka  
Subject: FW: concept and protocol

Robin-  
Can you set up a protocol review call?  
Brenda - can you assign reviewers?

Thanks  
Rose  
Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network

---

From: Michael Cotten [mailto:[cotte010@mc.duke.edu](mailto:cotte010@mc.duke.edu)]  
Sent: Saturday, May 01, 2010 5:45 PM  
To: Higgins, Rosemary (NIH/NICHD) [E]  
Cc: 'goldb008@mc.duke.edu'; John  
Subject: Re: concept and protocol

Hi Rose...

here's the protocol submission for the SUPPORT secondary to test for associations between genetic variants in angiogenesis and oxygen response pathway genes and ROP, w/ assessment of interactions with the oxygen sat target.

thanks

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: 919-681-6024  
fax: 919-681-6065  
email: cotte010@mc.duke.edu  
"Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>

05/01/2010 09:14 AM

To

"cotte010@mc.duke.edu" <cotte010@mc.duke.edu>

cc

"goldb008@mc.duke.edu" <goldb008@mc.duke.edu>

Subject

Re: concept and protocol

Mike

We are currently tracking the neuroimaging cohort (approx 560). There is a protocol to follow the breathing outcomes infants, but this requires revisions and needs to go back to protocol review. This also would exclude the deaths from the study (slightly over 200).

Hope this helps

Rose

---

From: Michael Cotten <cotte010@mc.duke.edu>  
To: Higgins, Rosemary (NIH/NICHD) [E]  
Sent: Sat May 01 01:55:41 2010  
Subject: Re: concept and protocol

Hi Rose..in finalizing the SUPPORT secondary to submit, I've come to realize that the follow up is complete for the study kids....except maybe about 100 still missing....per the montly report....is there longer term followup in the works for the SUPPORT cohort?

I've asked John Dagle whether or not they are sending out buccal swabs to homes for samples from kids and if they've had success...otherwise..w/o further followup for the SUPPORT kids, I don't think we'll be able to do the oxygen-genomics proposal....

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: 919-681-6024  
fax: 919-681-6065  
email: cotte010@mc.duke.edu  
"Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>

04/05/2010 04:18 PM

To

"Michael Cotten" <cotte010@mc.duke.edu>

cc

"Archer, Stephanie (NIH/NICHD) [E]" <archerst@mail.nih.gov>, "Ron Goldberg (goldb008@mc.duke.edu)" <goldb008@mc.duke.edu>

Subject

concept and protocol

Mike

We have the following concept you presented which is overdue for a protocol submission. If we do not receive a protocol by May 1, we will remove this from the pending list:

SUPPORT DNA collection for ROP risk

We also have the following protocol which is overdue for a protocol resubmission. IF we do not receive a revision by June 1, we will remove it from the list:

Prospective DNA Repository

Thanks

Rose

Rosemary D. Higgins, MD

Program Scientist for the Neonatal Research Network

Pregnancy and Perinatology Branch

Center for Developmental Biology and Perinatal Medicine

Eunice Kennedy Shriver National Institute of Child Health and Human Development

National Institutes of Health

6100 Executive Blvd., Room 4B03

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For overnight delivery use Rockville, MD 20852

301-496-5575

301-496-3790 (FAX)

[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)



**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Robin E." Webb  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; Das, Abhik; kristin.zaterka  
**Subject:** FW: SUPPORT data queries  
**Date:** Wednesday, May 05, 2010 12:13:00 PM  
**Attachments:** [cpap center and learning effects 4-21-10final.docx](#)  
[oxygen-SUPPORT secondary 4-21-10final.docx](#)

---

Robin

Can you send to the SUPPORT subcommittee and set up a call??

Thanks

Rose

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network

---

**From:** Michael Cotten [mailto:cotte010@mc.duke.edu]  
**Sent:** Saturday, May 01, 2010 8:19 PM  
**To:** Neil Finer; Wally Carlo, M.D.  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]; Ronald N Goldberg  
**Subject:** SUPPORT data queries

Hi Neil and Wally, Rose and Ron...

first..congratulations on the first presentation of results and publication of the manuscripts!!!!

here are two secondary data analysis proposals for SUPPORT,,,,one looking at the DR CPAP portion of the study, the other at the oxygen sat target portion.

thanks

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: 919-681-6024  
fax: 919-681-6065  
email: cotte010@mc.duke.edu

## **Center Effects within the SUPPORT Trial**

Lenfestey, Cotten, Smith, Tanaka, Laughon, Goldberg, RTI, SUPPORT subcommittee (Finer)

### **Abstract**

The NICHD Neonatal Research Network's SUPPORT trial tested initiation of delivery room NCPAP followed by a mechanical ventilation algorithm intended to accelerate extubation if intubation was needed against use of delivery room intubation and administration of surfactant, followed by a mechanical ventilation algorithm that was less permissive of extubation. Variations in center expertise in interventions tested in clinical trials can impact overall trial outcome, as noted in the Neonatal HIFI trial.<sup>1</sup> When clinicians in the hundreds of centers caring for extremely low gestational age infants consider the results of the SUPPORT trial, they are likely to ask two questions: 1) If my centers' rate of survival free of chronic lung disease among infants of a similar demographic as the study is high, and the standard at my center is early intubation and surfactant, should I change practice and do as well and maybe better with a delivery room CPAP strategy? and 2) If I adopt NCPAP, will the first infants I try it on have as good a chance at success as the 40<sup>th</sup> or 50<sup>th</sup>? Data collected during the SUPPORT trial will be useful to address these questions. Prior to and throughout the period of enrollment in the SUPPORT trial, centers which had a standard approach of intubation and administering surfactant early in the delivery room or the first postnatal hour prior to study participation continued to have among the highest survival and lowest rates of chronic lung disease in the Network. It is unknown whether effects related to delivery room and respiratory support approach noted in the overall trial were consistently noted among the infants enrolled in the high performing centers, or if the centers with prior adoption of delivery room NCPAP saw a consistent outcome in the infants randomized to NCPAP compared to sites adopting this practice for the first time in the clinical trial. Because study randomization was stratified by site, and the 4 centers with high performance (Brown, UAB, Duke, and Miami) enrolled over 300 infants, a carefully done subgroup analysis to assess whether the effect noted in these 4 benchmark centers was consistent with overall trial results is feasible. Assessment of whether or not outcome of infants in the NCPAP arm is associated with center experience with delivery room NCPAP can be addressed with analysis of clusters of infants enrolled throughout the study at each centers, i.e., did infants enrolled in the NCPAP arm early in the study fare the same as infants enrolled later in the study at that center?

**Purpose:** The overall purpose of this proposal is to assess how adopting a new delivery room approach influenced survival and pulmonary outcomes, and whether adopting the new approach was equally successful early and late during the clinical trial.

**Aim 1:** Assess whether SUPPORT trial overall results were consistent with results in the 300+ subjects enrolled and randomized at centers with consistently good survival and low rates of chronic lung disease (Brown, UAB, Duke, Miami)

**Aim 2:** Assess whether there was a center-specific NCPAP training effect among infants enrolled in the NCPAP arm of the SUPPORT trial at sites which had not used delivery room NCPAP as usual care prior to the trial .

**Statement of the Problem:** Clinicians caring for extremely low gestational age newborn (ELGAN) infants have adopted strategies for initial respiratory support (use of surfactant after endotracheal intubation or initial use of continuous positive airway pressure and later rescue intubation and surfactant treatment) and ventilator management based on available evidence from high quality clinical trials, and the less validated but compelling single center reports and

“experience and reason.” Using this combination, there is extreme site variation in the rate of survival free of BPD at Network centers.<sup>2</sup> The NICHD neonatal Research network SUPPORT trial tested the hypothesis of whether or not initial NCPAP and subsequent stringent ventilator management parameters would improve survival free of bronchopulmonary dysplasia (BPD) compared with initial intubation with surfactant administration and more conservative ventilator management. Before initiation of the study, and throughout the study period, several centers, all of whom primarily used initial intubation and surfactant administration prior to the study, consistently had the highest survival free of BPD. It is not known whether the trend in the primary outcome noted in the overall trial was noted in the cohort of subjects enrolled and randomized at the benchmark centers that used initial intubation and surfactant for ELGANs. This query will inform potential adopters of NCPAP regarding the potential clinical and economic impact of adopting NCPAP in the delivery room in sites with high rates of survival free of BPD. It is also not known whether infants enrolled at sites which had not made initial NCPAP standard practice prior to the study start-up were as successful maintaining infants randomized to NCPAP on NCPAP throughout the first 14 postnatal days at the start of study enrollment as at the end of enrollment. This query would be important to inform new adopters of the likelihood of a learning curve for adopting NCPAP in the delivery room.

### ***Aims 1 and 2:***

Study Design: Retrospective post hoc subgroup analysis (Aim 1) and retrospective cohort study (Aim 2).

### Study population:

#### *Inclusion criteria*

1. Infants in enrolled in the SUPPORT trial

#### *Exclusion criteria*

1. None

### Study intervention:

There is no specific study intervention. This will be analysis of existing data.

### Primary and Secondary Outcomes:

Aim 1:

Primary outcome: death or BPD

Secondary outcomes: death or BPD separately.

Aim 2:

Primary Outcome: death or intubated during the first 14 postnatal days.

Secondary Outcome: death or BPD

### Statistical Plans:

#### *Outcome variables*

1. Death or BPD

2. Death
3. BPD
4. Completion of 14 days of NCPAP

*Predictor variables for multivariable analyses*

1. gestational age
2. gender
3. race
4. antenatal steroids
5. multiple birth
6. small for gestational age (SGA)

**Targeted Analyses**

**Aim 1. Testing results in 4 benchmark centers**

Consistent with recently published subgroup analysis guidelines<sup>3</sup>, We will perform two post-hoc subgroup analyses with 2 levels comparing heterogeneity of odd ratios for the primary outcomes between group 1 defined as the 4 Low BPD and High survival sites vs. Group 2, the 11 remaining centers (Cincinnati is excluded as it was a training site for NCPAP in the delivery room). We also will assess whether or not the primary outcome measured among infants enrolled at the 4 Low BPD and high survival sites before the study is homogenous with the overall outcome of the clinical trial using methodologies testing for homogeneity of study results for subgroup analysis. These analyses will involve statistical tests for interaction between the center level variable and the outcome. We plan to calculate point estimates and confidence intervals for effect size of the center level variable using the Breslow-Day test for heterogeneity of odds ratios. We will use multivariable logistic regression to determine if group has an effect on outcome. Finally we will correct p-values for multiple comparisons using the equation  $1-(1-p)^K$  where p is our accepted alpha error and K is the number of comparisons<sup>3</sup>.

**Aim 2. Testing for consistency of successful NCPAP maintenance throughout enrollment.**

We will perform two exploratory visual analyses and more traditional exploratory multivariable logistic regression models

**Visual Analysis #1.** Each center would have enrollment in the CPAP arm (X axis) and primary outcome (Y axis) plotted in two dimensions. The Y axis score of 0 for the outcome, survival without intubation in the first 14 postnatal days and a score of 1 for death or intubation within the first 14 postnatal days. The X axis would be the order of enrollment at each site. The first baby enrolled at a site would be plotted at the X axis point of '1', the second baby at '2', and so on. This would be the equivalent of a multivariable logistic regression predicting the primary outcome for NCPAP arm infants testing whether order enrolled was associated with outcome.

**Visual Analysis #2,** using each center's cohort randomized to NCPAP, would plot by month of study enrollment, to assess whether the course of the study use of NCPAP (and familiarity with the procedure overall) was associated with outcome among the NCPAP enrolled infants. Again, the score "0" would be assigned if the infant survived the first 14 postnatal days and was not intubated, and "1" would be assigned if the baby was intubated or died in the first 14 postnatal days. For example, the X axis would have a block for September 2008, 0's and 1's would be plotted, within each month of enrollment block.

These 2 visual models would be the equivalent of a logistic regression predicting the primary outcome for NCPAP arm infants testing whether order enrolled or time during the study was associated with outcome.

We will perform two exploratory analyses using multivariable logistic regression using infants assigned to the NCPAP arm to determine if centers became more successful at maintaining subjects on NCPAP as they gained experience. The outcome for these two analyses is the composite of intubation during the first 14 postnatal days or death. Analysis 1#: Each infant would be assigned a variable based on the order of enrollment at their respective site. We will then perform a multivariable logistic regression to determine magnitude of enrollment order effect, with the additional predictor variables as listed (GA, gender, race, antenatal steroids, multiple birth, and SGA)

Analysis 2: Each infant would be assigned a variable based on the study month of enrollment at their respective site. We will then perform a multivariable logistic regression to determine magnitude of enrollment order effect on the composite outcome of intubation during the first 14 postnatal days or death, with the additional predictor variables as listed (GA, gender, race, antenatal steroids, multiple birth, and SGA).

## References

1. Bryan AC, Froese AB. Reflections on the HIFI trial. *Pediatrics*. 1991;87:565-567.
2. Fanaroff, A.A., et al., Trends in neonatal morbidity and mortality for very low birthweight infants. *Am J Obstet Gynecol*. 2007;196:e1-8.
3. Lagakos SW. The challenge of subgroup analyses--reporting without distorting. *N Engl J Med*. 2006;354:1667-1669.

## **NICHD Neonatal Research Network Protocol Outline**

Title: Oxygen saturations and risk of mortality and morbidity in the SUPPORT trial.

### **Authors:**

P. Brian Smith MD MPH MHS

C. Michael Cotten MD MHS

Ronald N. Goldberg MD

RTI and SUPPORT Subcommittee (Carlo)

for the Eunice Kennedy Shriver NICHD Neonatal Research Network

### **A. Statement of the Problem**

Previous studies demonstrated increased rates of mortality, ROP, BPD, PVL and CP among infants with higher exposures to oxygen.<sup>1-6</sup> The SUPPORT study demonstrated lower rates of severe ROP in the lower saturation group but higher rates of mortality. No difference in severe ROP/death was observed between the two groups. Because many infants in the low saturation group spent time with saturations >89% and many infants in the high saturation group spent time with saturations <91%, there was a great deal of overlap in oxygen saturations between the two groups.

The SUPPORT study's finding that higher oxygen saturation limits are associated with lower mortality but higher rates of severe ROP leaves uncertainty for clinicians. The rationale for this proposal is that evidence for determining the safest range for oxygen saturation for premature infants is conflicting.<sup>5,6</sup> In the protocol described below, we will be able to examine the association between the actual recorded oxygen saturation with the clinical outcomes of the infants. *We propose to examine the incidence of mortality and morbidities using actual oxygen saturations as a predictor for infants enrolled in the SUPPORT trial.*

### **B. Hypothesis**

*Hypothesis:* Higher oxygen saturations are associated with an increased risk of death, ROP, BPD, death/ROP, or death/BPD for infants receiving supplemental oxygen.

### **C. Specific Aim**

*Specific Aim:* Determine whether oxygen saturations for infants receiving supplemental oxygen are related to death, ROP, BPD, death/ROP, or death/BPD.

### **D. Method/ Procedures**

1. Study Design: Retrospective cohort study.

2. Study population:

*Inclusion criteria*

1. 1316 infants in enrolled in the SUPPORT trial

### *Exclusion criteria*

1. None
3. Study intervention:  
There is no specific study intervention. This will be analysis of existing data.
4. Primary and Secondary Outcomes:  
Primary outcome:           Death  
Secondary outcomes:       ROP, BPD, death/ROP, death/BPD
5. Statistical Plans:  
*Outcome variables*
  1. death
  2. ROP
  3. BPD
  4. death/ROP
  5. death/BPD

### *Predictor variables*

Oxygen saturation for each infant while receiving supplemental oxygen

### *Confounding variables*

1. saturation group (low vs. high)
2. gestational age
3. birth weight
4. sex
5. singleton vs. multiple birth

### *Observations for analysis*

Observations recorded when the infant's SaO<sub>2</sub> could not be altered will not be used in the analysis.

1. Infant receiving 21% FiO<sub>2</sub> with SaO<sub>2</sub> > than upper target limit range
2. Infant receiving 100% FiO<sub>2</sub> with SaO<sub>2</sub> < than lower target limit range

### *Weighting of observations*

Although the number of observations varied by subject in the dataset, each infant will contribute equally to the overall statistical calculations.

### *Bivariable analysis*

We will compare mean oxygen saturations for infants that died vs. those that lived using the Student's t-test. The comparison will be repeated for each of the secondary outcomes: ROP, BPD, death/ROP, and death/BPD.

### *Multivariable analysis*

We will build a multivariable logistic regression model to determine the relationship between outcome variables and mean oxygen saturation for each infant (continuous variable) controlling for saturation group (low vs. high), mean FiO<sub>2</sub> (continuous variable), gestational age, birth weight, sex, and singleton birth.

## E. References

1. Jobe, A.H. and Bancalari, E., Bronchopulmonary dysplasia. *Am J Respir Crit Care Med.* 163, 1723-9(2001).
2. Flynn, J.T., Bancalari, E., Snyder, E.S., Goldberg, R.N., Feuer, W., Cassady, J., Schiffman, J., Feldman, H.I., Bachynski, B., Buckley, E., and et al., A cohort study of transcutaneous oxygen tension and the incidence and severity of retinopathy of prematurity. *N Engl J Med.* 326, 1050-4(1992).
3. Saugstad, O.D., Bronchopulmonary dysplasia-oxidative stress and antioxidants. *Semin Neonatol.* 8, 39-49(2003).
4. Haynes, R.L., Baud, O., Li, J., Kinney, H.C., Volpe, J.J., and Folkerth, D.R., Oxidative and nitrative injury in periventricular leukomalacia: a review. *Brain Pathol.* 15, 225-33(2005).
5. Anderson, C.G., Benitz, W.E., and Madan, A., Retinopathy of prematurity and pulse oximetry: a national survey of recent practices. *J Perinatol.* 24, 164-8(2004).
6. Tin, W., Milligan, D.W., Pennefather, P., and Hey, E., Pulse oximetry, severe retinopathy, and outcome at one year in babies of less than 28 weeks gestation. *Arch Dis Child Fetal Neonatal Ed.* 84, F106-10(2001).



**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Hale, Ellen"  
**Subject:** RE: SUPPORT FU OUTCOMES  
**Date:** Wednesday, May 05, 2010 11:53:00 AM

---

Ok, thanks  
Rose

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network

---

**From:** Hale, Ellen [mailto:ehale@emory.edu]  
**Sent:** Monday, May 03, 2010 2:48 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: SUPPORT FU OUTCOMES

Rose,  
This child is lost to follow-up.  
Ellen

Ellen Hale, RN, BS, CCRC  
Neonatal Research Network  
Emory University School of Medicine  
Department of Pediatrics - Division of Neonatology  
Office: 404-778-1679  
Fax: 404-778-1467

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]  
**Sent:** Monday, April 19, 2010 4:16 PM  
**To:** Hale, Ellen; Barbara Stoll; Ira Adams-Chapman; Ellen Hale  
**Cc:** Gantz, Marie  
**Subject:** SUPPORT FU OUTCOMES

Hi,  
We are missing the following infants from the SUPPORT FU. Let us know how you are doing. Thanks for all the effort!!!  
Rose

CENTER	NETWORK	FU_message
--------	---------	------------

9	(b) (6)	FU window has closed but NF05 and NF09a have not been completed.
---	---------	--

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network  
Pregnancy and Perinatology Branch  
Center for Developmental Biology and Perinatal Medicine  
Eunice Kennedy Shriver National Institute of Child Health and Human Development  
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[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

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**From:** Bock, Robert (NIH/NICHD) [E]  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Release?  
**Date:** Monday, May 03, 2010 11:29:31 AM

---

Yes, most definitely.

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Monday, May 03, 2010 11:27 AM  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Subject:** Re: Release?

Once cleared, can i send to confidentially to our network sites??

---

**From:** Bock, Robert (NIH/NICHD) [E]  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Mon May 03 11:18:58 2010  
**Subject:** RE: Release?

Thanks Rose.

Yes, that's the hope. Susan said she's ok with it. John found a couple last minute copy edits and when I get them back from him, I'll send it to NIH OD for DHHS clearance.

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Monday, May 03, 2010 11:18 AM  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Subject:** Re: Release?

Bob

I just looked this over - very nice!

I don't have any other suggestions - can it be released on Sunday May 16 concurrent with the on-line publication and presentation at ATS in New Orleans?

Thanks for all your help.

FYI - both presentations here is Vancouver at PAS were very well received.

Rose

---

**From:** Bock, Robert (NIH/NICHD) [E]  
**To:** Dambruskas, Susan (NIH/NHLBI) [E]  
**Cc:** McGrath, John (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Willis, Lindsey (NIH/NHLBI) [E]

**Sent:** Mon May 03 10:35:49 2010  
**Subject:** RE: Release?

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**Sent:** Friday, April 30, 2010 5:57 PM  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Cc:** McGrath, John (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Willis, Lindsey (NIH/NHLBI) [E]  
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**Cc:** Dambraskas, Susan (NIH/NHLBI) [E]  
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301-594-1950

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**Sent:** Wednesday, April 28, 2010 1:10 PM  
**To:** Bock, Robert (NIH/NICHD) [E]; Dambraskas, Susan (NIH/NHLBI) [E]  
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**To:** Dambrauskas, Susan (NIH/NHLBI) [E]  
**Cc:** Willis, Lindsey (NIH/NHLBI) [E]  
**Subject:** RE: Preterm oxygenation studies

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**Cc:** Striar, Diane (NIH/NHLBI) [E]; Willis, Lindsey (NIH/NHLBI) [E]  
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**Sent:** Monday, April 26, 2010 11:48 AM  
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**Subject:** RE: Preterm oxygenation studies

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I want to clarify the comment re: CPAP – the earlier version of the release included mention of (b) (5) [REDACTED]  
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[REDACTED] (which Lindsey just sent to you, Bob). I think it's worthwhile to include the mention that the (b) (5) [REDACTED]  
[REDACTED].

Sorry for the confusion.

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**Sent:** Monday, April 26, 2010 11:41 AM  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Cc:** Dambrauskas, Susan (NIH/NHLBI) [E]  
**Subject:** RE: Preterm oxygenation studies

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release and made a number of edits. Unfortunately, they did not track their changes, so I hope you are able to tell what changes were made. They moved some paragraphs around, and in the course of things removed any reference to NIH near the beginning of the release; I just wanted to point that out to you so that you can make a note to edit in something to remedy this.

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- 2) (b) (5) [redacted]
- 3) (b) (5) [redacted]
- 4) (b) (5) [redacted]
- 5) (b) (5) [redacted]
- 6) (b) (5) [redacted] in case you would like to include it.

FYI, Our Lung staff has sent this to Dr. Higgins, so she may have some other comments for you at this point.

We look forward to reviewing your next draft. Please let me know if we can provide any clarification on any of the above points or any of our edits.

Lindsey Willis

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**To:** Dambrasukas, Susan (NIH/NHLBI) [E]  
**Cc:** Striar, Diane (NIH/NHLBI) [E]; Willis, Lindsey (NIH/NHLBI) [E]  
**Subject:** RE: Preterm oxygenation studies

Thanks Susan.

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**From:** Dambrasukas, Susan (NIH/NHLBI) [E]  
**Sent:** Thursday, April 22, 2010 12:52 PM  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Cc:** Striar, Diane (NIH/NHLBI) [E]; Willis, Lindsey (NIH/NHLBI) [E]  
**Subject:** RE: Preterm oxygenation studies

Bob,

I'm sure you are aware of the NEJM pub date now, but just in case, I'm passing along what our lung division folks shared with us. We are circulating your draft release to them for review.

I am copying Lindsey Willis of our press team, who is our lung division press liaison and will help coordinate the release with you, etc.

Susan Dambrasukas  
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dambrasukas@nhlbi.nih.gov

**From:** Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]  
**Sent:** Tuesday, April 20, 2010 12:46 PM  
**To:** Zeis, Jennifer  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Online First release schedule for NEJM 09-11781

Dear Ms. Zeis:

Thanks very much for the information. Enclosed is my contact information. I am copying this to Dr. Rose

Higgins at the NIH who probably should be the other contact person rather than our institution's press office.

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: 205 266 (b) (6)

**From:** Zeis, Jennifer [mailto:jzeis@nejm.org]  
**Sent:** Tuesday, April 20, 2010 11:37 AM  
**To:** Wally Carlo, M.D.  
**Subject:** Online First release schedule for NEJM 09-11781

Dear Dr. Carlo,

As you know, your NEJM Original Article is on an accelerated Online First release schedule to coincide with your presentation of the results at the American Thoracic Society's annual meeting. I am writing to share the details of that schedule and to request your preferred media points of contact.

We will provide your article to reporters at 10 AM EDT Thursday, May 13. When we provide your article to the media under embargo, we will post the material on our password-protected NEJM Media Center, where only journalists who have agreed to

respect our embargo may access it. I will email you this final file and any related material at that time

**Your article will be embargoed until 1 PM EDT Sunday, May 16**, the start of your ATS presentation on the trial. The ATS and NEJM embargoes are coordinated to lift simultaneously so you may reference your NEJM publication at the meeting, if you wish. Your paper will be published on NEJM.org as soon as the embargo lifts, and will later be published in the May 27 printed issue.

And finally, please let me know what **contact information you would like me to provide to journalists** who wish to interview you and/or your co-authors. You may include your institution's press office in addition to, or instead of, your personal contact information.

Many thanks. If you have any questions, please don't hesitate to ask.

Best regards,

Jen Zeis

Jennifer Zeis  
Media Relations  
The New England Journal of Medicine  
office: 781-434-7186  
MEDIA CENTER <http://media.nejm.org>  
twitter <http://twitter.com/nejm>

**From:** [Bock, Robert \(NIH/NICHD\) \[E\]](#)  
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**Subject:** RE: Release?  
**Date:** Monday, May 03, 2010 11:11:01 AM

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Thanks, Susan.

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**Sent:** Monday, May 03, 2010 11:11 AM  
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**Cc:** McGrath, John (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Willis, Lindsey (NIH/NHLBI) [E]  
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Thanks, Bob. Looks good. I will share with our lung experts just to be sure no errors were introduced (including by my comments) and will send to Dr. Shurin to clear her quote. Will let you know if anything comes up, but I feel OK with it going to HHS for clearance.

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- 5) (b) (5) [REDACTED]
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**Sent:** Thursday, April 22, 2010 12:52 PM  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Cc:** Striar, Diane (NIH/NHLBI) [E]; Willis, Lindsey (NIH/NHLBI) [E]  
**Subject:** RE: Preterm oxygenation studies

Bob,

I'm sure you are aware of the NEJM pub date now, but just in case, I'm passing along what our lung division folks shared with us. We are circulating your draft release to them for review.

I am copying Lindsey Willis of our press team, who is our lung division press liaison and will help coordinate the release with you, etc.

Susan Dambraskas  
NHLBI Press Team Leader  
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dambraskass@nhlbi.nih.gov

**From:** Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]  
**Sent:** Tuesday, April 20, 2010 12:46 PM  
**To:** Zeis, Jennifer  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Online First release schedule for NEJM 09-11781

Dear Ms. Zeis:

Thanks very much for the information. Enclosed is my contact information. I am copying this to Dr. Rose Higgins at the NIH who probably should be the other contact person rather than our institution's press office.

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: 205 266 (b)

**From:** Zeis, Jennifer [mailto:jzeis@nejm.org]  
**Sent:** Tuesday, April 20, 2010 11:37 AM  
**To:** Wally Carlo, M.D.  
**Subject:** Online First release schedule for NEJM 09-11781

Dear Dr. Carlo,

As you know, your NEJM Original Article is on an accelerated Online First release schedule to coincide with your presentation of the results at the American

Thoracic Society's annual meeting. I am writing to share the details of that schedule and to request your preferred media points of contact.

We will provide your article to reporters at 10 AM EDT Thursday, May 13. When we provide your article to the media under embargo, we will post the material on our password-protected NEJM Media Center, where only journalists who have agreed to respect our embargo may access it. I will email you this final file and any related material at that time

**Your article will be embargoed until 1 PM EDT Sunday, May 16**, the start of your ATS presentation on the trial. The ATS and NEJM embargoes are coordinated to lift simultaneously so you may reference your NEJM publication at the meeting, if you wish. Your paper will be published on NEJM.org as soon as the embargo lifts, and will later be published in the May 27 printed issue.

And finally, please let me know what **contact information you would like me to provide to journalists** who wish to interview you and/or your co-authors. You may include your institution's press office in addition to, or instead of, your personal contact information.

Many thanks. If you have any questions, please don't hesitate to ask.

Best regards,

Jen Zeis

Jennifer Zeis  
Media Relations  
The New England Journal of Medicine  
office: 781-434-7186  
MEDIA CENTER <http://media.nejm.org>  
twitter <http://twitter.com/nejm>



**From:** Bock, Robert (NIH/NICHD) [E]  
**To:** Dambrauskas, Susan (NIH/NIDCD) [E]  
**Cc:** McGrath, John (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Willis, Lindsey (NIH/NHLBI) [E]  
**Subject:** RE: Release?  
**Date:** Monday, May 03, 2010 10:35:51 AM  
**Attachments:** NICHD NHLBI 2 SUPPORT News Release.docx

---

Thanks Susan. This was helpful. Please see attached revised version.

I made all your changes, with the exception of including the d (b) (5)

It is true that the (b) (5)

However, I can understand NHLBI's concern that (b) (5)

Thanks.

Bob

---

**From:** Dambrauskas, Susan (NIH/NHLBI) [E]  
**Sent:** Friday, April 30, 2010 5:57 PM  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Cc:** McGrath, John (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Willis, Lindsey (NIH/NHLBI) [E]  
**Subject:** RE: Release?

Bob,

Attached is the release with a few comments (these are from me, based on our lung experts' earlier comments). Key items:

- (b) (5)
- (b) (5)
- (b) (5)

(b) (5)

• (b) (5)

We have not yet cleared Dr. Shurin's quote with her; she has been traveling, and I wanted to wait until the news release was in more final shape. Please copy us on NIH/HHS clearance submission, and we'll run it by her then.

Let us know if you have any questions. I know it's been a trying experience .... I'm sure our next collaboration will be easier!

Susan Dambrauskas  
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---

**From:** Bock, Robert (NIH/NICHD) [E]  
**Sent:** Friday, April 30, 2010 5:04 PM  
**To:** Dambrauskas, Susan (NIH/NHLBI) [E]  
**Cc:** McGrath, John (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Willis, Lindsey (NIH/NHLBI) [E]  
**Subject:** Release?

Hi Susan. Will you be able to get this to us today?

---

**From:** Dambrauskas, Susan (NIH/NHLBI) [E]  
**Sent:** Friday, April 30, 2010 12:05 PM  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Cc:** McGrath, John (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Willis, Lindsey (NIH/NHLBI) [E]  
**Subject:** RE: Preterm oxygenation studies

Thanks, Bob. Please give us some time (at least until the end of the day?) to review your revised release before you submit for departmental clearance. We understand that you want to limit the complexity in the release, but some of the suggested changes were more substantive than stylistic and we'd like to review to see that the substantive concerns were addressed.

Can we have until the end of the day to review? (We have a staff meeting this afternoon.)

Thanks,

Susan Dambrauskas  
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301 496-4236 - office  
301 828-(b) (6) BlackBerry  
301 402-2405 - fax  
dambrauskass@nhlbi.nih.gov

---

**From:** Bock, Robert (NIH/NICHD) [E]  
**Sent:** Friday, April 30, 2010 11:57 AM  
**To:** Willis, Lindsey (NIH/NHLBI) [E]  
**Cc:** Dambrauskas, Susan (NIH/NHLBI) [E]; McGrath, John (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Preterm oxygenation studies

Hi Lindsey and Susan. I've attached the version of the release I'm planning to submit for departmental clearance, along with the version you sent earlier.

I'm very sorry, but we're not able to accept most of your institute's stylistic changes. We feel that the changes to the headline, the lead, and most of the stylistic changes in the remainder of the release are better suited to a scientific audience than to the general audience that we're trying to reach. We know that many researchers will learn of the findings through the release. However, our release isn't a substitute for the journal article. Researchers who want to learn more about the study would be better served by consulting the final article than by looking to the release. Similarly we feel that the proposed revision to the lead and headline are too general, and blunt the impact of the findings.

We'd also rather not introduce the SUPPORT acronym into the release. Including the acronym and its definition introduces additional complexity, and we're trying to keep the release as simple as possible.

We're very happy to have Dr. Shurin's quote. It does a very nice job of explaining the (b) (5) [REDACTED]. I've included her quote as well as many of the other additions to the release's content that NHLBI has proposed.

Please let me know if you have any questions.

Thanks.

Bob

---

**From:** Willis, Lindsey (NIH/NHLBI) [E]  
**Sent:** Thursday, April 29, 2010 1:03 PM  
**To:** Bock, Robert (NIH/NICHHD) [E]  
**Cc:** Dambrauskas, Susan (NIH/NHLBI) [E]  
**Subject:** Re: Preterm oxygenation studies

Hi Bob,

Our division staff had no additional comments to the draft we sent to you yesterday (attached again.) The only question they raised, that is only slightly addressed by Dr. Higgins' quote, (b) (5) [REDACTED]? That bit of information is saved for the end and may be better explained.

Let us know how else we can assist,

Lindsey Willis

Office of Communications

National Heart, Lung, and Blood Institute

National Institutes of Health

301-594-1950

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---

**From:** Willis, Lindsey (NIH/NHLBI) [E]  
**Sent:** Wednesday, April 28, 2010 1:10 PM  
**To:** Bock, Robert (NIH/NICHHD) [E]; Dambrauskas, Susan (NIH/NHLBI) [E]  
**Subject:** RE: Preterm oxygenation studies

Bob, we are just awaiting a review from our Director of the Division of Lung Diseases. Attached is what we sent them for review, just FYI. There may be additional suggestions from them once we hear back.

Lindsey Willis

Office of Communications

National Heart, Lung, and Blood Institute

National Institutes of Health

301-594-1950

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---

**From:** Bock, Robert (NIH/NICHD) [E]  
**Sent:** Tuesday, April 27, 2010 4:13 PM  
**To:** Dambrauskas, Susan (NIH/NHLBI) [E]  
**Cc:** Willis, Lindsey (NIH/NHLBI) [E]  
**Subject:** RE: Preterm oxygenation studies

Will you be able to send this along soon?

---

**From:** Dambrauskas, Susan (NIH/NHLBI) [E]  
**Sent:** Monday, April 26, 2010 2:07 PM  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Cc:** Striar, Diane (NIH/NHLBI) [E]; Willis, Lindsey (NIH/NHLBI) [E]  
**Subject:** RE: Preterm oxygenation studies

Bob,

Want to let you know that we (Lindsey and I) spoke with Dr. Carol Blaisdell, the NHLBI project officer for the SUPPORT study. She explained some of the concerns with the news release as originally drafted. We will send you another version with tracked changes in the next few days.

One issue is that (b) (5)

Dr. Blaisdell believes that the authors and Dr. Higgins will be OK with changes in how the results are described and the emphasis of certain results, but you'll probably want to recirculate the revised release to them. In the meantime, please let us know if you receive any additional feedback from Dr. Higgins while Lindsey is working on

the next version.

Thanks for your cooperation. Please let us know if you have any questions.

Susan Dambrauskas  
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301 496-4236 - office  
301 828-7689 - BlackBerry  
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dambrauskass@nhlbi.nih.gov

---

**From:** Dambrauskas, Susan (NIH/NHLBI) [E]  
**Sent:** Monday, April 26, 2010 11:48 AM  
**To:** Willis, Lindsey (NIH/NHLBI) [E]; Bock, Robert (NIH/NICHD) [E]  
**Subject:** RE: Preterm oxygenation studies

Thanks, Lindsey.

I want to clarify the comment re: CPAP – the earlier version of the release included mention of (b) (5) [REDACTED]. This mention of the (b) (5) [REDACTED] (which Lindsey just sent to you, Bob). I think it's worthwhile to include the mention that the (b) (5) [REDACTED].

Sorry for the confusion.

Susan Dambrauskas  
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301 496-4236 - office  
301 828-(b) (6) BlackBerry  
301 402-2405 - fax  
dambrauskass@nhlbi.nih.gov

---

**From:** Willis, Lindsey (NIH/NHLBI) [E]  
**Sent:** Monday, April 26, 2010 11:41 AM  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Cc:** Dambrauskas, Susan (NIH/NHLBI) [E]  
**Subject:** RE: Preterm oxygenation studies

Hi Bob,

Thank you for the opportunity to collaborate and co-issue this release with NICHD. Our Lung Division staff has reviewed the SUPPORT release and made a number of edits. Unfortunately, they did not track their changes, so I hope you are able to tell what changes were made. They moved some paragraphs around, and in the course of things removed any reference to NIH near the beginning of the release; I just wanted to point that out to you so that you can make a note to edit in something to remedy this.

There are a few notes on the release, with the following additional suggestions for you to consider:

- 1) (b) (5) [redacted];
- 2) (b) (5) [redacted];
- 3) (b) (5) [redacted];
- 4) (b) (5) [redacted];
- 5) (b) (5) [redacted];
- 6) (b) (5) [redacted] in case you would like to include it.

FYI, Our Lung staff has sent this to Dr. Higgins, so she may have some other comments for you at this point.

We look forward to reviewing your next draft. Please let me know if we can provide any clarification on any of the above points or any of our edits.

Lindsey Willis

Office of Communications

National Heart, Lung, and Blood Institute

National Institutes of Health

301-594-1950

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---

**From:** Bock, Robert (NIH/NICHD) [E]  
**Sent:** Thursday, April 22, 2010 12:53 PM  
**To:** Dambrauskas, Susan (NIH/NHLBI) [E]  
**Cc:** Striar, Diane (NIH/NHLBI) [E]; Willis, Lindsey (NIH/NHLBI) [E]  
**Subject:** RE: Preterm oxygenation studies

Thanks Susan.

---

**From:** Dambrauskas, Susan (NIH/NHLBI) [E]  
**Sent:** Thursday, April 22, 2010 12:52 PM  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Cc:** Striar, Diane (NIH/NHLBI) [E]; Willis, Lindsey (NIH/NHLBI) [E]  
**Subject:** RE: Preterm oxygenation studies

Bob,

I'm sure you are aware of the NEJM pub date now, but just in case, I'm passing along what our lung division folks shared with us. We are circulating your draft release to them for review.

I am copying Lindsey Willis of our press team, who is our lung division press liaison and will help coordinate the release with you, etc.

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301 496-4236 - office  
301 828-(b) (6)- BlackBerry  
301 402-2405 - fax  
dambrauskass@nhlbi.nih.gov

**From:** Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]  
**Sent:** Tuesday, April 20, 2010 12:46 PM  
**To:** Zeis, Jennifer  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Online First release schedule for NEJM 09-11781



Dear Ms. Zeis:

Thanks very much for the information. Enclosed is my contact information. I am copying this to Dr. Rose Higgins at the NIH who probably should be the other contact person rather than our institution's press office.

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: 205 266 (b)

**From:** Zeis, Jennifer [mailto:jzeis@nejm.org]

**Sent:** Tuesday, April 20, 2010 11:37 AM

**To:** Wally Carlo, M.D.

**Subject:** Online First release schedule for NEJM 09-11781

Dear Dr. Carlo,

As you know, your NEJM Original Article is on an accelerated Online First release schedule to coincide with your presentation of the results at the American Thoracic Society's annual meeting. I am writing to share the details of that schedule and to request your preferred media points of contact.

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And finally, please let me know what **contact information you would like me to provide to journalists** who wish to interview you and/or your co-authors. You may include your institution's press office in addition to, or instead of, your personal contact information.

Many thanks. If you have any questions, please don't hesitate to ask.

Best regards,

Jen Zeis

Jennifer Zeis  
Media Relations  
The New England Journal of Medicine  
office: 781-434-7186  
MEDIA CENTER <http://media.nejm.org>  
twitter <http://twitter.com/nejm>

**From:** Susan Hintz  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** the subcommittee issue  
**Date:** Monday, May 03, 2010 3:59:28 AM

---

Hi Rose

I was looking back at stuff re: the original SUPPORT neuroimaging secondary history. I think because it was part of my MSCIDA, there WAS a subcommittee - as pasted below, from the front page of the approved secondary. But, all these folks are on the SUPPORT subcommittee - except for Alan Jobe, correct? So, going through the SUPPORT subcommittee still might make most sense. What do you think?

Susan

**Subcommittee Members:**

**Susan Hintz, MD**

**Jon Tyson, MD, MPH**

**David Stevenson, MD**

**Neil Finer, MD**

**Alan Jobe, MD**

**Abhik Das, PhD**

**Rosemary Higgins, MD**

**Final May 25, 2005**

**Minor revisions June 17, 2005**

**From:** [Michael Cotten](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Cc:** ["goldb008@mc.duke.edu"](#); [John](#)  
**Subject:** Re: concept and protocol  
**Date:** Saturday, May 01, 2010 5:45:01 PM  
**Attachments:** [rop support genomics protocol 5-1-2010.docx](#)

---

Hi Rose...

here's the protocol submission for the SUPPORT secondary to test for associations between genetic variants in angiogenesis and oxygen response pathway genes and ROP, w/ assessment of interactions with the oxygen sat target.

thanks

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: 919-681-6024  
fax: 919-681-6065  
email: [cotte010@mc.duke.edu](mailto:cotte010@mc.duke.edu)

"Higgins, Rosemary (NIH/NICHD) [E]"  
<[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)>

05/01/2010 09:14 AM

To ""[cotte010@mc.duke.edu](mailto:cotte010@mc.duke.edu)"" <[cotte010@mc.duke.edu](mailto:cotte010@mc.duke.edu)>  
cc ""[goldb008@mc.duke.edu](mailto:goldb008@mc.duke.edu)"" <[goldb008@mc.duke.edu](mailto:goldb008@mc.duke.edu)>  
Subject Re: concept and protocol

Mike

We are currently tracking the neuroimaging cohort (approx 560). There is a protocol to follow the breathing outcomes infants, but this requires revisions and needs to go back to protocol review. This also would exclude the deaths from the study (slightly over 200).

Hope this helps

Rose

---

**From:** Michael Cotten <[cotte010@mc.duke.edu](mailto:cotte010@mc.duke.edu)>  
**To:** Higgins, Rosemary (NIH/NICHD) [E]

**Sent:** Sat May 01 01:55:41 2010  
**Subject:** Re: concept and protocol

Hi Rose..in finalizing the SUPPORT secondary to submit, I've come to realize that the follow up is complete for the study kids....except maybe about 100 still missing....per the montly report....is there longer term followup in the works for the SUPPORT cohort?

I've asked John Dagle whether or not they are sending out buccal swabs to homes for samples from kids and if they've had success...otherwise..w/o further followup for the SUPPORT kids, I don't think we'll be able to do the oxygen-genomics proposal....

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  
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"Higgins, Rosemary (NIH/NICHD) [E]"  
<higginsr@mail.nih.gov>

04/05/2010 04:18 PM

To "Michael Cotten" <cotte010@mc.duke.edu>

cc "Archer, Stephanie (NIH/NICHD) [E]" <archerst@mail.nih.gov>, "Ron Goldberg (goldb008@mc.duke.edu)" <goldb008@mc.duke.edu>

Subject concept and protocol

Mike

We have the following concept you presented which is overdue for a protocol submission. If we do not receive a protocol by May 1, we will remove this from the pending list:

SUPPORT DNA collection for ROP risk

We also have the following protocol which is overdue for a protocol resubmission. IF we do not receive a revision by June 1, we will remove it from the list:

Prospective DNA Repository

Thanks

Rose

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network

Pregnancy and Perinatology Branch  
Center for Developmental Biology and Perinatal Medicine  
Eunice Kennedy Shriver National Institute of Child Health and Human Development  
National Institutes of Health  
6100 Executive Blvd., Room 4B03  
MSC 7510  
Bethesda, MD 20892  
For overnight delivery use Rockville, MD 20852  
301-496-5575  
301-496-3790 (FAX)  
higginsr@mail.nih.gov

## **Do Genetic Variations in Angiogenesis and Oxygen Response Genes Influence ROP Risk in Infants in the High and Low Oxygen Saturation Ranges tested in SUPPORT?**

**CM Cotten, J Dagle (co - PI's)**

**RN Goldberg, E Bell, J Murray + SUPPORT and SUPPORT Neuroimaging subcommittee (if approved)**

### **Abstract**

Retinopathy of prematurity (ROP) is a leading cause of childhood blindness among extremely low gestational age (< 28 weeks gestation) infants worldwide. Epidemiologic studies reinforce *in vivo* animal experiments that demonstrate postnatal oxygen exposure contributes to risk of ROP. Studies in mono- and di-zygotic premature twins indicate that more than 2/3rds of an individual preterm infant's risk of ROP can be attributed to genetic variation. Candidate gene studies have identified a small number of biologically plausible risk alleles, but these have not been tested in populations with adequate data to test interactions of genetic variation with level of oxygen exposure and risk of ROP. The NICHD Neonatal Research Network recently completed the Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants (SUPPORT) clinical trial with over 1300 extremely low gestational age infants randomized to one of two target oxygen saturation arms. The study collected an unprecedented amount of oxygen exposure and continuous oxygen saturation monitoring data on each infant. Results indicated reduction in risk of severe ROP in the lower saturation goal arm, but with a tradeoff of increased mortality. More focused characterization of infants at highest risk of severe ROP via identifiable genetic susceptibility could focus screening and inform efforts to reduce ROP risk without increasing mortality. For this study, we propose that DNA samples be collected from participating infants returning for follow-up to perform targeted analyses to identify associations between single nucleotide polymorphisms from VEGF- angiogenesis and oxygen responsive pathway genes and ROP, and test for interactions with oxygen saturation target group. This study can support suspected pathways and mechanisms of disease identified in prior studies and identify novel components in candidate pathways that could contribute to risk of ROP in the context of level of oxygen exposure. It will also provide genotype and phenotype data from a unique population of extremely low gestational age infants that can be shared for validation of findings in other similar population based enquiries.

### **Statement of the Problem**

Retinopathy of prematurity is a major cause of childhood blindness worldwide. (Steinkuller 1999, Gilbert 2008) Screening resources even in the U.S. are increasingly limited. (Kemper 2008) Identifying higher risk infants would be beneficial, and identifying genetic variations that are associated with ROP could help researchers gain a better understanding of ROP pathophysiology and targets for development of novel interventions. Heritable factors are likely to play a significant role in ROP, accounting to 70% of the variation in individual risk (Bizarro 2007). To date, lack of cohorts with definitive data on ROP phenotype and available DNA have prevented identification of links between specific genes and disease. These studies have also lacked any information on the interaction between genetics and oxygen exposure in the development of ROP. (Holmström 2007)

## Hypotheses

Our hypotheses are:

- 1) Genetic variations in VEGF-pathway and oxygen response pathways will be associated with ROP risk
- 2) Genotype effects will vary in the two oxygen exposure groups.

## Specific Aims

To test these hypotheses, our Aims are:

- 1) To collect DNA samples from infants enrolled in the Network SUPPORT trial and conduct candidate gene studies for risk of ROP among a cohort of infants who survived to be screened for ROP.
- 2) To test for interactions between oxygen saturation target group and genotypes for risk of ROP.

## Rationale/Justification

The Network SUPPORT infants are the largest and best characterized cohort of premature infants available for DNA sample collection and assessment of the interaction of genetic and environmental (oxygen exposure) influence on risk of ROP. Although the cohort numbers in the hundreds rather than the thousands, the opportunity to test for associations in the cohort, and share data with cohorts in ongoing and future studies testing similar intervention strategies for this uniquely highly heritable disease is unique and important.

## Background & Significance – ROP and Oxygen.

Evidence for oxygen exposure influencing risk of ROP among extremely premature infants is strong. Recent studies indicated management with lower oxygen saturation targets throughout the NICU stay may reduce ROP risk without increasing risk of mortality or other morbidities, but even with reduction in oxygen exposure, disease is not eliminated completely. (Tin 2001, Chow 2003) Recent randomized trials identified trends suggesting higher oxygen saturation targets later in postnatal life (after 32 and 36 postnatal weeks) may be protective against development of ROP, but later lower oxygen targets may be protective against lung injury without significantly adding to risk of worse ROP outcome. (Phelps 2000, Askie 2003) The SUPPORT trial results imply a trade off of between higher mortality and lower risk for severe ROP in the lower vs. the higher oxygen saturation target group when those goals are set and maintained from the first postnatal day. (Table 1)

**Table 1. SUPPORT Trial results for severe ROP and mortality**

	Low oxygen group: 85 to 89% (n =654 )	High oxygen group: 91 – 95% (n =662)	Relative Risk	95% Confidence interval
<b>Severe ROP</b>	8.6%	17.9%	0.52	0.37, 0.73
<b>Mortality</b>	19.9%	16.2%	1.27	1.01; 1.60

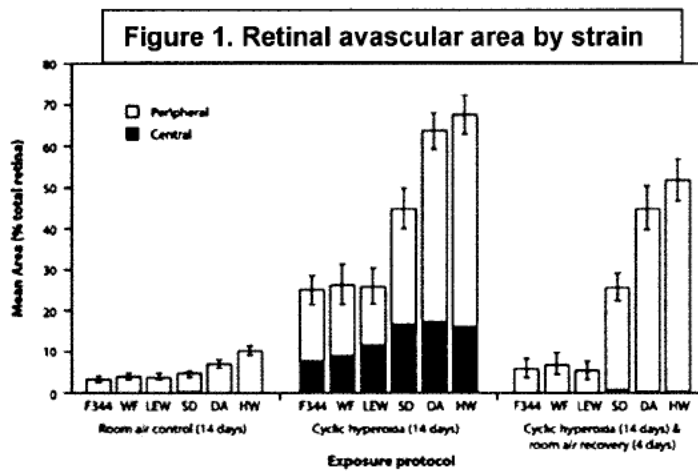


### Genetic basis of ROP.

Holmström et al, have provided a summary of epidemiologic studies, candidate gene analyses, and genetic manipulations of animal models that provide a compelling argument for further investigation of genetic variations that contribute to ROP pathogenesis (Holmström 2007) Some of the reviewed studies are briefly described below.

*Twin Studies suggest a genetic contribution to ROP risk.* In a multicenter study of prevalence of ROP among mono- compared with di-zygotic twins born prior to 32 weeks post conception. (Bizarro 2007) In the mixed-effects logistic regression analysis for ROP, gestational age and duration of supplemental oxygen use were significant covariates. After controlling for known and unknown non-genetic factors, genetic factors accounted

for 70.1% of the variance in liability for ROP.



*Animal model suggests genetic variation plays a role.* In an animal study attempting to simulate the genetic diversity in response to oxygen exposure, van Wijngaarden exposed newborns from 6 inbred strains of rat to 3 oxygen conditions: room air; hyperoxia for two weeks alone; hyperoxia for two weeks followed by two weeks of room air recovery. Avascular regions of the central and peripheral retina were

measured and compared. Results are presented in Figure 1. (van Wijngaarden 2005) The apparent variation in vascular response to similar oxygen environments suggests that genetic variations among the strains contribute to the development of strain phenotype after hyperoxia exposure. In a subsequent paper, these investigators found associations between susceptibility to have ongoing pathology despite room air recovery and pigmentation traits and erythropoietin expression. (van Wijngaarden 2007) Further studies are needed to determine the exact genetic loci responsible for these apparently heritably susceptible (or resistant) rats.

*Candidate gene studies for ROP.* Candidate gene analyses testing variations in a limited number of genes that investigators hypothesize have a major role in ROP development have also revealed promising results that need further clarification and validation in larger sample size populations. (Ioannides 2001) Cooke et al published a positive association between a single VEGF polymorphism (the -G- allele at VEGF-634 G/C) and risk of treatment for threshold ROP in a study of 91 infants with threshold ROP and 97 comparison infants. (Cooke 2004) This study did not account for environmental covariables including oxygen use. The opposite effect was described by Vannay et al, with a much higher prevalence of the -C- allele among those with severe ROP. (Vannay 2005) Accounting for multiple factors will require large sample sizes as well as accurate exposure data as well as outcome.

In a recent family based study, Mohamed et al, using samples from 330 preterm infants (102 with ROP of any stage) from a single current Network center (Iowa) identified 6 single nucleotide polymorphisms (SNPs) in six candidate genes associated with

development of ROP. Included in these was a protective polymorphism in the complement factor H (CFH) gene. In this study, oxygen exposure was not considered as a covariable. There were statistically significant differences between the birthweight and gestational age of the ROP and control groups, and the primary outcome, ROP, was any stage ROP. In this study cohort, only 62 infants had stage II-III ROP, and none had stage IV-V ROP. (Mohamed 2008) Other CFH SNPs have been associated with risk of age related macular degeneration (AMD). (Spencer 2007)

Investigators have also described a genetic polymorphism that is linked to low IGF-1 levels and IUGR, both of which have been linked with ROP. (Hellstrom 2001, 2003, 2004) The IGF-1 allele 191, a cytosine-thymine repeat in the intronic region of the gene between exons 2 and 3, was present in 8.5% of the sample of 124 Dutch children and their parents, and it was associated with reduction in birth weight, length, and head circumference. This association has not been assessed in growing premature infants for any association with ROP. (Arends 2002) Variation from a site in the promoter region of the IGF-1 gene has been associated with lower birth weight in other populations, as well as age-related IGF-1 decline in adults. (Rietveld 2003) This polymorphism was not associated with growth restriction in the study by Arends et al (Arends 2002) and has not been assessed for association with ROP.

*Defining ROP Phenotype.* In any candidate gene study, a key aspect of analysis is defining phenotype of the complex disease in question. As a primary aim of the SUPPORT trial, ROP data was collected through 55 weeks postmenstrual age when eyes should be fully vascularized (SUPPORT Manual of Operations, Chapter 15). This outcome data, based on the ETROP study intervention criteria (Good 2003), is among the most robust ROP phenotype data available in any study cohort with corresponding exhaustive detailed data on oxygen exposure. In the studies by Mohammed and Cooke, ROP was defined as threshold ROP (Cooke) or any ROP, or stage II or III ROP (Mohammed). The SUPPORT cohort offers the largest sample of specifically characterized infants, and 132 enrolled infants who had ROP outcome determined had severe ROP, defined as threshold retinopathy and/or ophthalmologic surgery and/or use of bevacizumab treatment for retinopathy (Two infants with threshold disease were treated with bevacizumab). For this study, severe retinopathy will be the primary outcome disease phenotype for comparisons.

**Significance-** Identifying genetic loci whose association with ROP is amplified by interaction with level of oxygen exposure is significant for two reasons: 1) Screening for ROP in a growing population of preterm infants worldwide is a growing logistical challenge, so identification of infants at high risk for ROP with genomic techniques could guide screening resources; and 2) genetic variants in pathways related to angiogenesis and oxygen exposure that are identified to interact with oxygen exposure to influence risk of ROP will further clarify ROP pathophysiology and lead to better understanding of pathogenesis and new treatment approaches that could reduce severe ROP and avoid the apparent rise in mortality that occurs with restrictive oxygen policies, that so far appear to be one predictable way to prevent severe ROP.

*Screening resources:* ROP continues to be a leading cause of blindness among extremely preterm infants in the developed world, and is rapidly increasing among later gestation preterm infants in countries with emerging economies. (Gilbert 2008) Screening for the disease is labor intensive and the supply of appropriate screeners

using current techniques and epidemiologic risk identification is dropping to critically low levels. (Kemper 2008)

*Enhanced understanding of mechanism:* The SUPPORT trial results indicated trade off between mortality and severe ROP, with the higher oxygen target group having lower mortality, but more severe ROP. Clarifying the mechanisms underlying oxygen's benefits and risks in human infants will guide the next steps to reduce severe ROP in preterm infants without increasing mortality.

By taking advantage of the opportunity afforded by the robust data collection on oxygen exposure and ROP phenotype in the SUPPORT trial, the proposed study will provide insights into pathophysiology of ROP that will greatly enhance and economize our approach to screening, treating, and ultimately, preventing ROP.

## **Methods/Procedures**

### *Study design*

The study will be a prospective cohort study to identify associations between genetic variants and retinopathy of prematurity and how oxygen exposure interacts with the genetic variants to modify these associations.

### *Study population*

#### *Inclusion criteria*

The inclusion criteria include infants who were enrolled in the SUPPORT trial, and are being seen in follow-up for neurodevelopmental and neuroimaging outcomes, and whose parent/guardian provides written informed consent.

#### *Exclusion criteria*

Infants not enrolled in the SUPPORT trial.

*Primary outcome:* Severe ROP defined as in the study: "threshold retinopathy and/or ophthalmologic surgery and/or use of bevacizumab treatment for retinopathy".

### *Methods.*

*Obtaining consent and samples.* Families of infants enrolled in the SUPPORT trial would be contacted to return for follow-up visits; they will be approached for consent to participate in the ROP-oxygen genomics study by study staff at participating sites. For those that provide written informed consent, samples will be collected with an Oragene swab using standardized protocols which provide a consistent yield of over 3 ug of genomic DNA which would be an optimal amount for TaqMan genotyping with > 1 ug genomic DNA remaining. (Oragene white paper:

[http://www.dnagenotek.com/pdf\\_files/PD-WP-007\\_DNA%20yield%20using%20sponges%20whitepaper\\_Issue%201\\_1.pdf](http://www.dnagenotek.com/pdf_files/PD-WP-007_DNA%20yield%20using%20sponges%20whitepaper_Issue%201_1.pdf))

In the consent form, subjects' parents/guardians will be informed that the genotyping is for research purposes only, but there is a small chance for incidental findings related to an inherited risk for a disease known at the time of testing to be likely to cause premature death if untreated. The possibility of incidental findings will be included in the consent process, and contact information for accessibility to genetic counseling at Network sites will be made available.

Samples will be labeled with a bar code label allocated from the Duke Center for Human Genetics (CHG) as part of the CHG Sample Acquisition Form (SAF), which will be maintained always at the study site. The SAF will link the subject's identify to the bar code number and the subject's assigned Network number. The site will provide the linked Network number and the SAF number to the data coordinating center, so that when the sample is logged in at Duke CHG, information derived from the sample can be sent to RTI and linked with previously collected information about that subject.

Once at Duke CHG, DNA will be extracted from Oragene swabs using standardized methods and assessed for quality.

*Candidate genes and SNP selection.* Genes in biological pathways relating to angiogenesis and response to hypoxia were selected for study. The selection of SNP's was made based on maximizing haplotype information and selecting tagSNP's (loci that can serve as predictors of SNP's in close proximity to the tagSNP) to provide coverage of most of the exon regions of the 104 candidate genes listed in the proposals that have been either associated with ROP or code for proteins involved in angiogenesis or oxygen response pathways. Tagging single nucleotide polymorphisms were chosen that were generally informative for both African American and Caucasians. Priority was given to tagging SNPs with the highest possible minor allele frequency for each haplotype block. In cases where no SNPs were available that covered both racial groups adequately, race specific SNPs were chosen.

TagSNP genotypes will be assessed for their independent associations with ROP, and then assessed in multivariable models including high and low oxygen range to assess interactions between oxygen exposure and each identified SNP.

#### *Statistical Analyses*

Statistical analyses will begin with assessments of Hardy Weinberg equilibrium for appropriate distribution of genotypes for each SNP analyzed. Once established for severe ROP cases and those without severe ROP, association studies testing the minor allele frequency in infants with and without the primary outcome will be made with logistic regressions. Multiple variables associated with risks of ROP in prior cohort studies will be added in stepwise fashion, including gestational age, Small for Gestational Age status, and race (Holmström 2007, Hellstrom 2001,2003, 2004)

SNP's associated with the primary outcome with  $p < 0.0001$  (Bonferroni correction 0.05/500 comparisons) will be considered significant.

#### *Sample size calculation*

Planned enrollment for the SUPPORT trial is 1310. 560 survivors are being tracked in the Neuroimaging/Neurodevelopmental follow-up. This will be the largest collection of extremely low gestational age infants with extremely well characterized ROP phenotypes and oxygen exposure data available for testing genetic associations with a disease that from epidemiologic evidence has a significant inherited basis.

Only one sibling of any sibship or multiple birth within the study population can be included in the genomic analysis of the cohort. Of the available 560, with an estimated prevalence of > Stage III ROP, we estimate then that approximately 500 infants could be included, with between 50 – 100 infants with severe ROP, the SUPPORT study's primary outcome, the largest cohort to date of infants with severe ROP in the ETROP

criteria era. Our analysis plan is to test associations between alleles and the primary ROP outcome, in multivariable models, along with covariables including gestational age, race/ethnicity, gender, and High or Low Oxygen Group.

Additional information can be gleaned from the genotypes with assessment for other outcomes that were collected in SUPPORT, including bronchopulmonary dysplasia as well as neuroimaging and neurodevelopmental outcomes which have been demonstrated to have plausible genetic contributions to risk, either through twin studies (BPD; Bhandari 2007, Lavoie 2008) or candidate gene analyses (cerebral palsy; Gibson 2008). These analyses will be much more exploratory than the ROP analysis, as there are major concerns that infants with the most significant pulmonary or neurologic injuries will not have survived to follow-up.

**Available population/compatibility with other ongoing protocols:**

Five hundred and sixty infants are currently being followed for the SUPPORT late outcomes/neuroimaging study. The study should not interfere with ongoing protocols as the subjects are already followed for the Network SUPPORT neuroimaging study.

**Estimate of projected recruitment time**

Enrollment of the cohort can begin at any time, but is likely to occur when the patients return for their follow-up assessments.

**Risks**

Samples will be obtained from buccal/oral saliva collection swabs, so risk will be minimal. Genotyping data will be limited to the pathway genes listed in the final protocol.

**Budget – We base our budget calculations on the following sample numbers:**

We expect to enroll and collect samples from 500 subjects.

- 500 CHG SAF forms @ \$2 each = \$1000
  - Coordinator time for tracking, consent, collection, storage on site, batch mailings—2 hours per family x 500 families @ \$35hr = \$35,000.
  - Oragene salivary samples, includes sign-in, EQ, Quantitation, and Storage of DNA, 500 estimated samples @ \$36.00 per sample = \$18,000
  - Batch mailing on dry ice: 2 mailings per center for dry ice and overnight FEDEX, @ \$165/shipment x 32 mailings to CHG = \$5280
  - Data Access license for RTI to maintain tracking of samples within CHG (placing orders for genotyping, storage, data transfer of genotyping and sample information); 2 licenses; \$1,000 each: \$2,000
- Total to collect and store samples and extract DNA ready for genotyping: \$61,280*
- Pathway targeted Genotyping using Illumina GoldenGate, up to 100 candidate genes (current selected list= 104 genes); inclusive of demographics/continental ancestry genes. Run 15 x 96 well plates to genotype 500 individual samples, 1536 SNPs (current list = 793 SNP's, but with protocol review this number may increase) each sample.
  - Total genotyping = Reagents + assays + raw data analysis (drop outs etc) = \$47,192.94
  - Statistical concerns: setting up database and conducting analyses (RTI) TBD

*Total cost: \$108,472.94*

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#### Appendix 1. List of Candidate genes

# SNP's to be tested	Gene
12	ACE
6	ACVRL1
10	ADIPOQ
8	ADIPOR1
10	ADIPOR2
3	ADM
10	AGTR1
5	AKT1
14	ANGPT1
14	ANGPT2
7	ANGPT4
6	ANGPTL1
9	ANXA2
6	ARNT
4	BNIP3
6	CASP9
3	CCL2
2	CCL3
13	CD44
6	CDH5
4	CDKN2A
9	CETP
5	CREB1
1	CTGF
6	CXCL12
23	EDIL3

7	EDN1
10	EFNB2
4	EGLN1
5	EGLN2
7	EGLN3
15	EPAS1
15	EPHA7
15	EPHB2
7	EPHB3
2	EPO
2	EPOR
10	FGF1
13	FGF2
4	FGFR1
6	FIGF
16	FLT1
4	FZD4
6	GABPA
4	GP1BA
6	HGF
7	HIF1A
4	HIF1AN
7	HIF3A
12	HK2
6	HSP90AA1
12	IGF1
23	IGF1R
7	IGFBP3
3	IHH
3	IL8
6	IL10
3	IL1B
3	JUN
12	KDR
4	LEP
5	MAP2K3
17	MAP2K6
7	MAPK1
5	MAPK8
6	MMP14
6	MMP2
4	MMP9
8	NDP
10	NOS2
6	NOS3
17	NRP1
17	NRP2
5	OXR1
5	PDGFB
9	PLG
9	PPARGC1A
6	PRL
5	PROK1



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27	ROBO1
6	ROBO4
14	SEMA3A
5	SERPINE1
4	SERPINF1
3	SLC16A3
7	TBX5
8	TEAD4
15	TEK
3	TFPI2
10	TGFA
3	TGFB1
4	THBS1
6	TIE1
4	TIMP1
11	TIMP2
8	TIMP3
5	TLR4
0	TNF
5	TSPAN12
4	VASH1
8	VEGFA
1	VEGFB
10	VEGFC
3	VHL
793 total SNPs	<b>104 total genes</b>

**From:** [Dambrauskas, Susan \(NIH/NHLBI\) \[E\]](#)  
**To:** [Bock, Robert \(NIH/NICHD\) \[E\]](#)  
**Cc:** [McGrath, John \(NIH/NICHD\) \[E\]](#); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Willis, Lindsey \(NIH/NHLBI\) \[E\]](#)  
**Subject:** RE: Release?  
**Date:** Friday, April 30, 2010 5:56:45 PM  
**Attachments:** [NICHD NHLBI 1 SUPPORT News Release 11 SD.docx](#)

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Bob,

Attached is the release with a few comments (these are from me, based on our lung experts' earlier comments). Key items:

- (b) (5) [Redacted]
- (b) (5) [Redacted]
- (b) (5) [Redacted]
- (b) (5) [Redacted]

We have not yet cleared Dr. Shurin's quote with her; she has been traveling, and I wanted to wait until the news release was in more final shape. Please copy us on NIH/HHS clearance submission, and we'll run it by her then.

Let us know if you have any questions. I know it's been a trying experience .... I'm sure our next collaboration will be easier!

Susan Dambrauskas  
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**From:** [Bock, Robert \(NIH/NICHD\) \[E\]](#)  
**Sent:** Friday, April 30, 2010 5:04 PM  
**To:** [Dambrauskas, Susan \(NIH/NHLBI\) \[E\]](#)  
**Cc:** [McGrath, John \(NIH/NICHD\) \[E\]](#); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Willis, Lindsey \(NIH/NHLBI\) \[E\]](#)  
**Subject:** Release?

Hi Susan. Will you be able to get this to us today?

---

**From:** Dambrauskas, Susan (NIH/NHLBI) [E]  
**Sent:** Friday, April 30, 2010 12:05 PM  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Cc:** McGrath, John (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Willis, Lindsey (NIH/NHLBI) [E]  
**Subject:** RE: Preterm oxygenation studies

Thanks, Bob. Please give us some time (at least until the end of the day?) to review your revised release before you submit for departmental clearance. We understand that you want to limit the complexity in the release, but some of the suggested changes were more substantive than stylistic and we'd like to review to see that the substantive concerns were addressed.

Can we have until the end of the day to review? (We have a staff meeting this afternoon.)

Thanks,

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**From:** Bock, Robert (NIH/NICHD) [E]  
**Sent:** Friday, April 30, 2010 11:57 AM  
**To:** Willis, Lindsey (NIH/NHLBI) [E]  
**Cc:** Dambrauskas, Susan (NIH/NHLBI) [E]; McGrath, John (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Preterm oxygenation studies

Hi Lindsey and Susan. I've attached the version of the release I'm planning to submit for departmental clearance, along with the version you sent earlier.

I'm very sorry, but we're not able to accept most of your institute's stylistic changes. We feel that the changes to the headline, the lead, and most of the stylistic changes in the remainder of the release are better suited to a scientific audience than to the

general audience that we're trying to reach. We know that many researchers will learn of the findings through the release. However, our release isn't a substitute for the journal article. Researchers who want to learn more about the study would be better served by consulting the final article than by looking to the release. Similarly we feel that the proposed revision to the lead and headline are too general, and blunt the impact of the findings.

We'd also rather not introduce the SUPPORT acronym into the release. Including the acronym and its definition introduces additional complexity, and we're trying to keep the release as simple as possible.

We're very happy to have Dr. Shurin's quote. It does a very nice job of explaining the (b) (5) [REDACTED]. I've included her quote as well as many of the other additions to the release's content that NHLBI has proposed.

Please let me know if you have any questions.

Thanks.

Bob

---

**From:** Willis, Lindsey (NIH/NHLBI) [E]  
**Sent:** Thursday, April 29, 2010 1:03 PM  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Cc:** Dambrauskas, Susan (NIH/NHLBI) [E]  
**Subject:** Re: Preterm oxygenation studies

Hi Bob,

Our division staff had no additional comments to the draft we sent to you yesterday (attached again.) The only question they raised, that is only slightly addressed by Dr. Higgins' quote, is, (b) (5) [REDACTED]. That bit of information is saved for the end and may be better explained.

Let us know how else we can assist,

Lindsey Willis

Office of Communications

National Heart, Lung, and Blood Institute

National Institutes of Health

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**From:** Willis, Lindsey (NIH/NHLBI) [E]  
**Sent:** Wednesday, April 28, 2010 1:10 PM  
**To:** Bock, Robert (NIH/NICHD) [E]; Dambrauskas, Susan (NIH/NHLBI) [E]  
**Subject:** RE: Preterm oxygenation studies

Bob, we are just awaiting a review from our Director of the Division of Lung Diseases. Attached is what we sent them for review, just FYI. There may be additional suggestions from them once we hear back.

Lindsey Willis

Office of Communications

National Heart, Lung, and Blood Institute

National Institutes of Health

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**From:** Bock, Robert (NIH/NICHD) [E]  
**Sent:** Tuesday, April 27, 2010 4:13 PM  
**To:** Dambrauskas, Susan (NIH/NHLBI) [E]  
**Cc:** Willis, Lindsey (NIH/NHLBI) [E]  
**Subject:** RE: Preterm oxygenation studies

Will you be able to send this along soon?

---

**From:** Dambrauskas, Susan (NIH/NHLBI) [E]  
**Sent:** Monday, April 26, 2010 2:07 PM

**To:** Bock, Robert (NIH/NICHD) [E]  
**Cc:** Striar, Diane (NIH/NHLBI) [E]; Willis, Lindsey (NIH/NHLBI) [E]  
**Subject:** RE: Preterm oxygenation studies

Bob,

Want to let you know that we (Lindsey and I) spoke with Dr. Carol Blaisdell, the NHLBI project officer for the SUPPORT study. She explained some of the concerns with the news release as originally drafted. We will send you another version with tracked changes in the next few days.

One issue is that (b) (5)

Dr. Blaisdell believes that the authors and Dr. Higgins will be OK with changes in how the results are described and the emphasis of certain results, but you'll probably want to recirculate the revised release to them. In the meantime, please let us know if you receive any additional feedback from Dr. Higgins while Lindsey is working on the next version.

Thanks for your cooperation. Please let us know if you have any questions.

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---

**From:** Dambrauskas, Susan (NIH/NHLBI) [E]  
**Sent:** Monday, April 26, 2010 11:48 AM  
**To:** Willis, Lindsey (NIH/NHLBI) [E]; Bock, Robert (NIH/NICHD) [E]  
**Subject:** RE: Preterm oxygenation studies

Thanks, Lindsey.

I want to clarify the comment re: CPAP – the earlier version of the release included mention of (b) (5). This mention of the common use (b) (5) (which Lindsey just sent to you, Bob). I think it's worthwhile to include (b) (5)

(b) (5)  
[Redacted]

Sorry for the confusion.

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---

**From:** Willis, Lindsey (NIH/NHLBI) [E]  
**Sent:** Monday, April 26, 2010 11:41 AM  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Cc:** Dambrauskas, Susan (NIH/NHLBI) [E]  
**Subject:** RE: Preterm oxygenation studies

Hi Bob,

Thank you for the opportunity to collaborate and co-issue this release with NICHD. Our Lung Division staff has reviewed the SUPPORT release and made a number of edits. Unfortunately, they did not track their changes, so I hope you are able to tell what changes were made. They moved some paragraphs around, and in the course of things removed any reference to NIH near the beginning of the release; I just wanted to point that out to you so that you can make a note to edit in something to remedy this.

There are a few notes on the release, with the following additional suggestions for you to consider:

- 1) (b) (5) [Redacted]; [Redacted]
- 2) (b) (5) [Redacted]
- 3) (b) (5) [Redacted]
- 4) (b) (5) [Redacted]
- 5) (b) (5) [Redacted]
- 6) (b) (5) [Redacted] and [Redacted]

(b) (5)

, in case you would like to include it.

FYI, Our Lung staff has sent this to Dr. Higgins, so she may have some other comments for you at this point.

We look forward to reviewing your next draft. Please let me know if we can provide any clarification on any of the above points or any of our edits.

Lindsey Willis

Office of Communications

National Heart, Lung, and Blood Institute

National Institutes of Health

301-594-1950

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---

**From:** Bock, Robert (NIH/NICHD) [E]  
**Sent:** Thursday, April 22, 2010 12:53 PM  
**To:** Dambraskas, Susan (NIH/NHLBI) [E]  
**Cc:** Striar, Diane (NIH/NHLBI) [E]; Willis, Lindsey (NIH/NHLBI) [E]  
**Subject:** RE: Preterm oxygenation studies

Thanks Susan.

---

**From:** Dambraskas, Susan (NIH/NHLBI) [E]  
**Sent:** Thursday, April 22, 2010 12:52 PM  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Cc:** Striar, Diane (NIH/NHLBI) [E]; Willis, Lindsey (NIH/NHLBI) [E]  
**Subject:** RE: Preterm oxygenation studies

Bob,

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I am copying Lindsey Willis of our press team, who is our lung division press liaison and will help coordinate the release with you, etc.

Susan Dambrauskas  
NHLBI Press Team Leader  
Technical Writer/Editor  
NHLBI Office of Communications  
301 594-1596 - direct  
301 496-4236 - office  
301 828-7689 - BlackBerry  
301 402-2405 - fax  
dambrauskass@nhlbi.nih.gov

**From:** Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]  
**Sent:** Tuesday, April 20, 2010 12:46 PM  
**To:** Zeis, Jennifer  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Online First release schedule for NEJM 09-11781

Dear Ms. Zeis:

Thanks very much for the information. Enclosed is my contact information. I am copying this to Dr. Rose Higgins at the NIH who probably should be the other contact person rather than our institution's press office.

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: 205 266 (b)

**From:** Zeis, Jennifer [mailto:jzeis@nejm.org]  
**Sent:** Tuesday, April 20, 2010 11:37 AM  
**To:** Wally Carlo, M.D.  
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Dear Dr. Carlo,

As you know, your NEJM Original Article is on an accelerated Online First release schedule to coincide with your presentation of the results at the American Thoracic Society's annual meeting. I am writing to share the details of that schedule and to request your preferred media points of contact.

We will provide your article to reporters at 10 AM EDT Thursday, May 13. When we provide your article to the media under embargo, we will post the material on our password-protected NEJM Media Center, where only journalists who have agreed to respect our embargo may access it. I will email you this final file and any related material at that time

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And finally, please let me know what **contact information you would like me to provide to journalists** who wish to interview you and/or your co-authors. You may include your institution's press office in addition to, or instead of, your personal contact information.

Many thanks. If you have any questions, please don't hesitate to ask.

Best regards,

Jen Zeis

Jennifer Zeis  
Media Relations  
The New England Journal of Medicine  
office: 781-434-7186  
MEDIA CENTER <http://media.nejm.org>  
twitter <http://twitter.com/nejm>

**From:** [Bock, Robert \(NIH/NICHD\) \[E\]](#)  
**To:** [Dambrauskas, Susan \(NIH/NIDCD\) \[E\]](#)  
**Cc:** [McGrath, John \(NIH/NICHD\) \[E\]](#); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Willis, Lindsey \(NIH/NHLBI\) \[E\]](#)  
**Subject:** RE: Preterm oxygenation studies  
**Date:** Friday, April 30, 2010 1:30:14 PM

---

OK. I'd appreciate your getting any comments back to me as soon as possible. I need to factor in time to make any additional changes and we need to submit this for clearance on Monday morning.

I think, though, that at this late time, it would be better if you express any concerns your institute may have by using the comments feature, rather than doing any rewriting.

Thanks.

---

**From:** [Dambrauskas, Susan \(NIH/NHLBI\) \[E\]](#)  
**Sent:** Friday, April 30, 2010 12:05 PM  
**To:** [Bock, Robert \(NIH/NICHD\) \[E\]](#)  
**Cc:** [McGrath, John \(NIH/NICHD\) \[E\]](#); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Willis, Lindsey \(NIH/NHLBI\) \[E\]](#)  
**Subject:** RE: Preterm oxygenation studies

Thanks, Bob. Please give us some time (at least until the end of the day?) to review your revised release before you submit for departmental clearance. We understand that you want to limit the complexity in the release, but some of the suggested changes were more substantive than stylistic and we'd like to review to see that the substantive concerns were addressed.

Can we have until the end of the day to review? (We have a staff meeting this afternoon.)

Thanks,

Susan Dambrauskas  
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[dambrauskass@nhlbi.nih.gov](mailto:dambrauskass@nhlbi.nih.gov)

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**From:** [Bock, Robert \(NIH/NICHD\) \[E\]](#)  
**Sent:** Friday, April 30, 2010 11:57 AM  
**To:** [Willis, Lindsey \(NIH/NHLBI\) \[E\]](#)  
**Cc:** [Dambrauskas, Susan \(NIH/NHLBI\) \[E\]](#); [McGrath, John \(NIH/NICHD\) \[E\]](#); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Subject:** RE: Preterm oxygenation studies

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I'm very sorry, but we're not able to accept most of your institute's stylistic changes. We feel that the changes to the headline, the lead, and most of the stylistic changes in the remainder of the release are better suited to a scientific audience than to the general audience that we're trying to reach. We know that many researchers will learn of the findings through the release. However, our release isn't a substitute for the journal article. Researchers who want to learn more about the study would be better served by consulting the final article than by looking to the release. Similarly we feel that the proposed revision to the lead and headline are too general, and blunt the impact of the findings.

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Please let me know if you have any questions.

Thanks.

Bob

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**From:** Willis, Lindsey (NIH/NHLBI) [E]  
**Sent:** Thursday, April 29, 2010 1:03 PM  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Cc:** Dambrauskas, Susan (NIH/NHLBI) [E]  
**Subject:** Re: Preterm oxygenation studies

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Let us know how else we can assist,

Lindsey Willis

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**From:** Willis, Lindsey (NIH/NHLBI) [E]  
**Sent:** Wednesday, April 28, 2010 1:10 PM  
**To:** Bock, Robert (NIH/NICHD) [E]; Dambrauskas, Susan (NIH/NHLBI) [E]  
**Subject:** RE: Preterm oxygenation studies

Bob, we are just awaiting a review from our Director of the Division of Lung Diseases. Attached is what we sent them for review, just FYI. There may be additional suggestions from them once we hear back.

Lindsey Willis

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**Sent:** Tuesday, April 27, 2010 4:13 PM  
**To:** Dambrauskas, Susan (NIH/NHLBI) [E]  
**Cc:** Willis, Lindsey (NIH/NHLBI) [E]  
**Subject:** RE: Preterm oxygenation studies

Will you be able to send this along soon?

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**From:** Dambrauskas, Susan (NIH/NHLBI) [E]  
**Sent:** Monday, April 26, 2010 2:07 PM  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Cc:** Striar, Diane (NIH/NHLBI) [E]; Willis, Lindsey (NIH/NHLBI) [E]  
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Thanks for your cooperation. Please let us know if you have any questions.

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dambrauskass@nhlbi.nih.gov

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**From:** Dambrauskas, Susan (NIH/NHLBI) [E]  
**Sent:** Monday, April 26, 2010 11:48 AM  
**To:** Willis, Lindsey (NIH/NHLBI) [E]; Bock, Robert (NIH/NICHD) [E]  
**Subject:** RE: Preterm oxygenation studies

Thanks, Lindsey.

I want to clarify the comment re: CPAP – the earlier version of the release included mention of (b) (5)

This mention (b) (5)

(b) (5)  
[Redacted]  
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Sorry for the confusion.

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- 2) (b) (5) [Redacted];
- 3) (b) (5) [Redacted];
- 4) (b) (5) [Redacted];
- 5) (b) (5) [Redacted];
- 6) (b) (5) [Redacted], in case you would like to include it.



FYI, Our Lung staff has sent this to Dr. Higgins, so she may have some other comments for you at this point.

We look forward to reviewing your next draft. Please let me know if we can provide any clarification on any of the above points or any of our edits.

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**To:** Zeis, Jennifer  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Online First release schedule for NEJM 09-11781

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**Jennifer Zeis**  
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**Subject:** RE: Preterm oxygenation studies  
**Date:** Friday, April 30, 2010 11:56:45 AM  
**Attachments:** [NHLBI Final SUPPORT news release.docx](#)  
[NICHD NHLBI 1 SUPPORT News Release 11.docx](#)

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**From:** Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]

**Sent:** Tuesday, April 20, 2010 12:46 PM  
**To:** Zeis, Jennifer  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]  
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Jen Zeis

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Media Relations  
The New England Journal of Medicine  
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MEDIA CENTER <http://media.nejm.org>  
twitter <http://twitter.com/nejm>

**From:** Das, Abhik  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** FW: \*\*\*\*SUPPORT MASTEHEADS  
**Date:** Friday, April 30, 2010 8:30:24 AM

---

I tend to agree with Michele and Ed on this one. And I admit to selfish motivation -- it is not every day I get two named authorships in the NEJM!

Thanks

Abhik

Abhik Das  
Senior Research Statistician  
RTI International

-----Original Message-----

From: Walsh, Michele [<mailto:Michele.Walsh@UHhospitals.org>]  
Sent: Thursday, April 29, 2010 06:31 PM Eastern Standard Time  
To: Wally Carlo, M.D.; Bell, Edward; Higgins, Rosemary (NIH/NICHD) [E]; Luc.Brion@UTSouthwestern.edu; rohls@unm.edu; aaf2@po.cwru.edu; Das, Abhik; alaptook@WIHRI.org; ambal@uab.edu; Bradley.yoder@hsc.utah.edu; Brenda Poindexter; cotte010@mc.duke.edu; Wallace, Dennis; Ed Donovan; Ehrenkranz Richard (E-mail); ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; Kristi Watterberg; kurt.schibler@cchmc.org; Matthew Bizzarro; Michelle Walsh; Mickey Caplan; Oh William (E-mail); Pablo Sanchez; Poole, W. Kenneth; Roger Faix; Ronald Goldberg; Seetha Shankaran; Stevenson David (E-mail); [SCRN] Stoll, Barbara; Tyson Jon (E-mail); VanMeurs, Krisa  
Cc: Archer, Stephanie (NIH/NICHD) [E]; Cunningham, Meg; Zaterka-Baxter, Kristin  
Subject: RE: \*\*\*\*SUPPORT MASTEHEADS

I see plenty of papers with long author lists in NEJM including

Most recently the NO CLD trial. I feel all deserve recognition.

Michele Walsh

beeper (b) (6)

Ph 216 844 3759

---

From: Wally Carlo, M.D. [<mailto:WCarlo@peds.uab.edu>]  
Sent: Thursday, April 29, 2010 3:58 PM  
To: Bell, Edward; Higgins, Rosemary (NIH/NICHD) [E]; Luc.Brion@UTSouthwestern.edu; rohls@unm.edu; aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; ambal@uab.edu; Bradley.yoder@hsc.utah.edu; Brenda Poindexter; cotte010@mc.duke.edu; Dennis Wallace; Ed Donovan; Ehrenkranz Richard (E-mail); ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; Kristi Watterberg; kurt.schibler@cchmc.org; Matthew Bizzarro; Michelle Walsh; Mickey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald Goldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa

Cc: Archer, Stephanie (NIH/NICHD) [E]; Cunningham, Meg; kristin zaterka  
Subject: RE: \*\*\*\*SUPPORT MASTEHEADS

The authors will be listed in the appendix although as I understand only on line.

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: 205 266 (b) (6)

From: Bell, Edward [<mailto:edward-bell@uiowa.edu>]

Sent: Thursday, April 29, 2010 2:15 PM

To: Higgins, Rosemary (NIH/NICHD) [E]; Luc.Brion@UTSouthwestern.edu; rohls@unm.edu; aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; ambal@uab.edu; Bradley.yoder@hsc.utah.edu; Brenda Poindexter; Wally Carlo, M.D.; cotte010@mc.duke.edu; Dennis Wallace; Ed Donovan; Ehrenkranz Richard (E-mail); ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; Kristi Watterberg; kurt.schibler@cchmc.org; Matthew Bizzarro; Michelle Walsh; Mickey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald Goldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa

Cc: Archer, Stephanie (NIH/NICHD) [E]; Cunningham, Meg; kristin zaterka

Subject: RE: \*\*\*\*SUPPORT MASTEHEADS

Sorry about my abrupt first response. If NEJM has a limit to the number of authors, they should have told us this up front. Difficulty fitting the authors, affiliations, and abstract on the first page seems like a lame excuse to drop on us at this point. Surely, there are other solutions. Put the affiliations in a footnote on the next page or at the end. If one less author will allow it to fit, take me off so the

rest of you can be there.

Ed

---

From: Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]  
Sent: Thursday, April 29, 2010 2:01 PM  
To: (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Bell, Edward; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Matthew Bizzarro; Michelle Walsh; Mickey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOLDBERG; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa  
Cc: Archer, Stephanie (NIH/NICHD) [E]; Cunningham, Meg; kristin zaterka  
Subject: \*\*\*\*SUPPORT MASTEHEADS  
Importance: High

HI,

Due to space limitations for the two SUPPORT papers, NEJM has requested to list the authorship as NICHD NRN and SUPPORT Study Group. Bothe Neil and Wally are ok with this and authors will be recognized on PubMed.

Rose

From: Hogan, Sharon [<mailto:shogan@nejm.org>]  
Sent: Thursday, April 29, 2010 9:13 AM  
To: 'Wally Carlo, M.D.'; Finer, Neil  
Cc: Moskowitz, Deborah  
Subject: RE: Your articles in the NEJM

Hello again,

We are still having difficulty fitting the list of authors, the authors' affiliations, and the abstract on the first page of each of these articles. We would like to simply list "The NICHD Neonatal Research Network and the SUPPORT Study Group" under the title and then move the list of authors and affiliations to the Appendix.

An example of this style is in our April 22 issue:

Volume 362:1477-1490

April 22, 2010

<http://content.nejm.org/content/vol362/issue16/index.dtl>

Number 16

Next

<http://content.nejm.org/cgi/content/short/362/16/1491?query=nextarrow>

Effect of Valsartan on the Incidence of Diabetes and Cardiovascular Events

The NAVIGATOR Study Group

Please confirm that these changes would be okay.

Rosemary D. Higgins, MD

Program Scientist for the Neonatal Research Network

Visit us at [www.UHhospitals.org](http://www.UHhospitals.org).

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anyone other than the 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 by law.



**From:** Ed Bell  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal(ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; CarloWaldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Donovan; EhrenkranzRichard (E-mail); Ivan Frantz(ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Matthew Bizzarro; Michelle Walsh; Mickey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald Goldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; Cunningham,Meg; kristin zaterka  
**Subject:** Re: \*\*\*\*\*SUPPORT MASTEHEADS  
**Date:** Thursday, April 29, 2010 3:08:41 PM

---

That's baloney. Tell them to use a smaller font.

Sent from my phone

---

**From:** "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>  
**Date:** Thu, 29 Apr 2010 15:01:20 -0400  
**To:** (Luc.Brion@UTSouthwestern.edu)<Luc.Brion@UTSouthwestern.edu>; (rohls@unm.edu)<rohls@unm.edu>; aaf2@po.cwru.edu<aaf2@po.cwru.edu>; Abhik Das<adas@rti.org>; alaptook@WIHRI.org<alaptook@WIHRI.org>; Ambal(ambal@uab.edu)<ambal@uab.edu>; Brad Yoder (Bradley.yoder@hsc.utah.edu)<Bradley.yoder@hsc.utah.edu>; Brenda Poindexter<bpoindex@iupui.edu>; CarloWaldemar (E-mail)<wcarlo@peds.uab.edu>; cotte010@mc.duke.edu<cotte010@mc.duke.edu>; Dennis Wallace<dwallace@rti.org>; Ed Bell<Edward-bell@uiowa.edu>; Ed Donovan<edward.donovan@cchmc.org>; EhrenkranzRichard (E-mail)<richard.ehrenkranz@yale.edu>; Ivan Frantz(ifrantz@tuftsmedicalcenter.org)<ifrantz@tuftsmedicalcenter.org>; Kennedy, Kathleen A<Kathleen.A.Kennedy@uth.tmc.edu>; Kristi Watterberg<kwatterberg@salud.unm.edu>; Kurt Schibler [kurt.schibler@cchmc.org]<kurt.schibler@cchmc.org>; Matthew Bizzarro<matthew.bizzarro@yale.edu>; Michelle Walsh<mcw3@po.cwru.edu>; Mickey Caplan<mcaplan@northshore.org>; Oh William (E-mail)<william\_oh@brown.edu>; Pablo Sanchez<Pablo.Sanchez@UTSouthwestern.edu>; Poole Kenneth (E-mail)<poo@rti.org>; Roger Faix<Roger.Faix@hsc.utah.edu>; Ronald Goldberg<goldb008@mc.duke.edu>; Seetha Shankaran<sshankar@med.wayne.edu>; Stevenson David (E-mail)<dstevenson@stanford.edu>; Stoll Barbara (E-mail)<barbara\_stoll@oz.ped.emory.edu>; Tyson Jon (E-mail)<Jon.E.Tyson@uth.tmc.edu>; VanMeurs, Krisa<vanmeurs@leland.stanford.edu>  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]<archerst@mail.nih.gov>; Cunningham,Meg<mcunningham@rti.org>; kristin zaterka<kzaterka@rti.org>  
**Subject:** \*\*\*\*\*SUPPORT MASTEHEADS

**HI,**

**Due to space limitations for the two SUPPORT papers, NEJM has requested to list the authorship as NICHD NRN and SUPPORT Study Group. Bothe Neil and Wally are ok with this and authors will be recognized on PubMed.**

**Rose**

**From:** Hogan, Sharon [mailto:shogan@nejm.org]  
**Sent:** Thursday, April 29, 2010 9:13 AM  
**To:** 'Wally Carlo, M.D.'; Finer, Neil  
**Cc:** Moskowitz, Deborah  
**Subject:** RE: Your articles in the NEJM

Hello again,

We are still having difficulty fitting the list of authors, the authors' affiliations, and the abstract on the first page of each of these articles. We would like to simply list "The NICHD Neonatal Research Network and the SUPPORT Study Group" under the title and then move the list of authors and affiliations to the Appendix.

An example of this style is in our April 22 issue:

**Volume 362:1477-1490**

**April 22, 2010**

**Number 16**

**Next▶**

## **Effect of Valsartan on the Incidence of Diabetes and Cardiovascular Events**

*The NAVIGATOR Study Group*

Please confirm that these changes would be okay.

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network

**From:** [Bock, Robert \(NIH/NICHD\) \[E\]](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Subject:** RE: May 12 Conference call  
**Date:** Thursday, April 29, 2010 2:15:35 PM

---

Just make sure you get quoted or else we might not be in the story.

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Thursday, April 29, 2010 2:12 PM  
**To:** Bock, Robert (NIH/NICHD) [E]; 'wacarlo@uab.edu'; 'nfiner@ucsd.edu'  
**Subject:** Re: May 12 Conference call

I will likely only need 2 minutes to give any overview of the NRN and study.

Rose

---

**From:** Bock, Robert (NIH/NICHD) [E]  
**To:** wacarlo@uab.edu <wacarlo@uab.edu>; 'Finer, Neil' <nfiner@ucsd.edu>  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Wed Apr 28 14:40:13 2010  
**Subject:** May 12 Conference call

Hello all. I just wanted to take a minute or so to go over our plan for the media briefing on May 12<sup>th</sup>.

Either I or someone from my office will make will make a very brief statement, something like "Thank you for joining our media availability at the National Institutes of Health. Researchers with the Neonatal Research Network will describe the results of a large clinical trial on oxygen and preterm infants. With us today are Dr. Rosemary Higgins, Program Scientist for the NICHD Neonatal Research Network, and two researchers with the network, Dr. Waldemar Carlo and Dr. Neil Finer. "

Then, I propose that Rose speak for about five minutes, explaining the need for the studies and their design.

After which, either I or Rose will introduce Dr. Carlo, who will speak for five minutes and describe his study and its findings, and then we will introduce Dr. Finer, who will talk for five minutes about his study and its findings.

After everyone is finished speaking, we'll invite calls from press in attendance.

Please let me know if you have any comments, questions or concerns.

Thanks.  
Bob

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Friday, April 23, 2010 4:07 PM  
**To:** wacarlo@uab.edu; 'Finer, Neil'; Martinez, Fernando  
**Cc:** Bock, Robert (NIH/NICHD) [E]  
**Subject:** Conference call for SUPPORT discussion - May 12 1 PM ET

**Confirmation #: 35225550**

Dear **SONDRA DIETZ**,

Your conference reservation is confirmed. Thank you for choosing Conference America.

KERIN REEVES

**Conference Leader:** SANDA PECINA

**Organization:** ACADEMY FOR EDUCATIONAL DEVELOP

**Conference Date:** 05/12/2010 Wednesday

**Conference Time:** 1:00PM Eastern Time

**Dial In Number:** 1-800-351-(b) USA

**Passcode:** (b) (6)

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network  
Pregnancy and Perinatology Branch  
Center for Developmental Biology and Perinatal Medicine  
Eunice Kennedy Shriver National Institute of Child Health and Human Development  
National Institutes of Health  
6100 Executive Blvd., Room 4B03  
MSC 7510  
Bethesda, MD 20892  
For overnight delivery use Rockville, MD 20852  
301-496-5575  
301-496-3790 (FAX)  
higginsr@mail.nih.gov

**From:** [Bock, Robert \(NIH/NICHD\) \[E\]](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Subject:** FW: Preterm oxygenation studies  
**Date:** Thursday, April 29, 2010 1:16:37 PM  
**Attachments:** [SUPPORT news release LW SD.docx](#)

---

Please see e-mail trail below and attached markup from NHLBI. I've sent our draft to Dr. G for his approval. When I get back, I'll reconcile the two versions. A lot of the NHLBI changes are

(b) (5)

(b) (5)

(b) (5) See also Lindsay's comment below about our explanation of the

(b) (5) I'd prefer to leave this in (b) (5)

(b) (5)

(b) (5)

(b) (5)

I neglected to mention our division staff also asked if you would consider (b) (5) I don't think this is a big deal to them, but wanted to do my diligence in passing along their request...

Lindsey Willis

Office of Communications  
National Heart, Lung, and Blood Institute  
National Institutes of Health  
301-594-1950  
Follow us on Twitter at [@NIH\\_NHLBI](#)

**From:** Bock, Robert (NIH/NICHD) [E]  
**Sent:** Thursday, April 29, 2010 1:06 PM  
**To:** Willis, Lindsey (NIH/NHLBI) [E]  
**Cc:** Dambrauskas, Susan (NIH/NHLBI) [E]  
**Subject:** RE: Preterm oxygenation studies

Thanks, Lindsay. I just submitted our draft to Dr. Guttmacher. When he sends it back to me, I'll go over the two versions and contact you and Susan about reconciling the differences.

In answer to your question, I can't speak for Dr. Higgins, but I think she would say that in all

(b) (5)

(b) (5)

Still, I'll put your question to her, and we'll go over the release again.

Thanks.

---

**From:** Willis, Lindsey (NIH/NHLBI) [E]  
**Sent:** Thursday, April 29, 2010 1:03 PM  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Cc:** Dambraskas, Susan (NIH/NHLBI) [E]  
**Subject:** Re: Preterm oxygenation studies

Hi Bob,

Our division staff had no additional comments to the draft we sent to you yesterday (attached again.) The only question they raised, that is only slightly addressed by Dr. Higgins' quote, is, (b) (5) ? That bit of information is saved for the end and may be better explained.

Let us know how else we can assist,

Lindsey Willis

Office of Communications  
National Heart, Lung, and Blood Institute  
National Institutes of Health  
301-594-1950  
Follow us on Twitter at [@NIH\\_NHLBI](#)

---

**From:** Willis, Lindsey (NIH/NHLBI) [E]  
**Sent:** Wednesday, April 28, 2010 1:10 PM  
**To:** Bock, Robert (NIH/NICHD) [E]; Dambraskas, Susan (NIH/NHLBI) [E]  
**Subject:** RE: Preterm oxygenation studies

Bob, we are just awaiting a review from our Director of the Division of Lung Diseases. Attached is what we sent them for review, just FYI. There may be additional suggestions from them once we hear back.

Lindsey Willis

Office of Communications  
National Heart, Lung, and Blood Institute  
National Institutes of Health  
301-594-1950  
Follow us on Twitter at [@NIH\\_NHLBI](#)

---

**From:** Bock, Robert (NIH/NICHD) [E]  
**Sent:** Tuesday, April 27, 2010 4:13 PM  
**To:** Dambrauskas, Susan (NIH/NHLBI) [E]  
**Cc:** Willis, Lindsey (NIH/NHLBI) [E]  
**Subject:** RE: Preterm oxygenation studies

Will you be able to send this along soon?

---

**From:** Dambrauskas, Susan (NIH/NHLBI) [E]  
**Sent:** Monday, April 26, 2010 2:07 PM  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Cc:** Striar, Diane (NIH/NHLBI) [E]; Willis, Lindsey (NIH/NHLBI) [E]  
**Subject:** RE: Preterm oxygenation studies

Bob,

Want to let you know that we (Lindsey and I) spoke with Dr. Carol Blaisdell, the NHLBI project officer for the SUPPORT study. She explained some of the concerns with the news release as originally drafted. We will send you another version with tracked changes in the next few days.

One issue is that (b) (5)

Dr. Blaisdell believes that the authors and Dr. Higgins will be OK with changes in how the results are described and the emphasis of certain results, but you'll probably want to recirculate the revised release to them. In the meantime, please let us know if you receive any additional feedback from Dr. Higgins while Lindsey is working on the next version.

Thanks for your cooperation. Please let us know if you have any questions.

Susan Dambrauskas  
NHLBI Press Team Leader  
Technical Writer/Editor  
NHLBI Office of Communications  
301 594-1596 - direct  
301 496-4236 - office  
301 828- (b) (6) BlackBerry  
301 402-2405 - fax  
dambrauskass@nhlbi.nih.gov

---

**From:** Dambrauskas, Susan (NIH/NHLBI) [E]  
**Sent:** Monday, April 26, 2010 11:48 AM  
**To:** Willis, Lindsey (NIH/NHLBI) [E]; Bock, Robert (NIH/NICHD) [E]  
**Subject:** RE: Preterm oxygenation studies

Thanks, Lindsey.

I want to clarify the comment re: CPAP – the earlier version of the release included mention

(b) (5) This mention of  
(b) (5)  
(b) (5) (which Lindsey just sent to you, Bob). I think it's worthwhile to include (b) (5)  
(b) (5)  
(b) (5)

Sorry for the confusion.

Susan Dambrauskas  
NHLBI Press Team Leader  
Technical Writer/Editor  
NHLBI Office of Communications  
301 594-1596 - direct  
301 496-4236 - office  
301 828-(b) (6) - BlackBerry  
301 402-2405 - fax  
dambrauskass@nhlbi.nih.gov

---

**From:** Willis, Lindsey (NIH/NHLBI) [E]  
**Sent:** Monday, April 26, 2010 11:41 AM  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Cc:** Dambrauskas, Susan (NIH/NHLBI) [E]  
**Subject:** RE: Preterm oxygenation studies

Hi Bob,

Thank you for the opportunity to collaborate and co-issue this release with NICHD. Our Lung Division staff has reviewed the SUPPORT release and made a number of edits. Unfortunately, they did not track their changes, so I hope you are able to tell what changes were made. They moved some paragraphs around, and in the course of things removed any reference to NIH near the beginning of the release; I just wanted to point that out to you so that you can make a note to edit in something to remedy this.

There are a few notes on the release, with the following additional suggestions for you to consider:

- 1) (b) (5)
- 2) (b) (5)
- 3) (b) (5)
- 4) (b) (5)



5) (b) (5)

6) (b) (5)

case you would like to include it.

FYI, Our Lung staff has sent this to Dr. Higgins, so she may have some other comments for you at this point.

We look forward to reviewing your next draft. Please let me know if we can provide any clarification on any of the above points or any of our edits.

Lindsey Willis

Office of Communications

National Heart, Lung, and Blood Institute

National Institutes of Health

301-594-1950

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---

**From:** Bock, Robert (NIH/NICHD) [E]  
**Sent:** Thursday, April 22, 2010 12:53 PM  
**To:** Dambrauskas, Susan (NIH/NHLBI) [E]  
**Cc:** Striar, Diane (NIH/NHLBI) [E]; Willis, Lindsey (NIH/NHLBI) [E]  
**Subject:** RE: Preterm oxygenation studies

Thanks Susan.

---

**From:** Dambrauskas, Susan (NIH/NHLBI) [E]  
**Sent:** Thursday, April 22, 2010 12:52 PM  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Cc:** Striar, Diane (NIH/NHLBI) [E]; Willis, Lindsey (NIH/NHLBI) [E]  
**Subject:** RE: Preterm oxygenation studies

Bob,

I'm sure you are aware of the NEJM pub date now, but just in case, I'm passing along what our lung division folks shared with us. We are circulating your draft release to

them for review.

I am copying Lindsey Willis of our press team, who is our lung division press liaison and will help coordinate the release with you, etc.

Susan Dambrauskas  
NHLBI Press Team Leader  
Technical Writer/Editor  
NHLBI Office of Communications  
301 594-1596 - direct  
301 496-4236 - office  
301 828-(b) (6)- BlackBerry  
301 402-2405 - fax  
dambrauskass@nhlbi.nih.gov

**From:** Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]  
**Sent:** Tuesday, April 20, 2010 12:46 PM  
**To:** Zeis, Jennifer  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Online First release schedule for NEJM 09-11781

Dear Ms. Zeis:

Thanks very much for the information. Enclosed is my contact information. I am copying this to Dr. Rose Higgins at the NIH who probably should be the other contact person rather than our institution's press office.

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: 205 266 (b)

**From:** Zeis, Jennifer [mailto:jzeis@nejm.org]  
**Sent:** Tuesday, April 20, 2010 11:37 AM  
**To:** Wally Carlo, M.D.  
**Subject:** Online First release schedule for NEJM 09-11781

Dear Dr. Carlo,

As you know, your NEJM Original Article is on an accelerated Online First release schedule to coincide with your presentation of the results at the American Thoracic Society's annual meeting. I am writing to share the details of that schedule and to request your preferred media points of contact.

We will provide your article to reporters at 10 AM EDT Thursday, May 13. When we provide your article to the media under embargo, we will post the material on our password-protected NEJM Media Center, where only journalists who have agreed to respect our embargo may access it. I will email you this final file and any related material at that time

**Your article will be embargoed until 1 PM EDT Sunday, May 16**, the start of your ATS presentation on the trial. The ATS and NEJM embargoes are coordinated to lift simultaneously so you may reference your NEJM publication at the meeting, if you wish. Your paper will be published on NEJM.org as soon as the embargo lifts, and will later be published in the May 27 printed issue.

And finally, please let me know what **contact information you would like me to provide to journalists** who wish to interview you and/or your co-authors. You may include your institution's press office in addition to, or instead of, your personal contact information.

Many thanks. If you have any questions, please don't hesitate to ask.

Best regards,

Jen Zeis

**Jennifer Zeis**  
**Media Relations**  
**The New England Journal of Medicine**  
**office: 781-434-7186**  
MEDIA CENTER <http://media.nejm.org>  
twitter <http://twitter.com/nejm>

**From:** [Wally Carlo, M.D.](mailto:WallyCarlo@ucsd.edu)  
**To:** [wrich@ucsd.edu](mailto:wrich@ucsd.edu); [nfiner@ucsd.edu](mailto:nfiner@ucsd.edu); Michele Walsh-Sukys; Edward Donovan; Duara, Shahnaz; Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Support Pilot Vs. Main Trial  
**Date:** Friday, April 29, 2005 10:37:08 AM

---

Wade: Good point. I forgot that. wally

---

**From:** Wade Rich [mailto:[wrich@ucsd.edu](mailto:wrich@ucsd.edu)]  
**Sent:** Friday, April 29, 2005 9:31 AM  
**To:** [nfiner@ucsd.edu](mailto:nfiner@ucsd.edu); 'Michele Walsh-Sukys'; 'Edward Donovan'; 'Duara, Shahnaz'; 'Rose'  
**Cc:** Wally Carlo, M.D.  
**Subject:** RE: Support Pilot Vs. Main Trial

Dr. Carlo et al. ,

It is important to remember that the unblinded oximeters which were sent out in August 2004 for the Pilot trial (noted as P16 and P17) have a different separation algorithm than those which eventually went into the main trial. (widened 12/13/2004). The separation we achieve with these units will not be equivalent to those currently being used for the main trial.

Wade

---

**From:** Neil Finer [mailto:[nfiner@ucsd.edu](mailto:nfiner@ucsd.edu)]  
**Sent:** Friday, April 29, 2005 6:59 AM  
**To:** [wrich@ucsd.edu](mailto:wrich@ucsd.edu)  
**Subject:** FW: Support Pilot Vs. Main Trial

**From:** Wally Carlo, M.D. [mailto:[WCarlo@peds.uab.edu](mailto:WCarlo@peds.uab.edu)]  
**Sent:** Thursday, April 28, 2005 11:34 AM  
**To:** [nfiner@ucsd.edu](mailto:nfiner@ucsd.edu); Michele Walsh; Avroy A. Fanaroff, M.D.; Edward Donovan; Ed Donovan; Shahnaz; Higgins, Rosemary (NIH/NICHD)  
**Subject:** FW: Support Pilot Vs. Main Trial

Dear All: Monica has put together this plan for our call to address what has to be done to continue the O2 sat pilot. Wally

---

**From:** Monica Collins  
**Sent:** Thursday, April 28, 2005 11:19 AM  
**To:** Wally Carlo, M.D.  
**Cc:** [bkh@rti.org](mailto:bkh@rti.org)  
**Subject:** Support Pilot Vs. Main Trial

Wally,

I have put together the points in the similarities and differences in the two trials and suggestions to incorporate the pilot into the main trial. It would be a shame and waste of time, effort, and money if the trial were to stop. I understand that we may not be able to utilize the data that had been collected previously because of the oximeter differences, but otherwise, RTI has used a lot of manpower and expertise in designing the trial. And, if all centers do not want to participate, I don't see a real problem--it will just take longer. I would like for those centers who will not participate to say so upfront.

This document is provided for reference purposes only. Persons with disabilities having difficulty accessing information in this document should e-mail NICHD FOIA Office at [NICHDFOIARequest@mail.nih.gov](mailto:NICHDFOIARequest@mail.nih.gov) for assistance.

**Monica**

**From:** [Wally Carlo, M.D.](#)  
**To:** [nfiner@ucsd.edu](mailto:nfiner@ucsd.edu); [Michele Walsh](#); [Avroy A. Fanaroff, M.D.](#); [Edward Donovan](#); [Ed Donovan](#); [Shahnaz Higgins](#); [Rosemary \(NIH/NICHD\) \[E\]](#)  
**Subject:** FW: Support Pilot Vs. Main Trial  
**Date:** Thursday, April 28, 2005 2:34:57 PM  
**Attachments:** [In order to continue the pilot study for the O2 saturation portion.doc](#)

---

Dear All: Monica has put together this plan for our call to address what has to be done to continue the O2 sat pilot. Wally

---

**From:** Monica Collins  
**Sent:** Thursday, April 28, 2005 11:19 AM  
**To:** Wally Carlo, M.D.  
**Cc:** [bkh@rti.org](mailto:bkh@rti.org)  
**Subject:** Support Pilot Vs. Main Trial

Wally,

I have put together the points in the similarities and differences in the two trials and suggestions to incorporate the pilot into the main trial. It would be a shame and waste of time, effort, and money if the trial were to stop. I understand that we may not be able to utilize the data that had been collected previously because of the oximeter differences, but otherwise, RTI has used a lot of manpower and expertise in designing the trial. And, if all centers do not want to participate, I don't see a real problem--it will just take longer. I would like for those centers who will not participate to say so upfront.

Monica

In order to continue the pilot study for the O<sub>2</sub> saturation portion, the following must be done:

- 1) Eligibility criteria is similar—
  - a. Infants are less than 7 days old- a specific day such as day 3, 4, or 5 could be designated as the desired date of monitoring.
  - b. Gestational age is the same.
  - c. Infant is receiving mech vent and/or CPAP—not all babies would qualify for the pilot if they do not meet this criteria at the time of pilot enrollment.
  - d. Infant is receiving FiO<sub>2</sub> > 0.30—not all babies would qualify for the pilot if they do not meet this criteria at the time of pilot enrollment.
  - e. *The main trial has an additional inclusion of full resuscitation intended—not necessary for the pilot.*
  - f. *The main trial has an additional exclusion of known major congenital anomalies—does not need to be changed for the pilot.*
  - g. *The main trial has an exclusion for research apparatus/personnel not available—does not need to be changed for the pilot.*
- 2) Consent—this is only data collection of existing data; therefore, it should fall under the umbrella of the main trial and not require an additional consent.
- 3) Data Collection—The data collection is different and will require three additional data forms to be completed for the pilot study (the same form repeated 3 days). We are collecting 4 time points of ABGs and vent settings each day. The time periods are 6, 12, 18, 2400 hours. It is strictly chart review. Also, we may or may not want to ask the nurses to answer the “is the baby in the higher/lower/normal/don’t know group?”. If we pick day 3 to collect for the monitoring day, the research nurse would complete data forms for days 2, 3, and 4.
- 4) Endpoints-The pilot study’s primary outcome is “Separation of median SpO<sub>2</sub> by at least 3%”. The main trial has nothing concerning the separation of saturations but rather the clinical outcomes.
- 5) Other issues—
  - a. The pilot study was designed to only use the study pulse oximeter for one day and the routine pulse oximeter for the other two days (one before and one after the monitoring). These infants would be on the study pulse oximeter for all three days and the data would reflect the study pulse oximeter readings for those four time points of ABG/vent settings.
  - b. We may want to download the pulse oximeters at the end of the first 14 days of the study rather than wait until the 30<sup>th</sup> day in order to obtain this data more quickly.
  - c. The pilot study would have to be monitored for equal randomization numbers because not all babies would be in the pilot study and therefore the groups could become unequal. We might want to monitor more babies



**to prevent unblinding the main trial but obtain the data for the pilot study.  
The sample size for the pilot study is 244.**

**From:** [Bock, Robert \(NIH/NICHD\) \[E\]](#)  
**To:** ["Wally Carlo, M.D."; wacarlo@uab.edu](#)  
**Cc:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Subject:** RE: Revision to your quote  
**Date:** Wednesday, April 28, 2010 12:01:29 PM

---

Thanks very much.

-----Original Message-----

From: Wally Carlo, M.D. [<mailto:WCarlo@peds.uab.edu>]  
Sent: Wednesday, April 28, 2010 11:00 AM  
To: Bock, Robert (NIH/NICHD) [E]; [wacarlo@uab.edu](mailto:wacarlo@uab.edu)  
Cc: Higgins, Rosemary (NIH/NICHD) [E]  
Subject: RE: Revision to your quote

Mr. Bock:

I agree your statement is better.

Wally

-----Original Message-----

From: Bock, Robert (NIH/NICHD) [E] <[bockr@exchange.nih.gov](mailto:bockr@exchange.nih.gov)>  
Sent: Wednesday, April 28, 2010 10:56 AM  
To: 'wacarlo@uab.edu' <[wacarlo@uab.edu](mailto:wacarlo@uab.edu)>  
Cc: Higgins, Rosemary (NIH/NICHD) [E] <[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)>  
Subject: Revision to your quote

Hi Dr. Carlo. After going over our release on the SUPPORT study, it occurred to us that your quote might be misconstrued that the lower end of the saturation range could be considered safe.

"Many doctors believe that optimal oxygen saturation levels fall between 85 and 95 percent," Dr. Carlo said. "But before our study, there was no evidence that the lower end of that range was safe."

Would you consider a small change? Something like:

"Many doctors believe that optimal oxygen saturation levels fall between 85 and 95 percent," Dr. Carlo said. "Our results offer much needed data on which to base treatment decisions."

Thank you.

Bob

**From:** Bock, Robert (NIH/NICHD) [E]  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** Does this work?  
**Date:** Wednesday, April 28, 2010 11:43:48 AM

---

I rewrote the paragraph talking about the study. However, since we (b) (5)

opted not to include them in the revision.

Does this work:

(b) (5)

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Tuesday, April 27, 2010 6:30 PM  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Revised release

minor suggestions.

I can't tell if the attachment is present

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 20592

301-435-7909

301-496-5575

301-496-3790 (FAX)

[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

---

**From:** Bock, Robert (NIH/NICHD) [E]  
**Sent:** Tuesday, April 27, 2010 5:57 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** Revised release

Hi Rose. Please see attached. I did some rearranging in response to Mona's comments. I also included Shurin's quote, revised the subhead a little, and included another sentence from the NHLBI version. I e-mailed the NHLBI staff earlier today, but haven't heard back. I'll show this to Mona, then to Dr. G. With any luck, we'll hear from NHLBI some time tomorrow, and I can merge their

release with ours before sending it downtown.

Version 8 is the full tracked changes version, to show the extent of the rearranging I did. Version 9 has most of the changes accepted, with the exception of the new content I outlined above.

Thanks.

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Eastman, Diane"; "Johnson, Karen"; "Bell, Edward"  
**Cc:** "Gantz, Marie"  
**Subject:** RE: Support trial pt.  
**Date:** Tuesday, April 27, 2010 10:17:00 AM

---

Great  
Thanks  
Rose

---

**From:** Eastman, Diane [mailto:diane-eastman@uiowa.edu]  
**Sent:** Tuesday, April 27, 2010 10:15 AM  
**To:** Johnson, Karen; Bell, Edward  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** Support trial pt.

The child who moved to Maryland and the folks in Delaware have graciously agreed to test her for us, is scheduled for May 7<sup>th</sup>!!

I have a time scheduled next week with mom to also get the questionnaires completed by phone. So she'll soon be completed.

Thanks. Diane

*Diane Eastman, ARNP*

*High Risk Infant Followup Program*

*Children's Hospital of Iowa*

*319-353-6880*

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Rich, Wade"; "Finer, Neil"  
**Subject:** FW: All forms in for Support papers  
**Date:** Monday, April 26, 2010 5:03:00 PM

---

---

**From:** Abel, Brendan [mailto:babel@nejm.org]  
**Sent:** Monday, March 01, 2010 11:01 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Finer, Neil; Wally Carlo, M.D.  
**Subject:** All forms in for Support papers

Hi Rose,

Wanted to let you know that all forms have now been received for both 09-11781 and 09-11783. Thank you VERY much for all of your help in tracking down the forms.

Let me know if you have any questions (forms related, or not).

Best,

Brendan

Brendan Abel  
Editorial Assistant  
New England Journal of Medicine  
(617) 487-6584

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**From:** [Wally Carlo, M.D.](mailto:Wally_Carlo_M.D.)  
**To:** [nfiner@ucsd.edu](mailto:nfiner@ucsd.edu)  
**Cc:** [Avroy A. Fanaroff, M.D.](mailto:Avroy_A_Fanaroff_M.D.); [Betty Hastings](mailto:Betty_Hastings); [Ed Donovan](mailto:Ed_Donovan); [Higgins, Rosemary \(NIH/NICHD\) \[F\]](mailto:Higgins_Rosemary_(NIH/NICHD)_[F]); [Ken Poole](mailto:Ken_Poole); [Michele](mailto:Michele); [Shahnaz Duara](mailto:Shahnaz_Duara); [Wade Rich](mailto:Wade_Rich)  
**Subject:** RE:  
**Date:** Tuesday, April 26, 2005 8:26:50 PM

---

Hi Neil: Yes, let's have the call so we can get our thoughts together. wally

---

**From:** Neil Finer [<mailto:nfiner@ucsd.edu>]  
**Sent:** Tuesday, April 26, 2005 3:11 PM  
**To:** Wally Carlo, M.D.  
**Cc:** 'Avroy A. Fanaroff, M.D.'; 'Betty Hastings'; 'Ed Donovan'; [higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov); 'Ken Poole'; 'Michele'; 'Neil Finer'; 'Shahnaz Duara'; 'Wade Rich'  
**Subject:**

Hi Wally

I am writing about the Oximeter secondary. I think that we had a different interpretation here at UCSD. When we began to enroll for the actual trial, we turned in our unblinded oximeters then we received the blinded ones. This secondary study as written requires that we know what type of oximeter the child is on (high or low), it requires a separate informed consent, and it has it's own screening criteria which are different than the trial.

I believe that the first 100-200 infants in the trial should be used for the secondary and I believe that this can be done by adding a questionnaire to the RNs for the first 3 days to determine if they feel that were unblinded and in which direction. The advantage of doing it this way, is that we are all truly blinded.

Let me know. We are planning a conference call

Neil

**From:** [Bock, Robert \(NIH/NICHD\) \[E\]](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Subject:** RE: Current draft  
**Date:** Monday, April 26, 2010 3:55:42 PM


---

I'm calling to explain.

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Monday, April 26, 2010 3:55 PM  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Subject:** RE: Current draft

I am ok with this, but wasn't (b) (5)



Rose

---

**From:** Bock, Robert (NIH/NICHD) [E]  
**Sent:** Monday, April 26, 2010 3:45 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** Current draft

Did you get a chance to look at the script yet?

Here's a current draft of the release, with slight changes to the third paragraph, to make it clear we're treating infants and not adults.



**From:** [Bock, Robert \(NIH/NICHD\) \[E\]](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Subject:** Current draft  
**Date:** Monday, April 26, 2010 3:44:48 PM  
**Attachments:** [SUPPORT News Release 8.doc](#)

---

Did you get a chance to look at the script yet?

Here's a current draft of the release, with slight changes to the third paragraph, to make it clear we're treating infants and not adults.

**From:** [Bock, Robert \(NIH/NICHD\) \[E\]](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Subject:** FW: Preterm oxygenation studies  
**Date:** Monday, April 26, 2010 2:11:44 PM

---

Please see below. Are you ok with this? I sent the NHLBI version of the release back to their press office. Their new press staffer forwarded it to me, and didn't work with the researcher to make sure that it (b) (5). A more senior press staffer is going to go through it now and send it back to us.

Until then, are you ok with (b) (5)

[REDACTED]

---

**From:** Dambrauskas, Susan (NIH/NHLBI) [E]  
**Sent:** Monday, April 26, 2010 2:07 PM  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Cc:** Striar, Diane (NIH/NHLBI) [E]; Willis, Lindsey (NIH/NHLBI) [E]  
**Subject:** RE: Preterm oxygenation studies

Bob,

Want to let you know that we (Lindsey and I) spoke with Dr. Carol Blaisdell, the NHLBI project officer for the SUPPORT study. She explained some of the concerns with the news release as originally drafted. We will send you another version with tracked changes in the next few days.

One issue is that (b) (5)

[REDACTED]

Dr. Blaisdell believes that the authors and Dr. Higgins will be OK with changes in how the results are described and the emphasis of certain results, but you'll probably want to recirculate the revised release to them. In the meantime, please let us know if you receive any additional feedback from Dr. Higgins while Lindsey is working on the next version.

Thanks for your cooperation. Please let us know if you have any questions.

Susan Dambrauskas  
NHLBI Press Team Leader  
Technical Writer/Editor  
NHLBI Office of Communications  
301 594-1596 - direct  
301 496-4236 - office  
301 828-(b) (6) BlackBerry  
301 402-2405 - fax  
dambrauskass@nhlbi.nih.gov

---

**From:** Dambrauskas, Susan (NIH/NHLBI) [E]  
**Sent:** Monday, April 26, 2010 11:48 AM  
**To:** Willis, Lindsey (NIH/NHLBI) [E]; Bock, Robert (NIH/NICHD) [E]  
**Subject:** RE: Preterm oxygenation studies

Thanks, Lindsey.

I want to clarify the comment re: CPAP – the earlier version of the release included mention (b) [REDACTED] This mention of (b) (5) [REDACTED] (which Lindsey just sent to you, Bob). I think it's worthwhile to include the mention (b) (5) [REDACTED]

Sorry for the confusion.

Susan Dambrauskas  
NHLBI Press Team Leader  
Technical Writer/Editor  
NHLBI Office of Communications  
301 594-1596 - direct  
301 496-4236 - office  
301 828-(b) (6) BlackBerry  
301 402-2405 - fax  
dambrauskass@nhlbi.nih.gov

---

**From:** Willis, Lindsey (NIH/NHLBI) [E]  
**Sent:** Monday, April 26, 2010 11:41 AM  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Cc:** Dambrauskas, Susan (NIH/NHLBI) [E]  
**Subject:** RE: Preterm oxygenation studies

Hi Bob,

Thank you for the opportunity to collaborate and co-issue this release with NICHD. Our Lung Division staff has reviewed the SUPPORT release and made a number of edits. Unfortunately, they did not track their changes, so I hope you are able to tell what changes were made. They moved some paragraphs around, and in the course of things removed any reference to NIH near the beginning of the release; I just wanted to point that out to you so that you can make a note to edit in something to remedy this.

There are a few notes on the release, with the following additional suggestions for you to consider:

- 1) (b) (5) [REDACTED];
- 2) (b) (5) [REDACTED]
- 3) (b) (5) [REDACTED]

- 4) (b) (5) [REDACTED]
  - 5) (b) (5) [REDACTED]; [REDACTED]
  - 6) (b) (5) [REDACTED]
- [REDACTED] in case you would like to include it.

FYI, Our Lung staff has sent this to Dr. Higgins, so she may have some other comments for you at this point.

We look forward to reviewing your next draft. Please let me know if we can provide any clarification on any of the above points or any of our edits.

Lindsey Willis

Office of Communications  
National Heart, Lung, and Blood Institute  
National Institutes of Health  
301-594-1950

Follow us on Twitter at [@NIH\\_NHLBI](https://twitter.com/NIH_NHLBI)

---

**From:** Bock, Robert (NIH/NICHD) [E]  
**Sent:** Thursday, April 22, 2010 12:53 PM  
**To:** Dambrauskas, Susan (NIH/NHLBI) [E]  
**Cc:** Striar, Diane (NIH/NHLBI) [E]; Willis, Lindsey (NIH/NHLBI) [E]  
**Subject:** RE: Preterm oxygenation studies

Thanks Susan.

---

**From:** Dambrauskas, Susan (NIH/NHLBI) [E]  
**Sent:** Thursday, April 22, 2010 12:52 PM  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Cc:** Striar, Diane (NIH/NHLBI) [E]; Willis, Lindsey (NIH/NHLBI) [E]  
**Subject:** RE: Preterm oxygenation studies

Bob,

I'm sure you are aware of the NEJM pub date now, but just in case, I'm passing along what our lung division folks shared with us. We are circulating your draft release to them for review.

I am copying Lindsey Willis of our press team, who is our lung division press liaison and will help coordinate the release with you, etc.

Susan Dambrauskas  
NHLBI Press Team Leader  
Technical Writer/Editor  
NHLBI Office of Communications  
301 594-1596 - direct  
301 496-4236 - office  
301 828-(b) (6) BlackBerry  
301 402-2405 - fax  
dambrauskass@nhlbi.nih.gov

**From:** Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]  
**Sent:** Tuesday, April 20, 2010 12:46 PM  
**To:** Zeis, Jennifer  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Online First release schedule for NEJM 09-11781

Dear Ms. Zeis:

Thanks very much for the information. Enclosed is my contact information. I am copying this to Dr. Rose Higgins at the NIH who probably should be the other contact person rather than our institution's press office.

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: 205 266 (b)

**From:** Zeis, Jennifer [mailto:jzeis@nejm.org]  
**Sent:** Tuesday, April 20, 2010 11:37 AM  
**To:** Wally Carlo, M.D.  
**Subject:** Online First release schedule for NEJM 09-11781

Dear Dr. Carlo,

As you know, your NEJM Original Article is on an accelerated Online First release schedule to coincide with your presentation of the results at the American Thoracic Society's annual meeting. I am writing to share the details of that schedule and to request your preferred media points of contact.

We will provide your article to reporters at 10 AM EDT Thursday, May 13. When we provide your article to the media under embargo, we will post the material on our password-protected NEJM Media Center, where only journalists who have agreed to respect our embargo may access it. I will email you this final file and any related material at that time

**Your article will be embargoed until 1 PM EDT Sunday, May 16**, the start of your ATS presentation on the trial. The ATS and NEJM embargoes are coordinated to lift simultaneously so you may reference your NEJM publication at the meeting, if you wish. Your paper will be published on NEJM.org as soon as the embargo lifts, and will later be published in the May 27 printed issue.

And finally, please let me know what **contact information you would like me to provide to journalists** who wish to interview you and/or your co-authors. You may include your institution's press office in addition to, or instead of, your personal contact information.

Many thanks. If you have any questions, please don't hesitate to ask.

**Best regards,**

**Jen Zeis**

**Jennifer Zeis**  
**Media Relations**  
**The New England Journal of Medicine**  
**office: 781-434-7186**  
MEDIA CENTER <http://media.nejm.org>  
twitter <http://twitter.com/nejm>

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**From:** [Bock, Robert \(NIH/NICHD\) \[E\]](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Subject:** Video script  
**Date:** Monday, April 26, 2010 12:22:02 PM  
**Attachments:** [Preterm Studies Script.docx](#)

---



**From:** Kurt Schibler  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** SUPPORT Secondary Review  
**Date:** Monday, April 26, 2010 11:48:32 AM  
**Attachments:** Review Intermittent Hypoxia Secondary\_Schibler.docx

---

Hi Rose,  
Attached is my review for the SUPPORT Intermittent Hypoxia Secondary for today's call.  
Thanks,  
Kurt

Kurt Schibler, MD  
Neonatology  
CCHMC ML #7009  
3333 Burnet Avenue  
Cincinnati, OH 45229  
513-636-3972 (office)  
513-736-(b) (6) (pager)

Review for Protocol Committee  
Kurt Schibler, MD  
April 26, 2010

Title: Intermittent Hypoxia in Preterm Infants enrolled in the SUPPORT trial  
Secondary Study

Investigators: Juliann Di Fiore, BSEE, Ryan Foglyano, BSBE, Richard Martin, MD,  
Chris Wilson PhD, Michele Walsh, MD

Aims: To expand the current database of infants with high resolution pulse oximetry data to include the remaining low-resolution pulse oximetry data SUPPORT infants. Using these two separate infant cohorts to:

1. Assess the effect of data resolution (2/2sec, averaging time/sample rate versus 16/10sec, averaging time/sample rate) on the incidence, duration and magnitude of desaturation events between low and high baseline SaO<sub>2</sub> infant groups.
2. Assess the relationship between the incidence of desaturation events and the development of Retinopathy of Prematurity (ROP).
3. Analyze the correlation between the incidence of desaturation events and neurodevelopmental outcome.
4. Analyze the correlation between the incidence of desaturation events and mortality.
5. Analyze the correlation between the incidence of desaturation events and bronchopulmonary dysplasia (BPD).

Comments.

1. The definition of desaturation episodes needs to be more explicit. Is desaturation defined as saturation  $\leq 80\%$  only in the low-resolution group? It is proposed to be a fall of 10% from baseline in the initial secondary protocol?

2. It appears to me that the infants at the two high-resolution centers received care based on the display of high-resolution saturation data and that low-resolution saturations were resolved for the SUPPORT database. The presumption of this line of investigations is that we could intervene to prevent these intermittent hypoxic events if we recognize them by refining the monitor display algorithm. Were infants from the two high-resolution study sites treated differently? Were the outcomes substantially different from those at other sites?

3. The relationship between desaturation episodes and the primary outcome of the main trial ROP /death should also be analyzed.

4. Are results available from the initial study looking at the occurrence, duration, and magnitude of desaturations in low versus high spO<sub>2</sub> groups?

5. It is unclear to me in the two phases of data cleaning, resolution of the skew between groups and analysis, what will be performed at CWR and what at RTI? How significant are the resources requested from RTI?

6. The budget appears to be primarily to support time commitment by investigators to do the analyses. Is this essentially the Network paying for investigators salaries or is this contract work?

**From:** [Blaisdell, Carol \(NIH/NHLBI\) \[E\]](#)  
**To:** [Dambrauskas, Susan \(NIH/NIDCD\) \[E\]](#); [Willis, Lindsey \(NIH/NHLBI\) \[E\]](#); [Striar, Diane \(NIH/NHLBI\) \[E\]](#)  
**Cc:** [Gail, Dorothy \(NIH/NHLBI\) \[E\]](#); [Weinmann, Gail \(NIH/NHLBI\) \[E\]](#); [Kiley, James \(NIH/NHLBI\) \[E\]](#); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Subject:** RE: SUPPORT - infant oxygenation studies news release  
**Date:** Monday, April 26, 2010 9:39:51 AM  
**Attachments:** SUPPORT news release 7 04 20 10 (cb3).docx

---

Dear Susan and Lindsey,

Drs Kiley, Weinmann, Gail, and I have looked over the draft press release and have made a lot of changes to improve the readability and make sure the message is more clear.

Attached is an edited copy of the press release, with the following additional suggestions for you to consider:

- 1) (b) (5) [REDACTED]
- 2) We added a statement as a quote from Dr. Shurin
- 3) (b) (5) [REDACTED]  
[REDACTED]
- 4) (b) (5) [REDACTED]  
[REDACTED]
- 5) (b) (5) [REDACTED]  
[REDACTED]

Please be sure that Dr. Higgins (NICHD) and I are copied on further edits.  
Our division would like to see other drafts before they go to Dr Shurin.

Thanks for your work on this,  
Carol

Carol J. Blaisdell, M.D.  
Medical Officer  
Lung Developmental Biology and  
Pediatric Pulmonary Diseases  
Division of Lung Diseases, NHLBI/NIH  
(301) 435-0222 phone

---

**From:** [Dambrauskas, Susan \(NIH/NHLBI\) \[E\]](#)  
**Sent:** Friday, April 23, 2010 10:16 AM  
**To:** [Blaisdell, Carol \(NIH/NHLBI\) \[E\]](#)  
**Cc:** [Gail, Dorothy \(NIH/NHLBI\) \[E\]](#); [Striar, Diane \(NIH/NHLBI\) \[E\]](#); [Willis, Lindsey \(NIH/NHLBI\) \[E\]](#)  
**Subject:** RE: SUPPORT - infant oxygenation studies news release

Thank you.

Susan Dambrauskas  
NHLBI Press Team Leader  
Technical Writer/Editor

NHLBI Office of Communications  
301 594-1596 - direct  
301 496-4236 - office  
301 828-(b) (6)- BlackBerry  
301 402-2405 - fax  
dambrauskass@nhlbi.nih.gov

---

**From:** Blaisdell, Carol (NIH/NHLBI) [E]  
**Sent:** Friday, April 23, 2010 8:33 AM  
**To:** Dambrauskas, Susan (NIH/NHLBI) [E]  
**Cc:** Gail, Dorothy (NIH/NHLBI) [E]; Striar, Diane (NIH/NHLBI) [E]; Willis, Lindsey (NIH/NHLBI) [E]  
**Subject:** RE: SUPPORT - infant oxygenation studies news release

Thanks, I will work on edits with DLD colleagues and send back our edits.

Carol

Carol J. Blaisdell, M.D.  
Medical Officer  
Lung Developmental Biology and  
Pediatric Pulmonary Diseases  
Division of Lung Diseases, NHLBI/NIH  
(301) 435-0222 phone

---

**From:** Dambrauskas, Susan (NIH/NHLBI) [E]  
**Sent:** Thursday, April 22, 2010 1:12 PM  
**To:** Blaisdell, Carol (NIH/NHLBI) [E]  
**Cc:** Gail, Dorothy (NIH/NHLBI) [E]; Striar, Diane (NIH/NHLBI) [E]; Willis, Lindsey (NIH/NHLBI) [E]  
**Subject:** SUPPORT - infant oxygenation studies news release

Hi Carol,

Attached is the draft news release from NICHD, with a few minor editorial suggestions from me. Please review for accuracy. Lindsey Willis, who serves as the DLD press liaison, will coordinate feedback to NICHD.

Also attached are the manuscripts (from NICHD).

A few questions for consideration:

- Do we want to request that this be a joint NICHD-NHLBI news release? (NICHD is open to that.) If so, we would add NHLBI press contact info to the top of the release as well as boilerplate language at the end. Do we also want to include a (b) (5) [REDACTED]

- (b) (5) [REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]

(b) (5)

Let us know what you think.

Susan Dambrauskas  
NHLBI Press Team Leader  
Technical Writer/Editor  
NHLBI Office of Communications  
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301 496-4236 - office  
301 828-(b) (6)- BlackBerry  
301 402-2405 - fax  
[dambrauskass@nhlbi.nih.gov](mailto:dambrauskass@nhlbi.nih.gov)

---

**From:** Dambrauskas, Susan (NIH/NHLBI) [E]  
**Sent:** Wednesday, April 21, 2010 3:53 PM  
**To:** Kiley, James (NIH/NHLBI) [E]; Blaisdell, Carol (NIH/NHLBI) [E]  
**Cc:** Weinmann, Gail (NIH/NHLBI) [E]; Gail, Dorothy (NIH/NHLBI) [E]; McDonough, Sally (NIH/NHLBI) [E]; Striar, Diane (NIH/NHLBI) [E]  
**Subject:** RE: Online First release schedule for NEJM 09-11781

Thanks. We received the draft news release from NICHD yesterday. Will forward it to you for review.

Susan Dambrauskas  
NHLBI Press Team Leader  
Technical Writer/Editor  
NHLBI Office of Communications  
301 594-1596 - direct  
301 496-4236 - office  
301 828-(b) (6)- BlackBerry  
301 402-2405 - fax  
[dambrauskass@nhlbi.nih.gov](mailto:dambrauskass@nhlbi.nih.gov)

---

**From:** Kiley, James (NIH/NHLBI) [E]  
**Sent:** Wednesday, April 21, 2010 3:52 PM  
**To:** Blaisdell, Carol (NIH/NHLBI) [E]  
**Cc:** Weinmann, Gail (NIH/NHLBI) [E]; Gail, Dorothy (NIH/NHLBI) [E]; Dambrauskas, Susan (NIH/NHLBI) [E]; McDonough, Sally (NIH/NHLBI) [E]  
**Subject:** RE: Online First release schedule for NEJM 09-11781

Carol:

Thanks, this is good news. The press office will loop in dr. Shurin with the clearance of the press release. Jim

---

**From:** Blaisdell, Carol (NIH/NHLBI) [E]  
**Sent:** Wednesday, April 21, 2010 1:57 PM  
**To:** Kiley, James (NIH/NHLBI) [E]  
**Cc:** Weinmann, Gail (NIH/NHLBI) [E]; Gail, Dorothy (NIH/NHLBI) [E]

**Subject: FW: Online First release schedule for NEJM 09-11781**

Dear Jim,

The SUPPORT trial is embargoed for release (NEJM), but press release will be coordinated with the ATS noon session—see bottom of email.

NICHD is working on the press release with Susan Dambrauskas and Diane Striar (who haven't contacted me yet, have they you?)

Is this something you can communicate with Susan Shurin? I haven't.

Not sure how these things go (with the embargo and all).

Carol

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Wednesday, April 21, 2010 1:48 PM  
**To:** Blaisdell, Carol (NIH/NHLBI) [E]  
**Subject:** FW: Online First release schedule for NEJM 09-11781

---

**From:** Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]  
**Sent:** Tuesday, April 20, 2010 12:46 PM  
**To:** Zeis, Jennifer  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Online First release schedule for NEJM 09-11781

Dear Ms. Zeis:

Thanks very much for the information. Enclosed is my contact information. I am copying this to Dr. Rose Higgins at the NIH who probably should be the other contact person rather than our institution's press office.

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: 205 266 (b)

---

**From:** Zeis, Jennifer [mailto:jzeis@nejm.org]  
**Sent:** Tuesday, April 20, 2010 11:37 AM  
**To:** Wally Carlo, M.D.  
**Subject:** Online First release schedule for NEJM 09-11781

Dear Dr. Carlo,

As you know, your NEJM Original Article is on an accelerated Online First release schedule to coincide with your presentation of the results at the American Thoracic Society's annual meeting. I am writing to share the details of that schedule and to request your preferred media points of contact.

We will provide your article to reporters at 10 AM EDT Thursday, May 13. When we provide your article to the media under embargo, we will post the material on our password-protected NEJM Media Center, where only journalists who have agreed to respect our embargo may access it. I will email you this final file and any related material at that time

**Your article will be embargoed until 1 PM EDT Sunday, May 16**, the start of your ATS presentation on the trial. The ATS and NEJM embargoes are coordinated to lift simultaneously so you may reference your NEJM publication at the meeting, if you wish. Your paper will be published on NEJM.org as soon as the embargo lifts, and will later be published in the May 27 printed issue.

And finally, please let me know what **contact information you would like me to provide to journalists** who wish to interview you and/or your co-authors. You may include your institution's press office in addition to, or instead of, your personal contact information.

Many thanks. If you have any questions, please don't hesitate to ask.

Best regards,  
Jen Zeis

Jennifer Zeis  
Media Relations  
The New England Journal of Medicine  
office: 781-434-7186  
MEDIA CENTER <http://media.nejm.org>  
twitter <http://twitter.com/nejm>

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**From:** [Wally Carlo, M.D.](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Subject:** RE: Pulse ox pilot  
**Date:** Monday, April 25, 2005 12:13:22 PM

---

Rose:

THANKS a lot!

Wally

---

**From:** Higgins, Rosemary (NIH/NICHD) [mailto:[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)]  
**Sent:** Monday, April 25, 2005 11:03 AM  
**To:** Wally Carlo, M.D.; [nfiner@ucsd.edu](mailto:nfiner@ucsd.edu); Edward Donovan; [sduara@miami.edu](mailto:sduara@miami.edu); [aaf2@po.cwru.edu](mailto:aaf2@po.cwru.edu); [mcw3@po.cwru.edu](mailto:mcw3@po.cwru.edu)  
**Cc:** Petrie, Carolyn  
**Subject:** RE: Pulse ox pilot

Wally

Carolyn will be setting up a SUPPORT Call and this can be discussed.

Thanks

Rose

---

**From:** Wally Carlo, M.D. [mailto:[WCarlo@peds.uab.edu](mailto:WCarlo@peds.uab.edu)]  
**Sent:** Monday, April 25, 2005 11:49 AM  
**To:** [nfiner@ucsd.edu](mailto:nfiner@ucsd.edu); Edward Donovan; Higgins, Rosemary (NIH/NICHD); [sduara@miami.edu](mailto:sduara@miami.edu); [aaf2@po.cwru.edu](mailto:aaf2@po.cwru.edu); [mcw3@po.cwru.edu](mailto:mcw3@po.cwru.edu)  
**Subject:** RE: Pulse ox pilot

Dear SUPPORT subcommittee:

I am concerned that we may not be collecting the data for the pilot in enough babies and that we need to be evaluating compliance with the O2 intervention.

Currently only three centers may be in the pilot. We need to get to two hundred babies as we planned. So it would be great if we could do the pilot in all 5 core centers.

I also want to start looking at the first downloads on babies from all centers to assess compliance.

Maybe we need a conf call to agree on a plan of action.

wally

**From:** [Conra Lacy](#)  
**To:** [joa@rti.org](mailto:joa@rti.org); [Kristin Zaterka-Baxter](#)  
**Cc:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Kristi Watterberg](#); [hpeceny@unm.edu](mailto:hpeceny@unm.edu)  
**Subject:** BGD f-u kids in SUPPORT f-u database  
**Date:** Friday, April 23, 2010 6:43:33 PM

---

Kris and Jenny,

I finally figured out why the monthly reports show us as having 11 follow-up kids in 2009 and I count 14. (b) (6) (b) (6) were in the SUPPORT Trial and were also eligible for GDB follow-up. Their forms were entered into the SUPPORT Follow-up data base and not the GDB follow-up data base. Do they need to be entered in both? Do all SUPPORT babies need to be entered in both data bases? Will all trials have a separate follow-up data base for trial subjects who are not <27 weeks? Do we also need separate GDB data bases for trial kids who are not otherwise eligible for GDB?

I know - Too many questions =0

Connie

Conra (Connie) Backstrom Lacy  
University of New Mexico  
Manager, Clinical Research  
(505) 272-0367  
pager (505) 951 (b) (6)  
fax (505) 272-5589  
[cbackstrom@salud.unm.edu](mailto:cbackstrom@salud.unm.edu)

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Susan Hintz"  
**Subject:** RE: RE:  
**Date:** Friday, April 23, 2010 3:36:00 PM

---

Overall- Fabulous – as I said, you could write a very complete review article from what you have in the slides!!!

---

**From:** Susan Hintz [mailto:srhintz@stanford.edu]  
**Sent:** Friday, April 23, 2010 3:35 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** Re: RE:

Thank you Rose!

I will take your advice on cuts - and I need to cut more. As much as it pains me to do it, I think I will need to cut some of the images too.

But - overall besides being too long - does it seem OK (interesting, worthwhile, I won't embarrass myself)?

Thanks

Susan

Sent from my iPhone

On Apr 23, 2010, at 10:48 AM, "Higgins, Rosemary (NIH/NICHD) [E]" <[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)> wrote:

Susan

You have a tremendous amount of material in this presentation. The literature review on previous publications is very complete. Would it be possible for you to get through all these slides in the time? If so, then keep what you have. If not, you could consider eliminating the sections on early single center studies and combining this into one slide, allowing 1-2 slides on the other publications, and eliminating the last two slides from the SUPPORT NEURO study (you can also combine the two "site slides" and simply use the 20 sites that recruited into SUPPORT on one slide – or just use the SUPPORT neuroimaging centers).

You could write an awesome review article from these slides.

Hope this helps

Rose

---

**From:** [srhintz@stanford.edu](mailto:srhintz@stanford.edu) [mailto:srhintz@stanford.edu]

**Sent:** Friday, April 23, 2010 12:59 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:**

Hi Rose

Thanks for looking at this. I am still tweaking and editing!

Susan

File(s) will be available for download until **22 June 2010**:

Attachment: [Hintz MRI and Outcomes\\_042310.pptx](#), 30,769.58 KB [**Fingerprint:**  
8105080221890d25fc4b0c2b1dc0d043]

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To retrieve the attachment(s), please click on the link(s) above.

You will be prompted to create an account if you do not have one.  
[Accellion File Transfer](#)

**From:** Archer, Stephanie (NIH/NICHD) [E]  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Finer OLF oa galleys  
**Date:** Friday, April 23, 2010 10:41:16 AM  
**Attachments:** Finer\_SUPPORT Ventilation, galleys, 2010-04-22 with corrections.pdf

---

Here are my changes.

---

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:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Friday, April 23, 2010 9:04 AM  
**To:** Archer, Stephanie (NIH/NICHD) [E]  
**Cc:** 'Finer, Neil'  
**Subject:** FW:

Here are Neil's changes.

Neil – we will work off this copy for the authorship/boilerplate issues. Of utmost importance, Brenda Morris needs to be deleted and Kathleen Kennedy added.

Thanks  
Rose

---

**From:** Finer, Neil [<mailto:nfiner@ucsd.edu>]  
**Sent:** Thursday, April 22, 2010 7:13 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.; Gantz, Marie; Das, Abhik; Rich, Wade  
**Subject:**

Hi Everyone

Please see my responses

I think we are OK

A few questions for Marie

The want to know why 2 Surf babies were not intubated – please review – ie missing data , protocol deviation etc

Marie please check their count for the survivors below Table 3

We need to put Death before discharge in the 2 Appendices – I don't know how to access these – we had used death at 36 weeks but the results describe death before discharge

Thanks everyone

Marie,

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:** Archer, Stephanie (NIH/NICHD) [E]  
**To:** "Wally Carlo, M.D."  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Carlo OA Galleys  
**Date:** Thursday, April 22, 2010 1:41:51 PM  
**Attachments:** Carlo, SUPPORT, galleys, 2010-04-21 with changes.pdf

---

Attached is a version with the boilerplate and author changes in it. Let me know if you need any additional help.

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:** Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]  
**Sent:** Thursday, April 22, 2010 1:12 PM  
**To:** Archer, Stephanie (NIH/NICHD) [E]  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** FW: Carlo OA Galleys

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: 205 266 (b)

---

**From:** NEJM Galleys [mailto:NejmGalleys@mms.org]  
**Sent:** Tuesday, April 20, 2010 2:04 PM  
**To:** Wally Carlo, M.D.  
**Subject:** Carlo OA Galleys

**PLEASE DO NOT REPLY TO THIS E-MAIL**

**AUTHOR:** Carlo

**MANUSCRIPT EDITOR:** Sharon Hogan (shogan@nejm.org); (800) 445-8080 or (617) 734-9800

Please check the attached galley proofs of your article

You will need Adobe Acrobat Reader software (version 4.0 or later) to view these files. Acrobat Reader is available free of charge on the Adobe Web site, <http://www.adobe.com/products/acrobat/readermain.html>.

If you have already made arrangements with Sharon Hogan to go over your galley changes, please call her at 800-445-8080 or 617-734-9800 at the time you have set up. If you cannot reach this Manuscript Editor, telephone our Manuscript Editing Department at 800-445-8080 or 617-734-9800 **no later than noon on Monday, April 26, 2010.**

**It is important that we speak to you by telephone. Please do not send us an annotated electronic file.**

For calls from outside the United States, we will pay the telephone charges; have the operator bill us.

Our switchboard is open from 8:30 a.m. to 5 p.m. Eastern time.

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**From:** Fanaroff, Avroy  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu; wrich@ucsd.edu; mgantz@rti.org; nxs5@case.edu; Anthony.Piazza@oz.ped.emory.edu; susie.buchter@oz.ped.emory.edu; brenda\_2759@msn.com; Nirupama\_Laroia@URMC.Rochester.edu; dale\_phelps@urmc.rochester.edu; SDuara@med.miami.edu; Vivek.Narendran@cchmc.org; vineet.bhandari@yale.edu; bsood@med.wayne.edu; moshea@wfubmc.edu; Luc.Brion@UTSouthwestern.edu; rohls@unm.edu; aaf2@po.cwru.edu; adas@rti.org; alaptook@wihri.org; ambal@uab.edu; Bradley.yoder@hsc.utah.edu; bpoindex@iupui.edu; wcarlo@peds.uab.edu; cotte010@mc.duke.edu; dwallace@rti.org; Edward-bell@uiowa.edu; edward.donovan@cchmc.org; richard.ehrenkranz@yale.edu; ifrantz@tuftsmedicalcenter.org; Kathleen.A.Kennedy@uth.tmc.edu; kwatterberg@salud.unm.edu; kurt.schibler@cchmc.org  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; kzaterka@rti.org; mcunningham@rti.org; petrie@rti.org  
**Subject:** Re: \*\*\*\*CONFIDENTIAL UPDATE ON SUPPORT PAPERS\*\*\*\*\*  
**Date:** Thursday, April 22, 2010 12:55:34 AM

---

Great news  
A big pat on the back all around  
NRN goes from strength to strength and remains a pathfinder in NPM  
Congrats  
Av from the Shinkasen

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov>  
**To:** Finer, Neil <nfiner@ucsd.edu>; 'Rich, Wade' <wrich@ucsd.edu>; Gantz, Marie <mgantz@rti.org>; Nancy Newman <nxs5@case.edu>; Anthony Piazza (Anthony.Piazza@oz.ped.emory.edu) <Anthony.Piazza@oz.ped.emory.edu>; (susie.buchter@oz.ped.emory.edu) <susie.buchter@oz.ped.emory.edu>; 'Brenda Morris' (b) (6); Laroia, Nirupama <Nirupama\_Laroia@URMC.Rochester.edu>; 'Phelps, Dale' <Dale\_Phelps@URMC.Rochester.edu>; 'Duara, Shahnaz' <SDuara@med.miami.edu>; Vivek Narendran <Vivek.Narendran@cchmc.org>; 'vineet.bhandari@yale.edu' <vineet.bhandari@yale.edu>; 'Sood, Beena' <bsood@med.wayne.edu>; 'Michael O' Shea' <moshea@wfubmc.edu>; (Luc.Brion@UTSouthwestern.edu) <Luc.Brion@UTSouthwestern.edu>; (rohls@unm.edu) <rohls@unm.edu>; aaf2@po.cwru.edu <aaf2@po.cwru.edu>; Abhik Das <adas@rti.org>; alaptook@WIHRI.org <alaptook@WIHRI.org>; Ambal (ambal@uab.edu) <ambal@uab.edu>; Brad Yoder (Bradley.yoder@hsc.utah.edu) <Bradley.yoder@hsc.utah.edu>; Brenda Poindexter <bpoindex@iupui.edu>; Carlo Waldemar (E-mail) <wcarlo@peds.uab.edu>; cotte010@mc.duke.edu <cotte010@mc.duke.edu>; Dennis Wallace <dwallace@rti.org>; Ed Bell <Edward-bell@uiowa.edu>; Ed Donovan <edward.donovan@cchmc.org>; Ehrenkranz Richard (E-mail) <richard.ehrenkranz@yale.edu>; Ivan Frantz (ifrantz@tuftsmedicalcenter.org) <ifrantz@tuftsmedicalcenter.org>; Kennedy, Kathleen A <Kathleen.A.Kennedy@uth.tmc.edu>; Kristi Watterberg <kwatterberg@salud.unm.edu>; Kurt Schibler [kurt.schibler@cchmc.org] <kurt.schibler@cchmc.org>; Matthew Bizzarro <matthew.bizzarro@yale.edu>; Michelle Walsh <mcw3@po.cwru.edu>; Mickey Caplan <mcaplan@northshore.org>; Oh William (E-mail) <william\_oh@brown.edu>; Pablo Sanchez <Pablo.Sanchez@UTSouthwestern.edu>; Poole Kenneth (E-mail) <poo@rti.org>; Roger Faix <Roger.Faix@hsc.utah.edu>; Ronald Goldberg <goldb008@mc.duke.edu>; Seetha Shankaran <sshankar@med.wayne.edu>; Stevenson David (E-mail) <d Stevenson@stanford.edu>; Stoll Barbara (E-mail) <barbara\_stoll@oz.ped.emory.edu>; Tyson Jon (E-mail) <Jon.E.Tyson@uth.tmc.edu>; VanMeurs, Krisa <vanmeurs@leland.stanford.edu>  
**Cc:** Archer, Stephanie (NIH/NICHD) [E] <archerst@mail.nih.gov>; 'Zaterka-Baxter, Kristin' <kzaterka@rti.org>; Cunningham, Meg <mcunningham@rti.org>; 'Huitema, Carolyn Petrie' <petrie@rti.org>  
**Sent:** Wed Apr 21 10:46:15 2010  
**Subject:** \*\*\*\*CONFIDENTIAL UPDATE ON SUPPORT PAPERS\*\*\*\*\*

Hi,

**We have been informed by NEJM that both SUPPORT Papers will be accelerated Online First release scheduled to coincide with the presentations of the results at the American Thoracic Society's annual meeting on Sunday May 16, 2010. The on-line**

**release will occur at 1 PM EDT on 5/16/2010. The print publication is slated to appear in the May 27, 2010 issue of NEJM.**

As far as I know, this will be a first for the Neonatal Research Network.

The SUPPORT abstracts will be presented in platforms at PAS. Neil will deliver the same talks will be given at a post-PAS meeting on neonatal resuscitation.

**We are not to discuss the fact that the papers have been reviewed or accepted by NEJM.** PI's - please insure that all of your staff with the confidential knowledge regarding the SUPPORT papers are aware of the NEJM rules!! This is particularly important for those attending the PAS meeting who may be asked about the status of the papers. **If asked, the appropriate response is "The manuscripts are in the peer review process."**

In addition, since the papers are not yet published in NEJM, we need to respect their embargo policy. This means that we are requested to follow the guidelines at <http://authors.nejm.org/Help/Embargo.asp>.

Specifically, the guidelines state:

- Please do not discuss the fact that the research has been submitted or accepted for publication in the *New England Journal of Medicine*.
- Please do not distribute any copies of the manuscript, tables, or figures. (It is acceptable to use the materials in a presentation, but they should not be distributed.)

**THANKS TO ALL OF YOU AND YOUR STAFF FOR THE EFFORT INVOLVED IN THIS LANDMARK STUDY.**

Rose

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network  
Pregnancy and Perinatology Branch  
Center for Developmental Biology and Perinatal Medicine  
Eunice Kennedy Shriver National Institute of Child Health and Human Development  
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301-496-5575  
301-496-3790 (FAX)  
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**From:** Archer, Stephanie (NIH/NICHD) [E]  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Carlo OA Galleys  
**Date:** Wednesday, April 21, 2010 9:38:41 PM

---

I was able to look at this this morning, but no wireless at the hospital to send you the changes. Plus my blackberry conked out when I was sending you an email about it. Have to put in a Help Desk ticket to get a new battery for it before PAS.

Not sure what the best way of sending changes back are for this. I've added some text edits in the attached PDF.

Main changes:

- Author list. Need to move Piazza ahead of Sanchez in both the author list and the affiliations
- Affiliations. Need to remove "W.R." from the Alabama list and add him to the UCSD list.
- Grant numbers. Per the comment, here is a revised Supporting paragraph:

Supported by grants from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (Grant numbers: U10 HD21364, U10 HD21373, U10 HD21385, U10 HD21397, U10 HD27851, U10 HD27853, U10 HD27856, U10 HD27880, U10 HD27871, U10 HD27904, U10 HD34216, U10 HD36790, U10 HD40461, U10 HD40492, U10 HD40498, U10 HD40521, U10 HD40689, U10 HD53089, U10 HD53109, U10 HD53119, U10 HD53124), co-funding from the National Heart, Lung, and Blood Institute, and grants from the National Institute of Health (Grant numbers: M01 RR30, M01 RR32, M01 RR39, M01 RR44, M01 RR54, M01 RR59, M01 RR64, M01 RR70, M01 RR80, M01 RR125, M01 RR633, M01 RR750, M01 RR997, M01 RR6022, M01 RR7122, M01 RR8084, M01 RR16587, UL1 RR25008, UL1 RR24139, UL1 RR24979, UL1 RR25744).

- Acknowledgements. Several names missing from Brown, Case, Duke, Emory, Rochester and Dallas.

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Wednesday, April 21, 2010 6:40 AM  
**To:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** Re: Carlo OA Galleys

Please do not feel obligated to work given the circumstances. Cathy will (b) (6)

(b) (6)

Good luck!

Keep us posted.

Regards,

Rose

---

**From:** Archer, Stephanie (NIH/NICHD) [E]  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Wed Apr 21 06:36:16 2010  
**Subject:** RE: Carlo OA Galleys

Great! I'll work on this first.

Email access will depend on when I'm working at home (no wireless access in the hospital).

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Wednesday, April 21, 2010 6:24 AM  
**To:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** Fw: Carlo OA Galleys

Stephanie

I hope all goes well (b) (6).

Since you can work at home this am, Here are Wally's galleys - can you check the acknowledgements?

This is the highest priority for the network.

Let me know when you will work by email-we have on on protocol review call at 3 today -

Thanks and good luck.

---

**From:** Wally Carlo, M.D. <WCarlo@peds.uab.edu>  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil <nfiner@ucsd.edu>; Gantz, Marie <mgantz@rti.org>; Abhik Das <adas@rti.org>  
**Sent:** Tue Apr 20 15:42:03 2010  
**Subject:** FW: Carlo OA Galleys

FYI. I will working on this tonight.

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: 205 266 (b)

---

**From:** NEJM Galleys [mailto:NejmGalleys@mms.org]  
**Sent:** Tuesday, April 20, 2010 2:04 PM  
**To:** Wally Carlo, M.D.  
**Subject:** Carlo OA Galleys

**PLEASE DO NOT REPLY TO THIS E-MAIL**

**AUTHOR:** Carlo

**MANUSCRIPT EDITOR:** Sharon Hogan (shogan@nejm.org); (800) 445-8080 or (617) 734-9800

Please check the attached galley proofs of your article

You will need Adobe Acrobat Reader software (version 4.0 or later) to view these files. Acrobat Reader is available free of charge on the Adobe Web site, <http://www.adobe.com/products/acrobat/readermain.html>.

If you have already made arrangements with Sharon Hogan to go over your galley changes, please call her at 800-445-8080 or 617-734-9800 at the time you have set up. If you cannot reach this Manuscript Editor, telephone our Manuscript Editing Department at 800-445-8080 or 617-734-9800 **no later than noon on Monday, April 26, 2010.**

**It is important that we speak to you by telephone. Please do not send us an annotated electronic file.**

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**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; "Abhik Das"; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); "Brenda Poindexter"; "Carlo Waldemar (E-mail)"; cotte010@mc.duke.edu; "Dennis Wallace"; "Ed Bell"; "Ed Donovan"; "Ehrenkranz Richard (E-mail)"; Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; "Kristi Watterberg"; Kurt Schibler (kurt.schibler@cchmc.org); "Matthew Bizzarro"; "Michelle Walsh"; "Mickey Caplan"; "Oh William (E-mail)"; "Pablo Sanchez"; "Poole Kenneth (E-mail)"; "Roger Faix"; "Ronald Goldberg"; "Seetha Shankaran"; "Stevenson David (E-mail)"; "Stoll Barbara (E-mail)"; "Tyson Jon (E-mail)"; VanMeurs, Krisa; (Karen.Osborne@hsc.utah.edu); Angelita Hensman; Becky bara; Bethany Ball; Brenda MacKinnon (bmackinnon@tuftsmedicalcenter.org); Cathy Grisby (cathy.grisby@uc.edu); Conra Backstrom; "Diana Vasil"; "Diane Wilson"; "Donia Campbell"; Elizabeth Billian; Ellen Hale; Georgia McDavid; Karen Johnson (karen-johnson@uiowa.edu); "Kimberly Fisher"; "Leslie Wilson"; Monica Collins; monica.konstantino@yale.edu; Nancy Miller; Nancy Newman; "Sandra Grimes"  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; "Cunningham, Meg"; "Zaterka-Baxter, Kristin"  
**Subject:** SurveyNeonatologists\_Treatment of Late Onset Sepsis-4-19-2010  
**Date:** Wednesday, April 21, 2010 1:16:00 PM  
**Attachments:** SurveyNeonatologists\_Treatment of Late Onset Sepsis-4-19-2010.doc

---

Hi

Can you please complete the survey for the GCSF/IVIG by April 30 for the development of the protocol for the recently approved concept.

Thanks  
Rose

April 19, 2010

*NICHD Neonatal Research Network*

The concept protocol A RANDOMIZED TRIAL OF RECOMBINANT GRANULOCYTE-COLONY STIMULATING FACTOR AND INTRAVENOUS IMMUNOGLOBULIN FOR INFANTS WITH SEPSIS AND NEUTROPENIA has been approved by the NRN Steering Committee to go to full protocol and review by the Protocol Subcommittee. To assist us in the development of the full protocol would you please complete this brief survey regarding Clinical Practices in Neonates with Suspected Late Onset Sepsis

Date:

Center:

Contact Name:

For each of the following clinical scenarios, please identify how frequently you use the following therapeutic modalities in your clinical practice.

Case 1. 10do 29 wk and 1100 gm at birth with mild RDS requiring oxygen supplementation only has two consecutive gastric residuals of 3 ml (of 20 ml/feed) with a 2 cm increase in abdominal girth noted by nursing staff today. Examination reveals an infant in no respiratory distress, pink and well-perfused, and a protuberant abdomen that is soft with good bowel sounds. ABG- pH 7.33, PaCO<sub>2</sub> 47, HCO<sub>3</sub>-21. WBC 12,000 cells/ml<sup>3</sup> and manual differential 53% Segs, 2% Bands, 37% Lymphocytes. How frequently would you use following therapeutic agents (if at all) for the described or similar patients:

a. Broad spectrum antibiotics

>90%  51-90%  10-50%  <10%

b. Intravascular volume support and vasopressor agents

>90%  51-90%  10-50%  <10%

c. Intravenous Immunoglobulin

>90%  51-90%  10-50%  <10%

d. Colony Stimulating Factors (G-CSF or GM-CSF)

>90%  51-90%  10-50%  <10%

Case 2. 18 do 25 wk and 680 gm at birth with RDS requiring mechanical ventilation has had two days of increasing ventilatory support. Examination reveals an active infant with deep subcostal retractions, tachycardic but without murmurs. The abdomen is distended without appreciable bowel sounds and a bile-tinged gastric secretions were noted in the OG tube. Abdominal radiograph shows mildly distended loops of bowel, but no free air, no pneumatosis and no portal venous gas. Complete blood count reveals a hemoglobin of 12 mg/dl, total WBC of 6000 cells/ml<sup>3</sup> (absolute neutrophil count of 1200) and platelets of 160,000. How frequently would you use following therapeutic agents (if at all) for the described or similar patients:

a. Broad spectrum antibiotics

>90%  51-90%  10-50%  <10%

b. Intravascular volume support and vasopressor agents

>90%  51-90%  10-50%  <10%

c. Intravenous Immunoglobulin

>90%  51-90%  10-50%  <10%

d. Colony Stimulating Factors (G-CSF or GM-CSF)

>90%  51-90%  10-50%  <10%



April 19, 2010

Case 3. 14do 26 wk and 746 gm at birth reintubated today because of respiratory distress with history of 7 days of mechanical ventilation and surfactant for RDS. Examination reveals a pale and mottled infant, hypotonic and obtunded. Complete blood count reveals a hemoglobin of 12 mg/dl, total WBC of 2500 cells/ml<sup>3</sup> (absolute neutrophil count of 800) and platelets of 80,000. How frequently would you use following therapeutic agents (if at all) for the described or similar patients:

- a. Broad spectrum antibiotics  
 >90%  51-90%  10-50%  <10%
- b. Intravascular volume support and vasopressor agents  
 >90%  51-90%  10-50%  <10%
- c. Intravenous Immunoglobulin  
 >90%  51-90%  10-50%  <10%
- d. Colony Stimulating Factors (G-CSF or GM-CSF)  
 >90%  51-90%  10-50%  <10%

Therapy with IVIg in infants with clinical signs of sepsis and neutropenia reduces mortality.

(Agree) 1  2  3  4  5  (Disagree)

Therapy with colony stimulating factors such as G-GCSF or GM-CSF in infants with clinical signs of sepsis and neutropenia reduces mortality.

(Agree) 1  2  3  4  5  (Disagree)

All attending physicians in our unit have a similar approach to the use of immunomodulatory agents such as IVIg and colony stimulating factors for infants with clinical sepsis and neutropenia.

(Agree) 1  2  3  4  5  (Disagree)

Would you be willing to randomize an infant with clinical signs of late onset sepsis with neutropenia to treatment with G-CSF and/or IVIg along with standard antimicrobial and supportive therapy **or** standard antimicrobial and supportive therapy alone?

Yes  No

Would you consider the responses to this survey a consensus response from your center?

Yes  No

Are the responses individual views and others at your center will complete the survey individually?

Yes  No

Comments:

Thank you for taking time to complete this survey. Please Fax or e-mail [schelonk@ohsu.edu](mailto:schelonk@ohsu.edu) your completed survey to Robert Schelonka at (503) 494-1542 by April 30, 2010.

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Conra Lacy"; "Janell Fuller"  
**Cc:** "Marie Gantz"; "Kristi Watterberg"  
**Subject:** RE: SUPPORT FU OUTCOMES  
**Date:** Wednesday, April 21, 2010 11:04:00 AM

---

Thanks for the heroic effort!  
Rose

-----Original Message-----

From: Conra Lacy [mailto:CBackstrom@salud.unm.edu]  
Sent: Monday, April 19, 2010 6:15 PM  
To: Higgins, Rosemary (NIH/NICHD) [E]; Janell Fuller  
Cc: Marie Gantz; Kristi Watterberg  
Subject: Re: SUPPORT FU OUTCOMES

Rose,  
I'm afraid our bloodhounds have lost the trail. We managed to follow this family to Oklahoma and on to Texas through the help of a relative. Even she hasn't heard from them. It is feared they have been deported. We have utilized our friends in the Medical Investigators office, who can track driver's licenses and other records (since Mom doesn't have a Social Security number) and they have come up with no leads on either parent. We plan to keep trying.  
Connie

Conra (Connie) Backstrom Lacy  
University of New Mexico  
Manager, Clinical Research  
(505) 272-0367  
pager (505) 951-(b)  
fax (505) 272-5589  
cbackstrom@salud.unm.edu

>>> "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> 4/19/2010 2:34 PM >>>

Hi,  
We are missing the following infants from the SUPPORT FU. Let us know how you are doing.  
Thanks for all the effort!!!  
Rose  
CENTER

NETWORK

FU\_message

26

(b) (6)

FU window has closed but NF05 and NF09a have not been completed.

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network

Pregnancy and Perinatology Branch  
Center for Developmental Biology and Perinatal Medicine  
Eunice Kennedy Shriver National Institute of Child Health and Human Development  
National Institutes of Health  
6100 Executive Blvd., Room 4B03  
MSC 7510  
Bethesda, MD 20892  
For overnight delivery use Rockville, MD 20852  
301-496-5575  
301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Eastman, Diane"; "Bell, Edward"; "Johnson, Karen"; "Acarregui, Michael"  
**Cc:** "Gantz, Marie"  
**Subject:** RE: SUPPORT FU OUTCOMES  
**Date:** Wednesday, April 21, 2010 10:58:00 AM

---

Great  
Thanks for the update

Rose

---

**From:** Eastman, Diane [mailto:diane-eastman@uiowa.edu]  
**Sent:** Monday, April 19, 2010 5:35 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Bell, Edward; Johnson, Karen; Acarregui, Michael  
**Cc:** Gantz, Marie  
**Subject:** RE: SUPPORT FU OUTCOMES

Rose,

This is the little girl who moved to Maryland. I've been in contact with the psychologist who is now done with her maternity leave and also the person who can arrange Dr. Paul's schedule to do the neuro exam. They are looking for some dates when they would both be able to see this child to save the family multiple trips. I will let you know as soon as we have a date scheduled. Hopefully it will be fairly soon. Diane

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Monday, April 19, 2010 3:32 PM  
**To:** Bell, Edward; Johnson, Karen; Acarregui, Michael; Eastman, Diane  
**Cc:** Gantz, Marie  
**Subject:** SUPPORT FU OUTCOMES

Hi,

We are missing the following infants from the SUPPORT FU. Let us know how you are doing.

Thanks for all the effort!!!

Rose

CENTER	NETWORK	FU_message
24	(b)	FU window has closed but NF05 and NF09a have not been completed.

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network  
Pregnancy and Perinatology Branch  
Center for Developmental Biology and Perinatal Medicine  
Eunice Kennedy Shriver National Institute of Child Health and Human Development  
National Institutes of Health  
6100 Executive Blvd., Room 4B03  
MSC 7510  
Bethesda, MD 20892  
For overnight delivery use Rockville, MD 20852  
301-496-5575  
301-496-3790 (FAX)  
higginsr@mail.nih.gov

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Hamer, Faithe Angeline"; "Wilson, Leslie Dawn"  
**Cc:** "Gantz, Marie"  
**Subject:** RE: SUPPORT FU OUTCOMES  
**Date:** Wednesday, April 21, 2010 8:56:00 AM

---

THANKS  
Rose

---

**From:** Hamer, Faithe Angeline [mailto:fahamer@iupui.edu]  
**Sent:** Tuesday, April 20, 2010 12:24 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Wilson, Leslie Dawn  
**Cc:** Gantz, Marie  
**Subject:** RE: SUPPORT FU OUTCOMES

Please see my response below in red.

Thank you,

*Faithe Hamer, BS*

Riley Hospital for Children  
NICHD Follow Up Coordinator  
fahamer@iupui.edu (email)  
278-7364 (phone)  
278-7856 (fax)  
312-2687 (pager)

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Monday, April 19, 2010 4:17 PM  
**To:** Poindexter, Brenda B; Dusick, Anna M.; Hamer, Faithe Angeline; Wilson, Leslie Dawn  
**Cc:** Gantz, Marie  
**Subject:** SUPPORT FU OUTCOMES

Hi,

We are missing the following infants from the SUPPORT FU. Let us know how you are doing. Thanks for all the effort!!!

Rose

CENTER	NETWORK	FU_message
12	(b)	FU window has closed but NF09a has not been completed. – in communication with the family to get Bayley testing scheduled.
12	(b)	FU window has closed but NF05 and NF09a have not been completed. - they have both been completed – data is being entered.

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network  
Pregnancy and Perinatology Branch  
Center for Developmental Biology and Perinatal Medicine  
Eunice Kennedy Shriver National Institute of Child Health and Human Development  
National Institutes of Health  
6100 Executive Blvd., Room 4B03  
MSC 7510

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301-496-5575

301-496-3790 (FAX)

[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

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**From:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**To:** [Rogers, Christine \(NIH/OD\) \[E\]](#)  
**Subject:** Breathing Outcomes Update-May-2010-Vancouver  
**Date:** Wednesday, April 21, 2010 8:42:00 AM  
**Attachments:** [Breathing Outcomes Update-May-2010-Vancouver.doc](#)

---

40 copies for PAS FOLLOW UP MEETING file

## **Breathing Outcomes Update**

May, 2010

Carl D'Angio, MD

Tim Stevens, MD, MPH

### ***Enrollment***

Of the 1316 patients enrolled in SUPPORT, 957 were eligible for Breathing Outcomes (enrolled after Breathing Outcomes began and survived to hospital discharge). Of these 906 infants (94.6% of those eligible) have consent to participate in the study and 880 completed the baseline interview (97.1%).

### ***Follow-up***

***The follow-up rate for the primary outcome (18-22 month questionnaire) is 96.1%!*** Follow up rates at each of the 4 time points have also been very strong, ranging from 93.5% - 97.1%. Nearly 86% have completed all 4 questionnaires. No issues regarding execution of the study have been raised in the last several quarters.

### ***Study End Date***

***The last patient enrolled into SUPPORT passes out of the Breathing Outcomes 18-22 month interview window on 4/30/2011.*** The study will be considered closed as of that date.

### ***Status of Concept Proposal***

The School Age Breathing Outcomes concept proposal was reviewed by the NRN protocol committee in November 2009. The proposal is in revision with planned resubmission by June 1, 2010. One of the main criticisms of the study was the lack of preliminary data from Breathing Outcomes to justify follow-up to school age. Approval for release of preliminary data from early time points (6 and 12 months) was requested from the Steering Committee, which decided to refrain from performing this analysis to better preserve the integrity of the Breathing Outcomes Study.

### ***NOTE***

Table 3.3 (Number of Patients Enrolled into the Breathing Outcomes Protocol by Center) of the monthly report and the table below uses a different definition of whether the interview is "complete". The table below reports the number of complete interviews that have been conducted in the series whereas the monthly report Table 3.3 reports how many forms have been keyed (which could simply include the interview outcome box stating that the interview was not done due to loss of contact, interviewee refused, child died, other).



*Breathing Outcomes Protocol*

*Table 1b - Data as of 04/12/2010  
 Number and Percent of Questionnaires Completed at Each Point in Time By Center*

Center Name	SUPF00 Consent Granted <sup>1</sup>	SUPF01 Baseline Complete <sup>2</sup>		SUPF02 6 Month Complete <sup>3</sup>		SUPF02 12 Month Complete <sup>4</sup>		SUPF03 18-22 Month Complete <sup>5</sup> *		Complete Series & Entered 18 Month Window <sup>6</sup>
	Number	Number	%	Number	%	Number	%	Number	%	% (count)
Case Western Univ	85	85	100.0%	85	100.0%	79	100.0%	65	95.6%	95.6% (65/68)
Univ. of Texas (D)	56	56	100.0%	56	100.0%	51	100.0%	44	100.0%	95.7% (44/46)
Wayne State Univ	37	37	100.0%	33	89.2%	28	82.4%	26	92.9%	89.3% (25/28)
Univ. of Miami	13	13	100.0%	13	100.0%	13	100.0%	13	100.0%	100.0% (13/13)
Emory University	44	44	100.0%	37	84.1%	37	88.1%	31	100.0%	81.6% (31/38)
Univ. of Cincinnati	71	71	100.0%	63	88.7%	66	94.3%	56	96.6%	70.3% (45/64)
Indiana Univ.	51	44	86.3%	40	78.4%	33	73.3%	32	78.0%	51.2% (22/43)
Yale University	31	31	100.0%	31	100.0%	30	100.0%	23	100.0%	100.0% (23/23)
Brown University	108	108	100.0%	107	99.1%	95	96.0%	81	97.6%	88.0% (81/92)
Stanford University	34	24	70.6%	24	70.6%	18	62.1%	11	91.7%	57.9% (11/19)
Univ. of Alabama	124	124	100.0%	122	100.0%	114	98.3%	97	99.0%	97.0% (97/100)
Univ. of Texas (H)	55	49	89.1%	48	87.3%	47	94.0%	36	97.3%	83.3% (35/42)
Duke University	12	11	91.7%	12	100.0%	11	100.0%	11	100.0%	100.0% (11/11)
Wake Forest	9	9	100.0%	9	100.0%	9	100.0%	9	100.0%	100.0% (9/9)
Children's (NY), U. Rochester	5	5	100.0%	5	100.0%	5	100.0%	5	100.0%	100.0% (5/5)
Univ. of Calif. At San Diego	43	42	97.7%	42	97.7%	41	97.6%	36	97.3%	92.1% (35/38)
Tufts NEMC	45	44	97.8%	38	86.4%	31	86.1%	29	93.5%	80.6% (25/31)
University of Iowa	28	28	100.0%	28	100.0%	26	100.0%	16	88.9%	72.7% (16/22)
University of Utah	40	40	100.0%	40	100.0%	38	100.0%	29	100.0%	85.3% (29/34)
University of NM	15	15	100.0%	15	100.0%	11	91.7%	7	87.5%	87.5% (7/8)
<b>TOTAL</b>	906	880	97.1%	848	93.9%	783	93.5%	657	96.1%	85.7% (629/734)

\* *primary outcome*

*Breathing Outcomes Protocol*

*Table 1b - Data as of 04/12/2010  
Number and Percent of Questionnaires Completed at Each Point in Time By Center*

**Footnotes**

<sup>1</sup> Column 1 “SUPF00 Consent Granted” - A simple count of the number of infants in each Center for which consent has been granted.

<sup>2</sup> Columns 2 and 3 “SUPF01 Baseline Complete” - The number of infants in each Center for which consent has been granted, have an answer to the question on form SUPF01 “Was the interview conducted,” and have a Baseline interview status of “Complete.” The denominator for the “%” column includes infants for which consent has been granted.

<sup>3</sup> Columns 4 and 5 “SUPF02 6 Month Complete” - The number of infants in each Center for which consent has been granted, have an answer to the question on form SUPF02 “Was the interview conducted,” and have a 6 Month interview status of “Complete.” The denominator for the “%” column includes infants for which consent has been granted and have a 6 Month interview status of “Complete” or “Out of Window.”

<sup>4</sup> Columns 6 and 7 “SUPF02 12 Month Complete” - The number of infants in each Center for which consent has been granted, have an answer to the question on form SUPF02 “Was the interview conducted,” and have a 12 Month interview status of “Complete.” The denominator for the “%” column includes infants for which consent has been granted and have a 12 Month interview status of “Complete” or “Out of Window.”

<sup>5</sup> Columns 8 and 9 “SUPF03 18-22 Month Complete” - The number of infants in each Center for which consent has been granted, have an answer to the question on form SUPF03 “Was the interview conducted,” and have an 18-22 Month interview status of “Complete.” The denominator for the “%” column includes infants for which consent has been granted and have an 18-22 Month interview status of “Complete” or “Out of Window.”

<sup>6</sup> Column 10 “Complete Series & Entered 18 Month Window” – The numerator is the number of infants in each Center for which consent has been granted, have an answer to the questions on forms SUPF01, SUPF02 (6 Month), SUPF02 (12 Month), and SUPF03 “Was the interview conducted,” and have an interview status of “Complete” for all 4 stages (Baseline, 6 Month, 12 Month, and 18-22 Month). The denominator is the number of infants for which consent has been granted and who have an 18-22 interview status of “Complete,” “Due,” “Overdue,” or “Out of Window” (i.e., all infants who have entered the window).

**NOTE:** Table 3.3 (Number of Patients Enrolled into the Breathing Outcomes Protocol by Center) of the monthly report and this table use a different definition of whether the interview is “complete”. This table reports the number of complete interviews have been conducted in the series whereas the monthly report Table 3.3 reports how many forms have been keyed (which could simply include the interview outcome box stating that the interview was not done due to loss of contact, interviewee refused, child died, other).

**From:** [Stevens, Timothy](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]; "Newman, Jamie"](#)  
**Cc:** [D'Angio, Carl](#)  
**Subject:** Breathing Outcomes Update  
**Date:** Tuesday, April 20, 2010 6:14:40 PM  
**Attachments:** [Breathing Outcomes Update-May-2010-Vancouver.doc](#)

---

Hi Rose and Jamie,

Here is the update on the Breathing Outcomes Study for Vancouver.

As I mentioned, Carl will be attending the follow up PI meeting in my stead.

Thanks

Tim

## **Breathing Outcomes Update**

May, 2010

Carl D'Angio, MD

Tim Stevens, MD, MPH

### ***Enrollment***

Of the 1316 patients enrolled in SUPPORT, 957 were eligible for Breathing Outcomes (enrolled after Breathing Outcomes began and survived to hospital discharge). Of these 906 infants (94.6% of those eligible) have consent to participate in the study and 880 completed the baseline interview (97.1%).

### ***Follow-up***

***The follow-up rate for the primary outcome (18-22 month questionnaire) is 96.1%!*** Follow up rates at each of the 4 time points have also been very strong, ranging from 93.5% - 97.1%. Nearly 86% have completed all 4 questionnaires. No issues regarding execution of the study have been raised in the last several quarters.

### ***Study End Date***

***The last patient enrolled into SUPPORT passes out of the Breathing Outcomes 18-22 month interview window on 4/30/2011.*** The study will be considered closed as of that date.

### ***Status of Concept Proposal***

The School Age Breathing Outcomes concept proposal was reviewed by the NRN protocol committee in November 2009. The proposal is in revision with planned resubmission by June 1, 2010. One of the main criticisms of the study was the lack of preliminary data from Breathing Outcomes to justify follow-up to school age. Approval for release of preliminary data from early time points (6 and 12 months) was requested from the Steering Committee, which decided to refrain from performing this analysis to better preserve the integrity of the Breathing Outcomes Study.

### ***NOTE***

Table 3.3 (Number of Patients Enrolled into the Breathing Outcomes Protocol by Center) of the monthly report and the table below uses a different definition of whether the interview is "complete". The table below reports the number of complete interviews that have been conducted in the series whereas the monthly report Table 3.3 reports how many forms have been keyed (which could simply include the interview outcome box stating that the interview was not done due to loss of contact, interviewee refused, child died, other).

Breathing Outcomes Protocol

Table 1b - Data as of 04/12/2010  
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Center Name	SUPF00 Consent Granted <sup>1</sup>	SUPF01 Baseline Complete <sup>2</sup>		SUPF02 6 Month Complete <sup>3</sup>		SUPF02 12 Month Complete <sup>4</sup>		SUPF03 18-22 Month Complete <sup>5</sup> *		Complete Series & Entered 18 Month Window <sup>6</sup>
	Number	Number	%	Number	%	Number	%	Number	%	% (count)
Case Western Univ	85	85	100.0%	85	100.0%	79	100.0%	65	95.6%	95.6%(65/68)
Univ. of Texas (D)	56	56	100.0%	56	100.0%	51	100.0%	44	100.0%	95.7%(44/46)
Wayne State Univ	37	37	100.0%	33	89.2%	28	82.4%	26	92.9%	89.3%(25/28)
Univ. of Miami	13	13	100.0%	13	100.0%	13	100.0%	13	100.0%	100.0%(13/13)
Emory University	44	44	100.0%	37	84.1%	37	88.1%	31	100.0%	81.6%(31/38)
Univ. of Cincinnati	71	71	100.0%	63	88.7%	66	94.3%	56	96.6%	70.3%(45/64)
Indiana Univ.	51	44	86.3%	40	78.4%	33	73.3%	32	78.0%	51.2%(22/43)
Yale University	31	31	100.0%	31	100.0%	30	100.0%	23	100.0%	100.0%(23/23)
Brown University	108	108	100.0%	107	99.1%	95	96.0%	81	97.6%	88.0%(81/92)
Stanford University	34	24	70.6%	24	70.6%	18	62.1%	11	91.7%	57.9%(11/19)
Univ. of Alabama	124	124	100.0%	122	100.0%	114	98.3%	97	99.0%	97.0%(97/100)
Univ. of Texas (H)	55	49	89.1%	48	87.3%	47	94.0%	36	97.3%	83.3%(35/42)
Duke University	12	11	91.7%	12	100.0%	11	100.0%	11	100.0%	100.0%(11/11)
Wake Forest	9	9	100.0%	9	100.0%	9	100.0%	9	100.0%	100.0%(9/9)
Children's (NY), U. Rochester	5	5	100.0%	5	100.0%	5	100.0%	5	100.0%	100.0%(5/5)
Univ. of Calif. At San Diego	43	42	97.7%	42	97.7%	41	97.6%	36	97.3%	92.1%(35/38)
Tufts NEMC	45	44	97.8%	38	86.4%	31	86.1%	29	93.5%	80.6%(25/31)
University of Iowa	28	28	100.0%	28	100.0%	26	100.0%	16	88.9%	72.7%(16/22)
University of Utah	40	40	100.0%	40	100.0%	38	100.0%	29	100.0%	85.3%(29/34)
University of NM	15	15	100.0%	15	100.0%	11	91.7%	7	87.5%	87.5%(7/8)
<b>TOTAL</b>	906	880	97.1%	848	93.9%	783	93.5%	657	96.1%	85.7%(629/734)

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*Breathing Outcomes Protocol*

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**Footnotes**

<sup>1</sup> Column 1 “SUPF00 Consent Granted” - A simple count of the number of infants in each Center for which consent has been granted.

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<sup>3</sup> Columns 4 and 5 “SUPF02 6 Month Complete” - The number of infants in each Center for which consent has been granted, have an answer to the question on form SUPF02 “Was the interview conducted,” and have a 6 Month interview status of “Complete.” The denominator for the “%” column includes infants for which consent has been granted and have a 6 Month interview status of “Complete” or “Out of Window.”

<sup>4</sup> Columns 6 and 7 “SUPF02 12 Month Complete” - The number of infants in each Center for which consent has been granted, have an answer to the question on form SUPF02 “Was the interview conducted,” and have a 12 Month interview status of “Complete.” The denominator for the “%” column includes infants for which consent has been granted and have a 12 Month interview status of “Complete” or “Out of Window.”

<sup>5</sup> Columns 8 and 9 “SUPF03 18-22 Month Complete” - The number of infants in each Center for which consent has been granted, have an answer to the question on form SUPF03 “Was the interview conducted,” and have an 18-22 Month interview status of “Complete.” The denominator for the “%” column includes infants for which consent has been granted and have an 18-22 Month interview status of “Complete” or “Out of Window.”

<sup>6</sup> Column 10 “Complete Series & Entered 18 Month Window” – The numerator is the number of infants in each Center for which consent has been granted, have an answer to the questions on forms SUPF01, SUPF02 (6 Month), SUPF02 (12 Month), and SUPF03 “Was the interview conducted,” and have an interview status of “Complete” for all 4 stages (Baseline, 6 Month, 12 Month, and 18-22 Month). The denominator is the number of infants for which consent has been granted and who have an 18-22 interview status of “Complete,” “Due,” “Overdue,” or “Out of Window” (i.e., all infants who have entered the window).

**NOTE:** Table 3.3 (Number of Patients Enrolled into the Breathing Outcomes Protocol by Center) of the monthly report and this table use a different definition of whether the interview is “complete”. This table reports the number of complete interviews have been conducted in the series whereas the monthly report Table 3.3 reports how many forms have been keyed (which could simply include the interview outcome box stating that the interview was not done due to loss of contact, interviewee refused, child died, other).

**From:** Bock, Robert (NIH/NICHD) [E]  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Online First release schedule for NEJM 09-11781  
**Date:** Tuesday, April 20, 2010 3:00:19 PM

---

OK. Jim Griffin is back on Monday, so I'll try to arrange something for next week.

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Tuesday, April 20, 2010 3:00 PM  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Subject:** Re: Online First release schedule for NEJM 09-11781

Yes-  
I am on (b) (6) and can discuss this with you tomorrow.

Thanks  
Rose

---

**From:** Bock, Robert (NIH/NICHD) [E]  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Tue Apr 20 14:57:00 2010  
**Subject:** RE: Online First release schedule for NEJM 09-11781

That's right—you said these papers were being presented on the 16<sup>th</sup>, correct? If so, if our release is out there, then you should expect calls.

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Tuesday, April 20, 2010 2:55 PM  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Subject:** Re: Online First release schedule for NEJM 09-11781

How about later this week or monday or tuesday??  
Also, do you think there will be press interviews for me (us) after the presentation on 5/16?

---

**From:** Bock, Robert (NIH/NICHD) [E]  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Tue Apr 20 14:53:22 2010  
**Subject:** RE: Online First release schedule for NEJM 09-11781

On the 7<sup>th</sup>, (b) (6), and from there I'm heading to (b) (6) and not back until the 24<sup>th</sup>.

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Tuesday, April 20, 2010 2:52 PM  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Subject:** Re: Online First release schedule for NEJM 09-11781

I am (b) (6) I am in all days the following week.

---

**From:** Bock, Robert (NIH/NICHD) [E]  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Tue Apr 20 14:37:06 2010  
**Subject:** RE: Online First release schedule for NEJM 09-11781

Wow. That doesn't give us much time. Unfortunately, I'm leaving town for a couple of weeks on the 7<sup>th</sup>. What's your availability like for the video shoot?

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Tuesday, April 20, 2010 2:35 PM  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Subject:** Fw: Online First release schedule for NEJM 09-11781

---

**From:** Wally Carlo, M.D. <WCarlo@peds.uab.edu>  
**To:** Zeis, Jennifer <jzeis@nejm.org>  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Tue Apr 20 12:45:36 2010  
**Subject:** RE: Online First release schedule for NEJM 09-11781

Dear Ms. Zeis:

Thanks very much for the information. Enclosed is my contact information. I am copying this to Dr. Rose Higgins at the NIH who probably should be the other contact person rather than our institution's press office.

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: 205 266 (b)

---

**From:** Zeis, Jennifer [mailto:jzeis@nejm.org]  
**Sent:** Tuesday, April 20, 2010 11:37 AM  
**To:** Wally Carlo, M.D.  
**Subject:** Online First release schedule for NEJM 09-11781

Dear Dr. Carlo,

As you know, your NEJM Original Article is on an accelerated Online First release schedule to coincide with your presentation of the results at the American Thoracic Society's annual meeting. I am writing to share the details of that schedule and to request your preferred media points of contact.



We will provide your article to reporters at 10 AM EDT Thursday, May 13. When we provide your article to the media under embargo, we will post the material on our password-protected NEJM Media Center, where only journalists who have agreed to respect our embargo may access it. I will email you this final file and any related material at that time

**Your article will be embargoed until 1 PM EDT Sunday, May 16**, the start of your ATS presentation on the trial. The ATS and NEJM embargoes are coordinated to lift simultaneously so you may reference your NEJM publication at the meeting, if you wish. Your paper will be published on NEJM.org as soon as the embargo lifts, and will later be published in the May 27 printed issue.

And finally, please let me know what **contact information you would like me to provide to journalists** who wish to interview you and/or your co-authors. You may include your institution's press office in addition to, or instead of, your personal contact information.

Many thanks. If you have any questions, please don't hesitate to ask.

Best regards,  
Jen Zeis

Jennifer Zeis  
Media Relations  
The New England Journal of Medicine  
office: 781-434-7186  
MEDIA CENTER <http://media.nejm.org>  
twitter <http://twitter.com/nejm>

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## **Higgins, Rosemary (NIH/NICHD) [E]**

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**From:** Finer, Neil <nfiner@ucsd.edu>  
**Sent:** Tuesday, April 20, 2010 12:22 PM  
**To:** Walsh, Michele; Wally\_Carlo\_M.D.; Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: SUPPORT slides

Michele  
I like your style  
Many thanks  
I have incorporated almost all of your suggestions  
Good luck with the Book!!  
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:** Walsh, Michele [<mailto:Michele.Walsh@UHhospitals.org>]  
**Sent:** Friday, April 16, 2010 11:45 AM  
**To:** Finer, Neil; Wally\_Carlo\_M.D.; Higgins\_Rosemary\_  
**Subject:** SUPPORT slides

Hi Neil: Sorry for the delay.  
I had to get some help on reformatting tables  
To get the lines to be white.  
Forgive me- but we are deep into the gallys of our textbook,  
And my editors red pencil went a bit wild...  
I have made editorial suggestions to reduce the number of words  
On the slides, and suggest 2 possible Methods tables (slide 9 and 10)  
Which could replace your word slides of 11-15. I think it may improve  
Clarity for the audience to be able to see CPAP vs Surf arm side by side.  
Hope this helps... I understand you may not wish to use this version.  
Best,

*Michele Walsh*

Medical Director NICU  
Co-Chief, Division of Neonatology  
Rainbow Babies & Childrens Hospital  
UH Case Medical Center  
Professor, Department of Pediatrics  
Case Western Reserve University  
phone: 216-844-3759

FAX: 216-844-3380

[michele.walsh@cwru.edu](mailto:michele.walsh@cwru.edu)

[michele.walsh@UHhospitals.org](mailto:michele.walsh@UHhospitals.org) (emails are interchangeable)

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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:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "VPhillips@peds.uab.edu"; "wcarlo@peds.uab.edu"; "ambal@uab.edu"; "mperalta@peds.uab.edu"; "SCosby@peds.uab.edu"; "mcollins@peds.uab.edu"  
**Cc:** "mgantz@rti.org"  
**Subject:** Re: SUPPORT FU OUTCOMES  
**Date:** Monday, April 19, 2010 5:14:01 PM

---

Great  
Thanks  
Rose

---

**From:** Vivien Phillips <VPhillips@peds.uab.edu>  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D. <WCarlo@peds.uab.edu>; ambal@uab.edu <ambal@uab.edu>; Myriam Peralta, M.D. <MPeralta@peds.uab.edu>; Shirley Cosby <SCosby@peds.uab.edu>; Monica Collins <MCollins@peds.uab.edu>  
**Cc:** Gantz, Marie <mgantz@rti.org>  
**Sent:** Mon Apr 19 17:11:40 2010  
**Subject:** RE: SUPPORT FU OUTCOMES

Child has been rescheduled several times but another appointment has been made again for this Friday. I hope they come!  
Vivien

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Monday, April 19, 2010 3:25 PM  
**To:** Wally Carlo, M.D.; 'Ambal (ambal@uab.edu)'; Myriam Peralta, M.D.; Shirley Cosby; Monica Collins; Vivien Phillips  
**Cc:** Gantz, Marie  
**Subject:** SUPPORT FU OUTCOMES

Hi,  
We are missing the following infants from the SUPPORT FU. Let us know how you are doing.  
**THIS IS AMAZING GIVEN YOUR RECRUITMENT INTO THE MAIN TRIAL!!!**

Thanks for all the effort!!!

Rose

CENTER	NETWORK	FU_message
16	(b)	FU window has closed but NF05 and NF09a have not been completed.

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network  
Pregnancy and Perinatology Branch  
Center for Developmental Biology and Perinatal Medicine  
Eunice Kennedy Shriver National Institute of Child Health and Human Development  
National Institutes of Health  
6100 Executive Blvd., Room 4B03  
MSC 7510  
Bethesda, MD 20892  
For overnight delivery use Rockville, MD 20852  
301-496-5575  
301-496-3790 (FAX)  
higginsr@mail.nih.gov

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Karen Osborne RN"; "Roger Faix"; "Bradley Yoder"; "Anna Bodnar"  
**Cc:** "Gantz, Marie"  
**Subject:** RE: SUPPORT FU OUTCOMES  
**Date:** Monday, April 19, 2010 4:57:00 PM

---

I had tried to recall the message, but I guess it went through –sorry for the miss up!!

Thanks for being on top of things!!!  
Rose

---

**From:** Karen Osborne RN [mailto:Karen.Osborne@hsc.utah.edu]  
**Sent:** Monday, April 19, 2010 4:46 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Roger Faix; Bradley Yoder; 'Anna Bodnar'  
**Cc:** Gantz, Marie  
**Subject:** RE: SUPPORT FU OUTCOMES

This was sent to us, but we are center 25, not 26. As Roger says, we like your following email a lot better!

*Karen*

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Monday, April 19, 2010 2:33 PM  
**To:** Roger Faix; Bradley Yoder; 'Anna Bodnar'; Karen Osborne RN  
**Cc:** Gantz, Marie  
**Subject:** SUPPORT FU OUTCOMES

Hi,  
We are missing the following infants from the SUPPORT FU. Let us know how you are doing.

Thanks for all the effort!!!

Rose

CENTER	NETWORK	FU_message
26	(b)	FU window has closed but NF05 and NF09a have not been completed.

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network  
Pregnancy and Perinatology Branch  
Center for Developmental Biology and Perinatal Medicine  
Eunice Kennedy Shriver National Institute of Child Health and Human Development  
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MSC 7510  
Bethesda, MD 20892  
For overnight delivery use Rockville, MD 20852  
301-496-5575  
301-496-3790 (FAX)  
higginsr@mail.nih.gov

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Furey, Anne M"; "Frantz, Ivan"; "Mackinnon, Brenda"; "McGowan, Elisabeth C"  
**Cc:** "Gantz, Marie"  
**Subject:** RE: SUPPORT FU OUTCOMES  
**Date:** Monday, April 19, 2010 4:44:00 PM

---

Great  
THANKS  
Rose

---

**From:** Furey, Anne M [mailto:afurey@tuftsmedicalcenter.org]  
**Sent:** Monday, April 19, 2010 4:39 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Frantz, Ivan; Mackinnon, Brenda; McGowan, Elisabeth C  
**Cc:** Gantz, Marie  
**Subject:** RE: SUPPORT FU OUTCOMES

The NF05 was entered as complete last week for this subject.

Anne Furey, MPH  
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: 617-604-(b)  
[afurey@tuftsmedicalcenter.org](mailto:afurey@tuftsmedicalcenter.org)

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Mon 4/19/2010 4:32 PM  
**To:** Frantz, Ivan; Mackinnon, Brenda; McGowan, Elisabeth C; Furey, Anne M  
**Cc:** Gantz, Marie  
**Subject:** SUPPORT FU OUTCOMES

Hi,  
We are missing the following infants from the SUPPORT FU. Let us know how you are doing.

Thanks for all the effort!!!

Rose

CENTER	NETWORK	FU_message
23	(b)	FU marked as complete (per NF10/SF10) but NF05 has not been completed.

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]  
**To:** "Susan Hintz"  
**Cc:** "VanMeurs, Krisa"; "Bethany Ball"; "Gantz, Marie"  
**Subject:** RE: SUPPORT FU  
**Date:** Monday, April 19, 2010 4:37:00 PM

---

OK thanks  
Rose

---

**From:** Susan Hintz [mailto:srhintz@stanford.edu]  
**Sent:** Monday, April 19, 2010 4:37 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** VanMeurs, Krisa; Bethany Ball; Gantz, Marie  
**Subject:** Re: SUPPORT FU

Hi Rose

This family has moved around a huge amount since discharge. We continue to look for them, and have a lead that we are currently pursuing. We are not giving up yet on this patient.

This is not the one that supposed to have had follow-up at UT Southwestern.

Susan

On Apr 19, 2010, at 1:23 PM, Higgins, Rosemary (NIH/NICHD) [E] wrote:

Hi,

We are missing the following infant from the SUPPORT FU. Let us know how you are doing. Is this the infant that was supposed to have been seen at UT Southwestern??

Thanks for all the effort!!!

Rose

CENTER	NETWORK	FU_message
15	(b)	FU window has closed but NF05 and NF09a have not been completed.

Rosemary D. Higgins, MD  
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[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)



**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Bell, Edward"; "Johnson, Karen"; "Acarregui, Michael"; "Eastman, Diane"  
**Cc:** "Gantz, Marie"  
**Subject:** SUPPORT FU OUTCOMES  
**Date:** Monday, April 19, 2010 4:31:00 PM

---

Hi,  
We are missing the following infants from the SUPPORT FU. Let us know how you are doing.

Thanks for all the effort!!!

Rose

CENTER	NETWORK	FU_message
24	(b)	FU window has closed but NF05 and NF09a have not been completed.

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301-496-5575  
301-496-3790 (FAX)  
higginsr@mail.nih.gov

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Evans, Patricia W."; "Poundstone, Margaret"; "Kennedy, Kathleen A."; "georgia.e.mcdavid@uth.tmc.edu"  
**Cc:** "Gantz, Marie"  
**Subject:** SUPPORT FU OUTCOMES  
**Date:** Monday, April 19, 2010 4:26:00 PM

---

Hi,

We are missing the following infants from the SUPPORT FU. Let us know how you are doing.

Thanks for all the effort!!!

Rose

CENTER	NETWORK	FU_message
18	(b)	FU window has closed but NF05 and NF09a have not been completed.
18	(b)	FU marked as complete (per NF10/SF10) but NF09a has not been completed.

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network  
Pregnancy and Perinatology Branch  
Center for Developmental Biology and Perinatal Medicine  
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301-496-5575  
301-496-3790 (FAX)  
higginsr@mail.nih.gov

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Wally Carlo, M.D."; "Ambal (ambal@uab.edu)"; "mperalta@peds.uab.edu"; "Shirley Cosby"; "Monica Collins"; "Vivien Phillips"  
**Cc:** "Gantz, Marie"  
**Subject:** SUPPORT FU OUTCOMES  
**Date:** Monday, April 19, 2010 4:25:00 PM

---

Hi,

We are missing the following infants from the SUPPORT FU. Let us know how you are doing.

**THIS IS AMAZING GIVEN YOUR RECRUITMENT INTO THE MAIN TRIAL!!!**

Thanks for all the effort!!!

Rose

CENTER	NETWORK	FU_message
16	(b)	FU window has closed but NF05 and NF09a have not been completed.

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network  
Pregnancy and Perinatology Branch  
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higginsr@mail.nih.gov

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Susan Hintz"; "VanMeurs, Krisa"; "Bethany Ball"  
**Cc:** "Gantz, Marie"  
**Subject:** SUPPORT FU  
**Date:** Monday, April 19, 2010 4:23:00 PM

---

Hi,

We are missing the following infant from the SUPPORT FU. Let us know how you are doing. Is this the infant that was supposed to have been seen at UT Southwestern??

Thanks for all the effort!!!

Rose

CENTER	NETWORK	FU_message
15	(b)	FU window has closed but NF05 and NF09a have not been completed.

Rosemary D. Higgins, MD  
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301-496-3790 (FAX)  
higginsr@mail.nih.gov

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Vohr, Betty"; "alaptook@WIHRI.org"; "Angelita Hensman"; "sventura@wihri.org"  
**Cc:** "Gantz, Marie"  
**Subject:** SUPPORT FU OUTCOMES  
**Date:** Monday, April 19, 2010 4:18:00 PM

---

Hi,

We are missing the following infants from the SUPPORT FU. Let us know how you are doing.

**THIS IS AMAZING GIVEN YOUR RECRUITMENT INTO THE MAIN TRIAL!!!**

Thanks for all the effort!!!

Rose

CENTER	NETWORK	FU_message
14	(b)	FU window has closed but NF05 and NF09a have not been completed.
14	(b)	FU window has closed but NF05 and NF09a have not been completed.

Rosemary D. Higgins, MD  
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301-496-3790 (FAX)  
higginsr@mail.nih.gov

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Kurt Schibler [kurt.schibler@cchmc.org]"; "Teresa.Gratton@uc.edu"; "Kim Yoltan"; "steichj@email.uc.edu"; "Grisby\_Cathy (grisbyca)"  
**Cc:** "Gantz, Marie"  
**Subject:** SUPPORT FU OUTCOMES  
**Date:** Monday, April 19, 2010 4:16:00 PM

---

Hi,

We are missing the following infants from the SUPPORT FU. Let us know how you are doing. Thanks for all the effort!!!

Rose

CENTER	NETWORK	FU_message
11	(b)	FU window has closed but NF05 and NF09a have not been completed.

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:** "Poindexter, Brenda B"; "adusick@iupui.edu"; "fahamer@iupui.edu"; "Leslie Wilson"  
**Cc:** "Gantz, Marie"  
**Subject:** SUPPORT FU OUTCOMES  
**Date:** Monday, April 19, 2010 4:16:00 PM

---

Hi,

We are missing the following infants from the SUPPORT FU. Let us know how you are doing. Thanks for all the effort!!!

Rose

CENTER	NETWORK	FU_message
12	(b)	FU window has closed but NF09a has not been completed.
12	(b)	FU window has closed but NF05 and NF09a have not been completed.

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

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Barbara Stol"; "Ira Adams-Chapman"; "Ellen Hale"  
**Cc:** "Gantz, Marie"  
**Subject:** SUPPORT FU OUTCOMES  
**Date:** Monday, April 19, 2010 4:14:00 PM

---

Hi,  
We are missing the following infants from the SUPPORT FU. Let us know how you are doing. Thanks for all the effort!!!  
Rose

<b>CENTER</b>	<b>NETWORK</b>	<b>FU_message</b>
9	(b)	FU window has closed but NF05 and NF09a have not been completed.

Rosemary D. Higgins, MD  
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higginsr@mail.nih.gov



**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Shankaran, Seetha"; "Sood, Beena"; "Pappas, Athina"; "Bara, Rebecca"  
**Cc:** "Gantz, Marie"  
**Subject:** SUPPORT FU OUTCOMES  
**Date:** Monday, April 19, 2010 4:14:00 PM

---

Hi,

We are missing the following infants from the SUPPORT FU. Let us know how you are doing. Thanks for all the effort!!!

Rose

CENTER	NETWORK	FU_message
5	(b)	FU window has closed but NF05 and NF09a have not been completed.
5	(b)	FU window has closed but NF09a has not been completed.
5	(b)	FU window has closed but NF05 and NF09a have not been completed.
5	(b)	FU window has closed but NF05 and NF09a have not been completed.
5	(b)	FU window has closed but NF05 and NF09a have not been completed.
5	(b)	FU window has closed but NF05 and NF09a have not been completed.

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301-496-3790 (FAX)  
higginsr@mail.nih.gov

**From:** [Bock, Robert \(NIH/NICHD\)](#) [E]  
**To:** [Higgins, Rosemary \(NIH/NICHD\)](#) [E]  
**Subject:** RE: Interview Request: Supplemental oxygen therapy in premature infants with modest ROP  
**Date:** Monday, April 19, 2010 10:23:42 AM

---

Thanks Rose. I just sent you this as an FYI. I don't think we'll be asked to comment. Our release is going through clearance. Jim has approved it. Today I'll put it into building 31 clearance before sending it down to the Dept. for review.

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Monday, April 19, 2010 10:21 AM  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Subject:** RE: Interview Request: Supplemental oxygen therapy in premature infants with modest ROP

NEI was NOT involved in our SUPPORT study- also, we have not gotten a publication date – How should we proceed??

If this is another paper, I could comment

Rose

---

**From:** Bock, Robert (NIH/NICHD) [E]  
**Sent:** Monday, April 19, 2010 10:19 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** FW: Interview Request: Supplemental oxygen therapy in premature infants with modest ROP

FYI.

---

**From:** Balintfy, Joseph (NIH/OD) [E]  
**Sent:** Monday, April 19, 2010 10:18 AM  
**To:** HHS/OS Interviews  
**Cc:** Burklow, John (NIH/OD) [E]; Allen, Marin (NIH/OD) [E]; Ralbovsky, Don (NIH/OD) [E]; Carper, Deborah (NIH/NEI) [E]; Collins, Allyson (NIH/NEI) [E]; Collins-Lee, Kym (NIH/NEI) [E]; Harper, Anna (NIH/NEI) [E]; Horrigan, Jean (NIH/NEI) [E]; Janiszewski, Rosemary (NIH/NEI) [E]; Walls, Sherrita (NIH/NEI) [C]; Bock, Robert (NIH/NICHD) [E]  
**Subject:** Interview Request: Supplemental oxygen therapy in premature infants with modest ROP

Jacqueline Salmon  
Pew Charitable Trust  
Subject: Supplemental oxygen therapy in premature infants with modest Retinopathy of Prematurity  
Deadline: today

Spokesperson: Dr. Brian Brooks, Staff Clinician, NEI Clinic

Ms. Salmon is writing a report for the Pew Charitable Trust's board members. Dr. Brooks will discuss the findings of NEI's study on administering supplemental oxygen to premature infants with pre-threshold cases of retinopathy of prematurity (ROP). The study found that modest supplemental oxygen given to premature infants with moderate cases of ROP, may not significantly improve ROP, but definitely does not make it worse.

## Higgins, Rosemary (NIH/NICHD) [E]

---

**From:** Finer, Neil <nfiner@ucsd.edu>  
**Sent:** Saturday, April 17, 2010 10:27 PM  
**To:** Susan Hintz; Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** das Das; Dorothy Bulas; Tom Slovis; vanmeurs Meurs  
**Subject:** RE: Updated DRAFT for CUS presentation at PAS

Hi Susan

This is very complete and somewhat complicated

I would think that there is too much – I know I speak fast but I would have trouble getting through this

I think that the slides for intraobserver differences and with the 2 reader results should mostly be summarized with the significant differences and a few examples

I can do about 22 slides with information in 10 minutes and I am moving

I would thin this down to 25 at a max

I would be glad to look at a revision

Be well

Neil

---

**From:** Susan Hintz [<mailto:srhintz@stanford.edu>]  
**Sent:** Saturday, April 17, 2010 10:11 AM  
**To:** higgins Higgins  
**Cc:** das Das; Dorothy Bulas; Tom Slovis; Finer, Neil; vanmeurs Meurs  
**Subject:** Updated DRAFT for CUS presentation at PAS

Hi all,

Attached is the updated draft of the powerpoint presentation of CUS results of the SUPPORT NEURO CUS cohort.

A few points:

- 1) PLEASE view this in full screen mode. Some of the table images don't look right in smaller mode.
- 2) It is rather dense. Lots of numbers, but not sure we can avoid that - after all, this is basically (I am stealing a phrase from Abhik) a "rigorous cataloging and description of early and late CUS in a large extremely preterm cohort".
- 3) There are a lot of slides, but MANY are repeats with just different results circled so as to focus attention for the audience.
- 4) I truly tried to include some of the images of the cranial US examples that Dorothy and Meg so painstakingly clipped. However, I am so short on time for this presentation (I have only 10 minutes) that I find I am very very pressed even with the basic information included - and may need to cut as it is. I think we will need to wait to use those great images in the paper, or perhaps another presentation (as we discussed - maybe a radiology conference?)
- 5) I believe questions will come up about SUPPORT randomized group comparisons, but I am planning on deflecting those questions. My basic stance will be 1) the comparison by randomized groups would best be undertaken when all neuroimaging is available (CUS and MRI), and 2) we are investigating the extent to which this subcohort is representative of the overall SUPPORT group in propensity analyses, but in preliminary

analyses it appears that indeed there are differences between the groups - not surprisingly primarily attributable to center differences.

I look forward to your comments and input. THANK YOU again for all your help -

Susan

**From:** Susan Hintz  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** das Das; Dorothy Bulas; Tom Slovis; neil finer; vanmeurs Meurs  
**Subject:** Updated DRAFT for CUS presentation at PAS  
**Date:** Saturday, April 17, 2010 1:11:51 PM  
**Attachments:** DRAFT Hintz NEURO SUPPORT CUS PAS2010.ppt  
ATT00001...htm

---

Hi all,

Attached is the updated draft of the powerpoint presentation of CUS results of the SUPPORT NEURO CUS cohort.

A few points:

1) PLEASE view this in full screen mode. Some of the table images don't look right in smaller mode.

2) It is rather dense. Lots of numbers, but not sure we can avoid that - after all, this is basically (I am stealing a phrase from Abhik) a "rigorous cataloguing and description of early and late CUS in a large extremely preterm cohort".

3) There are a lot of slides, but MANY are repeats with just different results circled so as to focus attention for the audience.

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I look forward to your comments and input. THANK YOU again for all your help -

Susan

NICHD



# Early and Late CUS Findings in the SUPPORT Neuroimaging and Neurodevelopmental Outcomes (NEURO) Cohort

SR Hintz, D Bulas, TL Slovis, H Cheng, N Finer, A Das,  
RD Higgins, SUPPORT Subcommittee, for NICHD  
Neonatal Research Network



Lucile Packard Children's Hospital  
STANFORD UNIVERSITY MEDICAL CENTER



# Cranial US: *Diagnostic*

---

- Cranial US is a crucial diagnostic tool in the neonatal intensive care unit
- Identifies some brain injury common in preterm infants
  - Non-invasive, easily repeatable, bedside
  - Current neuroimaging standard of care for preterm infants
    - Ment LR, et. al. Practice Parameter: Neuroimaging of the Neonate. *Neurology* 2002; 58:1726-1738



# Cranial US: *Prognostic*

---

- CUS findings are often used to assist in neurodevelopmental outcomes prognosis
  - Improved survival for extremely preterm infants; long-term outcomes central concern
- Data regarding serial CUS findings and outcomes in recent extremely preterm cohorts is essential
  - O'Shea TM, et. al. *Pediatrics* 2008;122:e662
  - Kuban KCK, et. al. *J Child Neurol* 2009;24:63





# Objective

---

- In the NEURO subcohort of the NICHD Neonatal Research Network Surfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT), we determined:
  - **Early and late CUS findings**
  - **Inter-rater reliability between central readers**
  - **Accuracy of local readings compared with central readings**



# SUPPORT Study

---

- SUPPORT was a randomized, multicenter trial of ventilation and oxygenation strategies in 24-27+6/7 week EGA infants; interventions began in the delivery room
  - **SUPPORT results will be presented:**
  - May 1, 2:45 pm. Neonatal Medicine: Clinical Trials (Neil Finer)
  - May 2, 4:15 pm. Perinatal Epidemiology (Wally Carlo)



# Methods: NEURO Study

---

- Prospective secondary study of **early CUS** (4-14 days) and **late CUS** (35-42 weeks PMA) in a subcohort of SUPPORT.
  - NEURO study also obtained brain MRI within 5 days of late CUS
  - Neurodevelopmental follow-up will occur at 18-22 months and 6 ½ to 7 ½ years



# Methods: Patients and Enrollment

---

- 16 Neonatal Research Network sites participated in NEURO secondary
  - Infants born May 2005 to February 2009
- Sites implemented secondary enrollment strategy best suited for their center
  - Consent with or after main trial consent
- NEURO launched after main trial start
  - IRB processes, neuroradiology arrangements for MRI portion of this study



# Methods: CUS Imaging

---

- CUS views and planes obtained per local site clinical protocol
  - “Standard procedure” considered as 6 paracoronal, 5 parasagittal views through AF
- NEURO protocol called for two CUS:
  - Early: 4-14 days of age
  - Late: 35-42 weeks PMA



# Methods: Local Reading and Data

---

- Trained research staff collected data from local radiologists' reports
- The NEURO study data form collected hemisphere-specific information:
  - Blood/echodensities (GM, ventricle, parenchyma, PVL)
  - Ventricular enlargement
  - Cysts/echolucencies (parenchyma, PVL)
  - Shunts or reservoirs



# Methods: Central Reading

---

- Copies of early and late CUS sent by centers to RTI International (data center)
- Two masked central readers reader CUS in two 2-day reading sessions
- Central reader form collected detailed hemisphere-specific radiologic and diagnostic data
  - Hintz SR, et. al. *J Pediatr* 2007;150:592



# Methods: Analysis

---

- **Reliability** analysis by kappa statistic
  - $\text{Kappa} = \frac{\% \text{ observed agreement} - \% \text{ expected agreement}}{100\% - \% \text{ expected agreement}}$
  - >0.75 considered “substantial” or “excellent” agreement (*Fleiss JL, 1981; Landis JR, 1977*)
- **Accuracy** analysis by sensitivity and specificity
  - Each central reader was “true value” against which the local reader was compared





# Results: Cohort and CUS scans

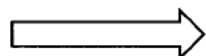
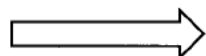
---

- **572 infants with complete early and late CUS**
- Early CUS obtained at  $8_{\pm}4$  days of age
  - Median: 7 days
- Late CUS obtained at  $37_{\pm}2$  weeks PMA
  - Median: 37 weeks PMA



# Baseline Characteristics

<b>N</b>	<b>572</b>
BW, mean (SD)	848 (190) grams
EGA, mean (SD)	25.9 (1) weeks
Multiple gestation	23%
Male	56%
Race	
Non-Hispanic Black	30%
Non-Hispanic White	43%
Male	56%
Antenatal steroids	95%
Cesarean section	69%
Apgar score <3 at 5 minutes	3%
Maternal education < HS	21%



# Central reader findings: **Early CUS**

	<b>Central Reader 1</b>	<b>Central reader 2</b>
<b>EARLY CUS findings</b>		
	N=572	N=572
Normal	72.0%	71.7%
Normal or choroid plexus bleed/cyst only	74.6%	72.6%
Any GMH or IVH	19.6%	20.8%
Grade 1 or 2	14.2%	12.2%
Grade 3 or 4	6.8%	9.6%
<b>Bilateral grade 3 or 4</b>	3.2%	5.9%
<b>Unilateral grade 3 or 4</b>	3.6%	3.7%
Any ventricular enlargement	8.8%	9.4%
Moderate-severe ventricular enlargement	4.6%	4.6%
Echolucent PVL	0.4%	0
Cerebellar/posterior fossa lesion	1.6%	1.2%



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# Central reader findings: Late CUS

	Central Reader 1	Central Reader 2
<b>LATE CUS findings</b>		
	N=571	N=572
Normal	70.8%	70.6%
Normal or choroid plexus bleed/cyst only	75.0%	73.1%
Any ventricular enlargement	7.7%	8.4%
Moderate-severe ventricular enlargement	4.4%	4.2%
Echolucent PVL (cPVL)	1.6%	1.1%
Porencephalic cyst (P-cyst)	2.1%	2.6%
cPVL or P-cyst or <b>any</b> ventriculomegaly or shunt	9.1%	9.6%
cPVL or P-cyst or <b>moderate to severe</b> ventriculomegaly or shunt	6.5%	6.6%
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Cerebellar/posterior fossa	1.1%	0.4%



# Progression of Findings

Early CUS finding	Late CUS finding	Central reader 1	Central reader 2
Normal	Normal	332 / 411 (81%)	336 / 410 (82%)
Normal	Any ventriculomegaly	11 / 411 (3%)	11 / 410 (3%)
Normal	Moderate-severe VM	6 / 411 (1%)	5 / 410 (1%)
Grade 3 or 4	Normal	4 / 39 (10%)	12 / 55 (22%)
Grade 3 or 4	Any ventriculomegaly	24 / 39 (62%)	29 / 55 (53%)
Grade 3 or 4	Moderate-severe VM	19 / 39 (49%)	19 / 55 (35%)
Grade 3 or 4	Porencephalic cyst	10 / 39 (26%)	14 / 55 (25%)
<b>UNILATERAL 3 or 4</b>	Normal	3 / 13 (23%)	4 / 15 (27%)



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<b>UNILATERAL 3 or 4</b>	Normal	<b>3 / 13 (23%)</b>	<b>4 / 15 (27%)</b>



# Central Reader Reliability: Early CUS

	<b>Kappa</b>	<b>95% CI</b>	<b>PPA</b>
<b>EARLY CUS</b>			
Normal vs. abnormal	0.76	(0.70, 0.82)	93%
Any GMH or IVH	0.79	(0.73, 0.85)	81%
Grade 1 or 2	0.52	(0.43, 0.61)	56%
Grade 3 or 4	0.77	(0.67, 0.87)	74%
Grade 3 or 4 or cPVL	0.75	(0.65, 0.85)	73%
ANY ventricular enlargement	0.62	(0.51, 0.72)	66%
Moderate-severe ventricular enlargement	0.84	(0.73, 0.95)	85%
PVL (echodense or echolucent)	0.22	(-0.15, 0.58)	22%



# Central Reader Reliability: Late CUS

	<b>Kappa</b>	<b>95% CI</b>	<b>PPA</b>
<b>LATE CUS</b>			
Normal vs. abnormal	0.66	(0.59, 0.73)	90%
ANY ventricular enlargement	0.88	(0.83, 0.94)	89%
Moderate-severe ventricular enlargement	0.90	(0.84, 0.97)	91%
Echolucent PVL (cPVL)	0.45	(0.19, 0.71)	46%
Porencephalic cyst (P-cyst)	0.76	(0.58, 0.93)	76%
cPVL or P-cyst or <b>any</b> ventriculomegaly or shunt	0.84	(0.79, 0.90)	86%
cPVL or P-cyst or <b>moderate to severe</b> ventriculomegaly or shunt	0.88	(0.82, 0.94)	89%



# Accuracy of Local Interpretation Early CUS

	Central Reader 1		Central Reader 2	
	Sensitivity	Specificity	Sensitivity	Specificity
Normal	90.3%	78.1%	88.0%	71.6%
Normal or choroid plexus bleed/cyst only	89.2%	82.1%	88.2%	73.9%
Any hemorrhage (grade 1-4)	92.0%	92.2%	80.7%	90.5%
Grade 1 or 2	90.1%	86.6%	71.4%	82.3%
Grade 3 or 4	89.7%	96.1%	72.7%	96.9%
Any ventricular enlargement	72.5%	97.1%	51.4%	97.2%
Any PVL	33.3%	98.2%	0%	97.9%



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# Accuracy of Local Interpretation Late CUS

	Central Reader 1		Central Reader 2	
	Sensitivity	Specificity	Sensitivity	Specificity
Normal	85.5%	59.9%	85.3%	58.9%
Normal or choroid plexus bleed/cyst only	84.5%	64.3%	84.3%	60.4%
Any ventricular enlargement	77.3%	96.2%	75.0%	96.5%
Cystic PVL (cPVL)	66.7%	98.4%	50.0%	97.9%
Porencephalic cyst (P-cyst)	50.0%	99.6%	33.3%	99.5%
cPVL or P-cyst or any ventriculomegaly or shunt	80.8%	95.0%	74.5%	94.7%



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# Summary

---

- In the NICHD NRN NEURO study:
  - Rates of major adverse findings on early and late CUS were low
    - Normal early to normal late CUS in ~80%
  - Central reader reliability and local reader accuracy were very good for major adverse or composite CUS findings
    - Poorer for normal late CUS and rare findings, poorer reliability for lower grade hemorrhage



# Discussion

- This study did not require special local radiologist training or specific CUS views
- Number of protocol scans was limited
- Unique cohort, part of a multicenter trial; therefore, results may not be generalizable
  - Despite limitations, NEURO will be the largest extremely preterm cohort to date with **CUS, brain MRI, and long-term follow-up**; not possible outside of a multicenter network



# Discussion

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- CUS were normal in ~70% of this cohort
  - But this does not assure normal outcome
    - O'Shea TM, et. al. *Pediatrics* 2008; Broitman E, et. al. *J Pediatr* 2007; Laptok A, et. al. *Pediatrics* 2005
  - Brain MRI results may augment CUS findings
- NEURO study will assess value of CUS and MRI, alone and with other risk factors, to predict neurologic and cognitive outcomes in early and later childhood



# NICHD Neonatal Research Network

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- **Special thanks to**
  - All NRN site Coordinators
  - Meg Cunningham
  - Kris Zaterka
  - Carolyn Petrie-Huitema
  - Amanda Irene
  - Julie Croxford



NICHD





# NICHD Neonatal Research Network Centers (1996-2006)

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- Brown University
- Case Western Reserve University
- Duke University
- Emory University
- Indiana University
- Research Triangle Institute
- Stanford University
- University of Alabama – Birmingham
- University of California – San Diego
- University of Cincinnati
- University of Miami
- University of New Mexico
- University of Rochester
- University of Tennessee – Memphis
- University of Texas, Southwestern – Dallas
- University of Texas – Houston
- Wake Forest University
- Wayne State University
- Yale University



NICHD



# NICHD Neonatal Research Network Centers (2006-2011)

- Brown University
- Case Western Reserve University
- Duke University
- Emory University
- Indiana University
- Research Triangle Institute
- Stanford University
- Tufts Medical Center
- University of Cincinnati
- University of Alabama – Birmingham
- University of Iowa
- University of New Mexico
- University of Texas, Southwestern – Dallas
- University of Texas – Houston
- University of Utah
- Wayne State University
- Yale University



NICHD



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**From:** Walsh, Michele  
**To:** Neil Finer; Wally Carlo M.D.; Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** SUPPORT slides  
**Date:** Friday, April 16, 2010 2:45:00 PM  
**Attachments:** SUPPORT Final rev PAS-ATS April 15 mw comments.ppt

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Hi Neil: Sorry for the delay.  
I had to get some help on reformatting tables  
To get the lines to be white.  
Forgive me- but we are deep into the gallys of our textbook,  
And my editors red pencil went a bit wild...  
I have made editorial suggestions to reduce the number of words  
On the slides, and suggest 2 possible Methods tables (slide 9 and 10)  
Which could replace your word slides of 11-15. I think it may improve  
Clarity for the audience to be able to see CPAP vs Surf arm side by side.  
Hope this helps... I understand you may not wish to use this version.  
Best,

*Michele Walsh*

Medical Director NICU  
Co-Chief: Division of Neonatology  
Rainbow Babies & Childrens Hospital  
UH Case Medical Center  
Professor, Department of Pediatrics  
Case Western Reserve University  
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NICHD



# Randomized Trial of Early CPAP versus Surfactant in Extremely Preterm Infants



## The SUPPORT Trial



The SUPPORT Study Group of the  
Eunice Kennedy Shriver NICHD  
Neonatal Research Network



## **Disclosure Statement**

Dr. Finer has documented that he has no relevant financial relationships to disclose or COIs to resolve

Dr. Finer has documented that his presentation will not involve discussion of unapproved or off-label, experimental or investigational use agents.

## Background

- ✓ Surfactant treatment at less than 2 hours of life significantly decreases death, air leak, and death or bronchopulmonary dysplasia (BPD) in preterm infants- but not BPD alone.
- ✓ However, no surfactant studies had a comparison group who received early CPAP
- ✓ Several studies have demonstrated that the use of surfactant does not significantly affect the risk of subsequent neurodevelopmental impairment



## Background



- ✓ Retrospective cohort studies demonstrated that the early use of CPAP in very preterm infants with respiratory distress may decrease mechanical ventilation without increased morbidity and without surfactant.
- ✓ Morley et al reported in the COIN Trial of 610 infants between 25 0/7 to 28 6/7 weeks gestation, who were able to breathe at 5 minutes of age and had evidence of respiratory distress.

## COIN Trial

**Morley et al. NEJM2008; 358(7):700-708**

- ✓ Randomized to intubation and ventilation, OR CPAP at 8 cm H<sub>2</sub>O; CPAP infants were intubated if they met failure criteria.
- ✓ No requirement for surfactant administration
- ✓ CPAP group had:
  - no significant reduction in death or oxygen at 36 weeks (the primary outcome),
  - significantly higher pneumothoraces (9.1% vs. 3.0%), most within the first 2 days



# Hypothesis

We hypothesized that early CPAP and a limited ventilator strategy compared to early Surfactant would reduce the incidence of death or survival with BPD at 36 weeks

## Method – Patients

- ✓ Inborn infants of 24<sup>0/7</sup> to 27<sup>6/7</sup> weeks gestation for whom a decision had been made to provide full resuscitation were eligible
- ✓ Antenatal Parental consent was obtained
- ✓ Enrollment from February 2005 to February 2009
- ✓ Randomization was stratified by center and by gestational age (24 and 25 weeks; 26 and 27 weeks)

## **Factorial Design**

- ✓ Infants also randomized to 2 ranges of SpO<sub>2</sub> using purpose built blinded oximeters
- ✓ Ranges 85% to 89% vs 91% to 95%
- ✓ Below 84% and above 96% oximeters read actual SpO<sub>2</sub> values
- ✓ Results of this Trial presented by Dr Carlo at Clinical Epidemiology Session

# Methods:

	<b>CPAP Arm</b>	<b>Surfactant</b>
Delivery Room	<ul style="list-style-type: none"><li>• 5 cm H<sub>2</sub>O</li><li>• Intubation per NRP</li><li>• If intubated, surfactant</li></ul>	
Intubation/ Surfactant	<ul style="list-style-type: none"><li>• Required if:</li><li>• FiO<sub>2</sub> &gt; 0.5</li><li>• PaCO<sub>2</sub> &gt; 65</li><li>• Hemodynamic instability</li></ul>	Prior to 1 hour

# Methods:

	<b>CPAP Arm</b>	<b>Surfactant</b>
Extubation	<ul style="list-style-type: none"><li>•Within 24 Hr of ALL :</li><li>•FiO<sub>2</sub> &lt; 0.35 and MAP 8</li><li>•PaCO<sub>2</sub> &lt; 65</li></ul>	<ul style="list-style-type: none"><li>•Within 24 Hr of ALL :</li><li>•FiO<sub>2</sub> &lt; 0.35 and MAP 8</li><li>•PaCO<sub>2</sub> &lt; 50</li></ul>

## **Methods – Intervention - CPAP**

- ✓ In the delivery room, a T-piece resuscitator, a neonatal ventilator, or an equivalent CPAP methodology was used for the administration of 5 cm H<sub>2</sub>O CPAP which was continued until NICU admission
- ✓ Intubation only for infants who required intubation for resuscitation based on standard NRP indications, not performed for the surfactant administration
- ✓ Intubated infants given surfactant

## Methods – Intervention - CPAP

In the NICU, infants randomized to CPAP could be intubated if they met any of the following criteria:

- ✓  $\text{FiO}_2$  greater than 0.50 required to maintain an indicated  $\text{SpO}_2 \geq 88\%$  for one hour,
- ✓ Arterial  $\text{PaCO}_2$  greater than 65 torr
- ✓ Hemodynamic = low blood pressure and/or poor perfusion, requiring volume and/or pressor support
- ✓ If intubated within the first 48 hours of life, infants were to receive surfactant.

## Methods – Intervention - CPAP

Extubation of infants in the CPAP arm to be attempted within 24 hours of meeting *all* following criteria:

- ✓ PaCO<sub>2</sub> below 65 torr with a pH greater than 7.20
- ✓ SpO<sub>2</sub> greater than 88% with an FiO<sub>2</sub> below 50%
- ✓ mean airway pressure (MAP) < 10 cm H<sub>2</sub>O,  
ventilator rate below 20 bpm,
- ✓ hemodynamically stable, and without a clinically significant patent ductus arteriosus



## Methods – Intervention - Surfactant

- ✓ Infants to receive surfactant within 1 hour of life, Infants extubated within 24 hours of meeting all of the following criteria:
  - ✓ PaCO<sub>2</sub> below 50 torr and pH greater than 7.30
  - ✓ FiO<sub>2</sub> ≤ .35 and SpO<sub>2</sub> ≥ 88% or higher, a MAP 8 cm H<sub>2</sub>O or lower , ventilator rate 20 bpm or less and hemodynamically stable without evidence of clinically significant PDA.
  - ✓ Once extubated, infants were treated using NICU standard practice.

## **Methods – Duration of Intervention**

- ✓ The criteria for both arms were in effect for the first 14 days of life, following which the infant was treated as per NICU standard practice.
- ✓ For both arms, intubation could be performed at any time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery.

## Methods – BPD Definitions

- ✓ For the primary outcome, BPD was defined using the physiologic definition:
- ✓ receipt  $>$  30% oxygen at 36 weeks
- ✓ need for positive pressure support
- ✓ If  $FiO_2 < .30$ , oxygen withdrawal performed
- ✓ Pre-specified secondary outcomes included the evaluation of BPD defined by the receipt of oxygen at 36 weeks.

3546 Infants were assessed for eligibility (3127 pregnancies)\*

235 Did not meet eligibility criteria  
125 Personnel/Equipment not available  
699 Eligible but consent not sought  
344 Parent unavailable for consent  
748 Consent denied by parent or guardian  
11 Excluded for other reasons  
68 Consented but not randomized

1316 Underwent randomization

663 Were assigned CPAP

653 Were assigned Surfactant

94 Died before discharge

569 Survived to discharge, transfer one year of life

114 Died before discharge

539 Survived to discharge, transfer or one year of life

223 BPD Physiologic

346 No BPD Physiologic

219 BPD Physiologic

320 No BPD Physiologic

## Results – Patient Population

	CPAP (N = 663)	Surfactant (N = 653)
Birthweight*	835 ± 188.2	826 ± 198.1
Gestational Age*	26.2 ± 1.1	26.2 ± 1.1
24 to 25 6/7ths (%)	43	43
26 to 27 6/7ths (%)	57	57
Race, White/Black/Hispanic (%)	38 / 38 / 21	36 / 42 / 19
Antenatal corticosteroids (%)	97	96
Multiple births (%)	27	24

\*Mean ± Standard Deviation

## Results – Primary Outcome

	CPAP N=663	Surfactant N=653	Adjusted Relative Risk (95% CI)
Death or BPD (Physiologic)	47.8%	51.0%	0.95 (0.85, 1.05)
BPD - Physiologic	39.2%	40.6%	0.99 (0.87, 1.14)
Death by 36 weeks PMA	14.2%	17.5%	0.81 (0.63, 1.03)

## Results – Delivery Room

<b>Variable</b>	<b>CPAP (N=663)</b>	<b>Surfactant (N=653)</b>	<b>Relative Risk for CPAP vs. Surfactant (95% CI)</b>	<b>Adjusted P- value</b>
Apgar at 1 minute <3	23.3%	25.6%	0.92 (0.76, 1.11)	0.38
Apgar at 5 minutes <3	3.9%	4.9%	0.82 (0.5, 1.34)	0.43
PPV in the DR	65.7%	92.9%	0.71 (0.67, 0.75)	<0.0001
Intubated in DR	34.4%	93.4%	0.37 (0.34, 0.42)	<0.0001
DR intubation for resuscitation	32.6%	27.0%	1.21 (1.02, 1.43)	0.02
Surfactant in DR or NICU	67.1%	98.9%	0.67 (0.64, 0.71)	<0.0001
Epinephrine in DR	2.0%	4.1%	0.48 (0.25, 0.91)	0.02

## Results – Other Pre-specified Outcomes \* = p<0.05

	CPAP N=663	Surfactant N=653	Relative Risk or Difference in Means
BPD (O <sub>2</sub> use at 36 wks)	40.2%	44.3%	0.94 (0.82, 1.06)
BPD (O <sub>2</sub> use)/Death, 36 wks	48.7%	54.1%	0.91 (0.83, 1.01)
Severe ROP- survivors	13.1%	13.7%	0.94 (0.69, 1.28)
Any air leaks (14 days)	6.8%	7.4%	0.89 (0.6, 1.32)
Mechanical Vent Survivors (Days)	24.8 ± 1.0	27.7 ± 1.1	-3.0 (-5.6, -0.3)*
Alive and off MV at 7 days	55.3%	48.8%	1.14 (1.03, 1.25)*
Postnatal steroids for BPD	7.2%	13.2%	0.57 (0.41, 0.78)*



## **SUPPORT – Other Results**

- ✓ No differences in the incidence of PDA, PDA requiring surgery, Medical or Surgical NEC
- ✓ No differences Severe IVH/PVL
- ✓ CPAP significantly decreased death in the 24 to 25 weeks strata:
  - CPAP 23.9% vs Surfactant 32.1%
  - Relative Risk difference 0.74 (0.57, 0.98)

## SUMMARY

- ✓ No significant difference for primary outcome of death or BPD
- ✓ Fewer CPAP infants were intubated in the DR or overall, ( $p < 0.001$ ), more were alive and off mechanical ventilation by day 7, ( $p = 0.011$ )
- ✓ CPAP infants received less postnatal steroids for BPD ( $p < 0.001$ ) and required fewer vent days ( $p = 0.03$ ).
- ✓ CPAP Infants 24 to 25 6/7 weeks had a significantly lower mortality rate while hospitalized
- ✓ CPAP infants did not have increased morbidities

## Conclusions

- ✓ Early CPAP and a limited ventilator strategy is comparable to early Surfactant for the initial stabilization and ongoing management of the extremely low birth weight infant
- ✓ CPAP was not associated with any increase in adverse neonatal outcomes including air leaks
- ✓ All surviving infants will have a full neurodevelopmental evaluation at 18 to 22 months

# Thanks to the many parents, infants, 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



## Consort Diagram

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125 Personnel/Equipment not available  
699 Eligible but consent not sought  
344 Parent or guardian unavailable  
748 Consent denied by parent or guardian  
11 Excluded for other reasons  
68 Consented but not randomized

1316 Underwent randomization

654 Randomized to oxygen saturation targeting 85-89%

662 Randomized to oxygen saturation targeting 91-95%

336 Randomized to early CPAP

318 Randomized to early surfactant

327 Randomized to early CPAP

335 Randomized to early surfactant

54 Died 282 Survived

60 Died 258 Survived

40 Died 287 Survived

54 Died 281 Survived

103 BPD 179 No BPD

102 BPD 156 No BPD

120 BPD 167 No BPD

117 BPD 164 No BPD

**From:** [Gantz, Marie](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Cc:** [Das, Abhik](#)  
**Subject:** SUPPORT missing FU  
**Date:** Friday, April 16, 2010 12:31:55 PM  
**Attachments:** [Infants with missing FU outcomes 16APR10.xls](#)

---

Rose,

Attached is the list of SUPPORT infants missing FU this month.

Marie

Marie Gantz, Ph.D.  
Research Statistician  
RTI International  
[mgantz@rti.org](mailto:mgantz@rti.org)  
828-254-6255

Missing\_FU

CENTER	NETWORK	FU_message
5	(b) (6)	FU window has closed but NF05 and NF09a have not been completed.
5		FU window has closed but NF09a has not been completed.
5		FU window has closed but NF05 and NF09a have not been completed.
5		FU window has closed but NF05 and NF09a have not been completed.
5		FU window has closed but NF05 and NF09a have not been completed.
5		FU window has closed but NF05 and NF09a have not been completed.
9		FU window has closed but NF05 and NF09a have not been completed.
11		FU window has closed but NF05 and NF09a have not been completed.
12		FU window has closed but NF09a has not been completed.
12		FU window has closed but NF05 and NF09a have not been completed.
14		FU window has closed but NF05 and NF09a have not been completed.
14		FU window has closed but NF05 and NF09a have not been completed.
15		FU window has closed but NF05 and NF09a have not been completed.
16		FU window has closed but NF05 and NF09a have not been completed.
18		FU window has closed but NF05 and NF09a have not been completed.
18		FU marked as complete (per NF10/SF10) but NF09a has not been completed.
23		FU marked as complete (per NF10/SF10) but NF05 has not been completed.
24		FU window has closed but NF05 and NF09a have not been completed.
26		FU window has closed but NF05 and NF09a have not been completed.



## **Higgins, Rosemary (NIH/NICHD) [E]**

---

**From:** Finer, Neil <nfiner@ucsd.edu>  
**Sent:** Friday, April 16, 2010 2:28 PM  
**To:** Das, Abhik; Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie  
**Cc:** Zaterka-Baxter, Kristin  
**Subject:** RE: SUPPORT CPAP Final??

Lets hope this is satisfactory  
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

-----Original Message-----

**From:** Das, Abhik [mailto:adas@rti.org]  
**Sent:** Friday, April 16, 2010 7:38 AM  
**To:** Wally Carlo, M.D.; Rose Higgins; Gantz, Marie; Finer, Neil  
**Cc:** Zaterka-Baxter, Kristin  
**Subject:** RE: SUPPORT CPAP Final??

Here you go. You will notice that the BPD composite is always stated with a time limitation of 36 weeks, whereas the ROP composite includes all deaths.

Thanks

Abhik

-----Original Message-----

**From:** Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]  
**Sent:** Friday, April 16, 2010 9:33 AM  
**To:** Das, Abhik; Wally Carlo, M.D.; Rose Higgins; Gantz, Marie; Neil Finer  
**Cc:** Zaterka-Baxter, Kristin  
**Subject:** RE: SUPPORT CPAP Final??

That would be great.

Sent from my Windows Mobile phone

-----Original Message-----

**From:** Das, Abhik <adas@rti.org>

Sent: Friday, April 16, 2010 5:17 PM

To: Wally Carlo, M.D. <WCarlo@peds.uab.edu>; Rose Higgins <higginsr@mail.nih.gov>; Gantz, Marie <mgantz@rti.org>; Neil Finer <nfiner@ucsd.edu>  
Cc: Zaterka-Baxter, Kristin <kzaterka@rti.org>  
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Thanks

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Sent: Friday, April 16, 2010 9:13 AM  
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Cc: Zaterka-Baxter, Kristin  
Subject: RE: SUPPORT CPAP Final??

But was the mortality component of the primary outcome defined as we have done it for the paper? It would be ideal to also submit the a Technical Memo or other documentation when this was changed. Marie's email in from Nov 2009 which is after the data were analyzed.

Wally

Sent from my Windows Mobile phone

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From: Das, Abhik <adas@rti.org>  
Sent: Friday, April 16, 2010 5:01 PM  
To: Wally Carlo, M.D. <WCarlo@peds.uab.edu>; Rose Higgins <higginsr@mail.nih.gov>; Gantz, Marie <mgantz@rti.org>; Neil Finer <nfiner@ucsd.edu>  
Cc: Zaterka-Baxter, Kristin <kzaterka@rti.org>  
Subject: RE: SUPPORT CPAP Final??

Yes; we have all the reports we prepared for the DSMC for all their meetings, and can make those available if needed.

Thanks

Abhik

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To: Das, Abhik; Wally Carlo, M.D.; Rose Higgins; Gantz, Marie; Neil Finer  
Subject: RE: SUPPORT CPAP Final??

Abhik.

Could someone find the evidence that the definition of mortality as Marie says waa indeed the way the DMC analyzed the primary outcome as early as its first meeting?

wally

Sent from my Windows Mobile phone

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To: Wally Carlo, M.D. <WCarlo@peds.uab.edu>; Rose Higgins <higginsr@mail.nih.gov>; Gantz, Marie <mgantz@rti.org>; Neil Finer <nfiner@ucsd.edu>

Subject: RE: SUPPORT CPAP Final??

I hope this one is acceptable to the NEJM. In fact, we have always used this definition of mortality for the ROP composite, right from the first 25% efficacy interim monitoring look at the data for the DSMC in early 2007. We can also provide them with the technical memo (#11) that Rose mentioned, but that may raise the question of why we did not use 55 weeks PMA as the death cut-off.

Thanks

Abhik

-----Original Message-----

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]

Sent: Friday, April 16, 2010 2:48 AM

To: Wally Carlo, M.D.; Rose Higgins; Gantz, Marie; Das, Abhik; Neil Finer

Subject: RE: SUPPORT CPAP Final??

This is the email whre Marie had mentioned the def of mort used.

Sent from my Windows Mobile phone

-----Original Message-----

From: Wally Carlo, M.D. <WCarlo@peds.uab.edu>

Sent: Friday, April 16, 2010 12:41 AM

To: Wally Carlo, M.D. <WCarlo@peds.uab.edu>; Rose Higgins <higginsr@mail.nih.gov>; mgantz@rti.org;sdas@rti.org <mgantz@rti.org;sdas@rti.org>

Subject: RE: SUPPORT CPAP Final??

Rose.

This may be the email we could use.

Marie:

Could you see if this is the best email that determines how we defined mort for the primary outcome?

wally

Sent from my Windows Mobile phone

-----Original Message-----

From: Wally Carlo, M.D. <WCarlo@peds.uab.edu>

Sent: Thursday, April 15, 2010 5:08 PM

To: Wally Carlo, M.D. <WCarlo@peds.uab.edu>  
Subject: FW: SUPPORT CPAP Final??

I believe this is the one you are looking for let me know if it is not

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: 205 266 (b)

-----Original Message-----

From: Gantz, Marie [mailto:mgantz@rti.org]  
Sent: Monday, November 23, 2009 10:55 AM  
To: Finer, Neil; Das, Abhik; Wally Carlo, M.D.; Rich, Wade; Higgins, Rosemary (NIH/NICHD) [E]  
Subject: RE: SUPPORT CPAP Final??

Neil,

I apologize if I was confusing about the ROP outcome. ROP was determined at the point at which an eye exam met criteria for final status. This could have been in the hospital or as an outpatient, and at no time was the outcome cut-off (at transfer, discharge, etc.). However, the outcome of survival is survival to discharge, 1 year of life, or in a few cases transfer because status after transfer was unknown per the GDB forms. I looked into the three cases where status after transfer was unknown, and found that one infant was seen at 18 month FU, one infant was transferred to a chronic care facility at 6 months (18 month FU window not yet open), and the last infant was transferred at 3 months and is listed as lost to FU for the 18 month visit because of noncompliance with last contact after 2 years of age (although the infant was not explicitly noted to be alive at that time on the NF12). Only this last infant is missing final ROP status - the other two met criteria for the positive ROP outcome (no severe ROP). I hope this helps clear things up.

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: Sunday, November 22, 2009 2:43 PM  
To: Das, Abhik; Gantz, Marie; Wally Carlo; Rich, Wade; Higgins, Rosemary (NIH/NICHD) [E]  
Subject: SUPPORT CPAP Final??

Hi Everyone

Here is my final

I have largely ignored Jon's comments

We were over words with Marie and Abhiks additions so I shortened them and other parts. I removed the number of analyses to save words.

Marie, I would like in Table 3 to replace ROP or Death with ROP in survivors. ROP or death is not a postulate of SUPPORT that I would report when Wally's paper is going in.

I have removed ROP from the Stratum tables - it is too uncertain when it includes ROP at discharge or transfer Have a look and make any further changes you think are essential. We are within the specified limits.

I will be travelling Tuesday but I can upload with Wades help anytime.

Thanks to you all - This has been a journey!!!

Neil

**From:** Das, Abhik  
**To:** Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie; Neil Finer  
**Cc:** Zaterka-Baxter, Kristin  
**Subject:** RE: SUPPORT CPAP Final??  
**Date:** Friday, April 16, 2010 10:38:21 AM  
**Attachments:** SUPPORT DSMC report (blinded) (3).doc

---

Here you go. You will notice that the BPD composite is always stated with a time limitation of 36 weeks, whereas the ROP composite includes all deaths.

Thanks

Abhik

-----Original Message-----

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]  
Sent: Friday, April 16, 2010 9:33 AM  
To: Das, Abhik; Wally Carlo, M.D.; Rose Higgins; Gantz, Marie; Neil Finer  
Cc: Zaterka-Baxter, Kristin  
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To: Das, Abhik; Wally Carlo, M.D.; Rose Higgins; Gantz, Marie; Neil Finer  
Cc: Zaterka-Baxter, Kristin  
Subject: RE: SUPPORT CPAP Final??

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-----Original Message-----

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]  
Sent: Friday, April 16, 2010 2:48 AM  
To: Wally Carlo, M.D.; Rose Higgins; Gantz, Marie; Das, Abhik; Neil  
Finer  
Subject: RE: SUPPORT CPAP Final??

This is the email whre Marie had mentioned the def of mort used.

Sent from my Windows Mobile phone

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Sent: Friday, April 16, 2010 12:41 AM  
To: Wally Carlo, M.D. <WCarlo@peds.uab.edu>; Rose Higgins  
<higginsr@mail.nih.gov>; mgantz@rti.org;sdas@rti.org  
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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: 205 266 (b)

-----Original Message-----

From: Gantz, Marie [mailto:mgantz@rti.org]  
Sent: Monday, November 23, 2009 10:55 AM  
To: Finer, Neil; Das, Abhik; Wally Carlo, M.D.; Rich, Wade; Higgins,



Rosemary (NIH/NICHD) [E]  
Subject: RE: SUPPORT CPAP Final??

Neil,

I apologize if I was confusing about the ROP outcome. ROP was determined at the point at which an eye exam met criteria for final status. This could have been in the hospital or as an outpatient, and at no time was the outcome cut-off (at transfer, discharge, etc.). However, the outcome of survival is survival to discharge, 1 year of life, or in a few cases transfer because status after transfer was unknown per the GDB forms. I looked into the three cases where status after transfer was unknown, and found that one infant was seen at 18 month FU, one infant was transferred to a chronic care facility at 6 months (18 month FU window not yet open), and the last infant was transferred at 3 months and is listed as lost to FU for the 18 month visit because of noncompliance with last contact after 2 years of age (although the infant was not explicitly noted to be alive at that time on the NF12). Only this last infant is missing final ROP status - the other two met criteria for the positive ROP outcome (no severe ROP). I hope this helps clear things up.

Marie

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-----Original Message-----

From: Finer, Neil [<mailto:nfiner@ucsd.edu>]  
Sent: Sunday, November 22, 2009 2:43 PM  
To: Das, Abhik; Gantz, Marie; Wally Carlo; Rich, Wade; Higgins, Rosemary (NIH/NICHD) [E]  
Subject: SUPPORT CPAP Final??

Hi Everyone

Here is my final

I have largely ignored Jon's comments

We were over words with Marie and Abhiks additions so I shortened them and other parts. I removed the number of analyses to save words.

Marie, I would like in Table 3 to replace ROP or Death with ROP in survivors. ROP or death is not a postulate of SUPPORT that I would report when Wally's paper is going in.

I have removed ROP from the Stratum tables - it is too uncertain when it includes ROP at discharge or transfer

Have a look and make any further changes you think are essential. We are within the specified limits.

I will be travelling Tuesday but I can upload with Wades help anytime.

Thanks to you all - This has been a journey!!!

Neil

**The First Data Safety and Monitoring Committee Report for  
The SURfactant Positive Airway Pressure and  
Pulse Oximetry Trial in Extremely Low Birth Weight Infants  
(SUPPORT Trial)**

**February 6, 2007**

**Prepared by the Neonatal Research Network Data Center at  
RTI International, Research Triangle Park, NC**

## A. Abstract

The SURfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants (SUPPORT Trial) is a prospective, randomized, factorial 2X2 design multi-center trial conducted by the NICHD Neonatal Research Network. The individual factors to be tested are:

1) A prospective comparison of CPAP and a permissive ventilatory strategy begun in the delivery room and continuing in the NICU (Treatment) with early ( $\leq 1$  hour) surfactant and mechanical ventilation (Control).

2) A prospective comparison of a lower SpO<sub>2</sub> range (85% to 89%) with a higher more conventional SpO<sub>2</sub> range (91% to 95%) until the infant is no longer requiring ventilatory support or oxygen.

The oxygen saturation monitoring portion of this study utilizes blinded oximeters developed by the Masimo Corporation (Irvine, CA). These devices display skewed SpO<sub>2</sub> values when the actual SpO<sub>2</sub> is between 85% and 95% and actual SpO<sub>2</sub> values when the SpO<sub>2</sub> is  $< 85\%$  or  $> 95\%$ . This allows for a blinded comparison of the two SpO<sub>2</sub> levels while providing the clinicians and caretakers with the infants' actual SpO<sub>2</sub> values during hypoxia and hyperoxia.

Infants are recruited for this study by approaching one or both parents at the time of admission to the hospital where there is deemed to be a risk of premature delivery at 27 6/7ths weeks or less. Randomization is stratified by gestational age group, occurs prior to delivery for consented deliveries, and is performed using specially prepared double-sealed envelopes. Deliveries are randomized as a unit, thus multiples, twins, triplets etc are randomized to the same arm of the trial.

The two primary hypothesis of the study are:

1). Relative to infants managed with prophylactic/early surfactant and conventional ventilation, the use of early CPAP and a permissive ventilatory strategy with continuing CPAP in the NICU will result in an increased survival without BPD at 36 weeks.

2). Relative to infants managed with a higher SpO<sub>2</sub> range (91-95%), the use of a lower SpO<sub>2</sub> range (85% to 89%) will result in an increase in survival without the occurrence of threshold ROP and/or the need for surgical intervention.

## B. Methods and Procedures

### Study Design

This is a prospective, randomized, factorial 2X2 design multi-center trial conducted by the NICHD Neonatal Research Network. The individual factors to be tested are:

1) A prospective comparison of CPAP and a permissive ventilatory strategy begun in the delivery room and continuing in the NICU with early ( $\leq 1$  hour) surfactant and mechanical ventilation.

2) A prospective comparison of a lower SpO<sub>2</sub> range (85% to 89%) with a higher more conventional SpO<sub>2</sub> range (91% to 95%) until the infant is no longer requiring ventilatory support or oxygen.

The oxygen saturation monitoring portion of the study is designed to allow a blinded comparison of 2 different SpO<sub>2</sub> levels using specially designed pulse oximeters. These devices have been developed by the Masimo Corporation (Irvine Ca) and tested prior to initiation of this trial. The oximeters are calibrated to provide actual SpO<sub>2</sub> values when the SpO<sub>2</sub> is  $< 85\%$  and  $> 95\%$  ( Personal communication, Cynthia Cole 2004). This methodology will provide the clinicians and caretakers with the infants' actual SpO<sub>2</sub> values during hypoxia and hyperoxia, within the current parameters of clinically accepted practice.

<b>SUPPORT Trial Treatment Combinations</b>		
<b>Randomized Intervention</b>	<b>Low SpO2 85% to 89%</b>	<b>High SpO2 91 to 95%</b>
<b>Treatment Early CPAP</b>	Early CPAP + Low SpO2	Early CPAP + High SpO2
<b>Control Prophylactic/Early Surfactant</b>	Control + Low SpO2	Control + High SpO2

### **Primary Hypotheses**

1). Relative to infants managed with prophylactic/early surfactant and conventional ventilation, the use of early CPAP and a permissive ventilatory strategy in infants of less than 28 weeks gestation with continuing CPAP in the NICU will result in an increased survival without BPD at 36 weeks.

2). Relative to infants managed with a higher SpO2 range, 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.

### **Secondary Hypotheses**

Use of continuous positive airway pressure (CPAP) with a permissive ventilator strategy and/or a lower SpO2 range starting at birth in the delivery room will result in the following:

- A decreased Mortality/NDI at 18-22 months corrected age.
- A decreased frequency of endotracheal intubation before 10 minutes of age
- A decrease of the total duration of mechanical ventilation during the entire NICU stay
- A decreased incidence of surfactant treatment
- A decreased incidence of air leaks on admission and overall
- A decreased duration of intubation
- A decreased duration of mechanical ventilation
- A decreased duration of oxygen supplementation
- A decreased duration of the percentage of pulse oximetry values > 90%
- A decreased incidence of blindness of at least one eye at 18-22 month follow-up
- A decrease in the percentage of infants who receive postnatal steroids to prevent or treat BPD
- A decreased incidence of BPD at 36 weeks using the physiologic definition of BPD
- A decreased incidence of ROP or Stage 3 ROP
- A decreased incidence of necrotizing enterocolitis (NEC)

- A decreased incidence of IVH and severe IVH
- A decreased incidence of periventricular leukomalacia
- A decreased incidence of neurodevelopmental impairment at 18-22 month follow-up
- A decreased incidence of cerebral palsy at 18-22 month follow-up

### **Study Population**

Study subjects are infants of 24 0/7 to 27 6/7 weeks gestational age (GA) at birth for which a decision has been made to provide full resuscitation as required. Infants 27 weeks or less gestation (completed weeks by best obstetric estimate) are enrolled because over 80% of such infants in the Network are intubated, usually early in their neonatal course. There are 2 randomization strata, infants of 24 0/7 to 25 6/7 weeks GA, and infants of 26 0/7-27 6/7 weeks GA by best obstetrical estimate. The purpose of stratification is to assure an appropriate distribution of risk among the four study arms. The study is not powered to detect outcome differences between strata.

### **Inclusion Criteria**

- Infants with a minimal gestational age of 24 weeks 0 days to 27 completed weeks (up to 27 6/7ths) by best obstetrical estimate
- Infants who will receive full resuscitation as necessary, i.e., no parental request or physician decision to forego resuscitation
- Infants whose parents/legal guardians have provided consent for enrollment, or
- Infants without known major congenital malformations

### **Exclusion Criteria**

- Any infant transported to the center after delivery
- Infants whose parents/legal guardians refuse consent
- Infants born during a time when the research apparatus/study personnel are not available
- Infants < 24 weeks 0 days or  $\geq$  28 weeks 0 days, completed weeks of gestation

### **Sampling Recruitment and Screening Procedures**

Infants are recruited for this study by approaching one or both parents at the time of admission to the hospital where there is deemed to be a risk of premature delivery at 27 6/7ths weeks or less.

### **Sample Size**

The required sample size for this trial was determined to be 1310 to ensure 80% power for detecting an absolute difference of 10% in the two primary outcomes and the NDI secondary outcome. These results were based on observed prevalence of these outcomes in the Network Generic Data Base (GDB, a registry of all <1500 g births in the Network), and corrected for two primary outcomes (assumed significance level of 2%), for a clustering effect because of multiples being randomized to the same treatment, as well as for attrition. Note that this sample size is not sufficient to permit detection of interaction effects between the two treatments with reasonable power.

### **Randomization**

Randomization is stratified by study site and gestational age group, occurs prior to delivery for consented deliveries, and is performed by utilizing specially prepared double-sealed envelopes. Deliveries are randomized as a unit, thus multiples, twins, triplets etc are

randomized to the same arm of the trial. Appropriate sample size adjustments have been made to account for this clustering effect.

### **Study Intervention**

The intervention begins after birth when the infant is given to the resuscitation team. The conduct of the resuscitation follows usual guidelines, and once stabilized, all Control infants in both strata receive prophylactic/early surfactant (within 1 hour of age) whereas all Treatment infants are placed on CPAP/PEEP following stabilization, and intubated only for resuscitation indications.

The assignment to either a high or low SpO<sub>2</sub> by study oximeter assignment is performed immediately following NICU admission, with a maximum allowable delay of 2 hours following NICU admission. There are two ranges of SpO<sub>2</sub> utilized during this trial. The Low target range is 85% to 89% and the High target range is 91% to 95%. The altered Pulse Oximeters (PO) display a range of 88% to 92% when the SpO<sub>2</sub> ranges are in the Target ranges indicated above. Thus a Low range PO reads 88% when the actual SpO<sub>2</sub> is approximately 86%, and 92% when the actual SpO<sub>2</sub> is 89%. Similarly the High range PO displays 88% when the actual SpO<sub>2</sub> is 91% and indicates 92% when the actual SpO<sub>2</sub> is approximately 95%.

### **Interim Monitoring Plan**

The Data Safety Monitoring Committee will review the progress of the study with respect to efficacy and adverse events in a sequential fashion using interim monitoring boundaries. Efficacy will be measured at approximately 25%, 50%, 75%, and 100% of outcome assessment. Primary outcomes will be analyzed at these time points by statistically adjusting for familial clustering and stratification by gestational age and center. To control for the inflation of Type I error associated with sequential testing, O'Brien-Fleming<sup>1</sup> boundaries will be calculated using a Lan-DeMets<sup>2</sup> spending function. Safety will be monitored at these time points as well using Pocock<sup>3</sup> boundaries for adverse event monitoring. Data on adverse events that occur within the first 14 days of life are collected on a designated SUPPORT Trial form, and additional adverse events are recorded on other SUPPORT and GDB forms.

## **C. Results**

### **Enrollment**

This is the first of four pre-planned interim analyses to be conducted for the SUPPORT Trial DSMC. As of January 24, 2007, 491 infants have been enrolled in SUPPORT. This number represents 37.5 percent of the expected total enrollment of 1,310. Table 1 below displays information related to enrollment.

Category		Number	Percent
Screened		1193	100%
Eligible		995	83%
Consented		515	43%
Randomized	% of Screened	491	41%
	% of Eligible		49%
	% of Consented		95%
<b>Eligible – Not randomized</b>			
Infants		504	100%
Reason – Parent unavailable		80	15.9%
Reason – Parent refusal		223	44.2%
Reason – Consent not requested		176	34.9%
Reason – Physician refusal		1	0.2%
Reason – Too old at delivery		7	1.4%
Reason – Parent withdrew consent		2	0.4%
Reason – Other		15	3.0%

**Table 1. Enrollment Information as of January 24, 2007**

Table 2 compares selected characteristics of infants enrolled in the two arms of the study. There are no statistically significant differences between infants enrolled in the two treatments for either arm.

Characteristic	Ventilation Arm		Oxygen Saturation Arm	
	Treatment A (N=258)	Treatment B (N=233)	Treatment A (N=239)	Treatment B (N=252)
Male	130 (50.6%)	133 (57.3%)	131 (55.3%)	132 (52.4%)
Birth Weight (grams)	824.2 ± 200.4	818.4 ± 198.2	816.6 ± 198.1	826.0 ± 200.5
Gestational age (weeks)	24-25	91 (39.2%)	101 (42.4%)	100 (39.7%)
	26-27*	148 (57.4%)	141 (60.8%)	137 (57.6%)
Multiple birth	73 (28.3%)	58 (25.0%)	57 (23.9%)	74 (29.4%)
Apgar at 5 minutes <math>\leq 3</math>	10 (3.9%)	13 (5.6%)	10 (4.2%)	13 (5.2%)
Infants with outcome for death/BPD	206 (79.8%)	186 (79.8%)	195 (81.6%)	197 (78.2%)
Infants with outcome for death/ROP	164 (63.6%)	153 (65.7%)	153 (64.0%)	164 (65.1%)

**Table 2. Infant Characteristics for Ventilation and Oxygen Saturation Arms**

\*The 26-27 week GA group includes one infant with a GA of 28 weeks

## Treatment Compliance in Oxygen Saturation Arm

The oxygen saturation arm of the SUPPORT trial requires that infants maintain saturations of 85-89% or 91-95% for the Low and High SpO<sub>2</sub> arms, respectively. Table 3 shows the percent of time infants on supplemental oxygen spend in various SpO<sub>2</sub> ranges. Supplemental oxygen is defined as FiO<sub>2</sub>>.21 during the first 14 days of life (FiO<sub>2</sub> is reported every two hours) or as documented oxygen use from day of life 15 through 36 weeks (oxygen use recorded every 6 hours).

Time on supplemental oxygen	Oxygen saturation arm	Percent in narrow target 88-92 (Display)	Percent <84	Percent 84-96	Percent >96
Days of life 1-14	Low O <sub>2</sub>	21.8	10.9	78.6	10.6
	High O <sub>2</sub>	50.5	5.9	80.5	13.6
	Total	39.7	7.8	79.8	12.4
Day 15 to 36 wks	Low O <sub>2</sub>	16.7	14.8	69.3	15.9
	High O <sub>2</sub>	38.0	9.9	68.0	22.1
	Total	29.2	11.9	68.5	19.6

**Table 3. Distribution of Time in SpO<sub>2</sub> Display Ranges while on Supplemental Oxygen**

## Primary Outcomes

Tables 4a and 4b compare the two primary outcomes for both the ventilation and oxygen saturation arms. There were 392 infants with a known outcome for survival without BPD at 36 weeks (30% of the total planned enrollment). Because it can take many weeks longer for ROP diagnosis, there were only 317 infants with a known outcome for survival without ROP (24% of the total planned enrollment). P-values for testing for treatment differences are adjusted for familial clustering and for stratification on gestational age group and center.

To adjust for the increased Type-I error rate associated with sequential testing, O'Brien-Fleming bounds were calculated using the Lan-DeMets spending function. For the outcome of survival without BPD at 36 weeks, significance bounds were calculated for expected tests at 30%, 50%, 75% and 100% of total enrollment. For survival without ROP, we calculated significance bounds for testing at 24%, 50%, 75% and 100% of enrollment. The O'Brien-Fleming bounds provide appropriate criteria for judging the significance of differences between treatments at each interim analysis. The p-values associated with the bounds are two-sided, with an overall cumulative significance of 0.025 to account for the fact that each primary outcome is tested for both the ventilation and oxygen saturation arms.

Primary outcomes	Ventilation Arm		P-value	O'Brien-Fleming bound p-value
	Treatment A	Treatment B		
Survival without BPD at 36 weeks	55.3% (114/206)	44.6% (83/186)	0.0327	0.00001
Survival without ROP	64.6% (106/164)	58.2% (89/153)	0.1968	0.00001

**Table 4a. Primary Outcome for Ventilation Arm**



Primary outcomes	Oxygen Saturation Arm		p-value	O'Brien-Eleming bound p-value
	Treatment A	Treatment B		
Survival without BPD at 36 weeks	48.2% (94/195)	52.3% (103/197)	0.5578	0.00001
Survival without ROP	62.1% (95/153)	61.0% (100/164)	0.5196	0.00001

**Table 4b. Primary Outcome for Oxygen Saturation Arm**

Though a trend in favor of treatment A seems to have emerged in the ventilation arm for survival free of BPD at 36 weeks postmenstrual age, it does not approach the sequential bounds for interim monitoring. No other trends are discernible at this point.

### Secondary Outcomes

Table 5 shows selected secondary outcomes, by treatment. Because some of the secondary outcomes are assessed at 18-22 months adjusted age, a threshold that has been reached by very few subjects at this point, only outcomes that are known shortly after birth are included. They are:

- A decreased incidence of surfactant treatment in the delivery room or NICU
- A decreased incidence of air leaks
- A decrease in the percentage of infants who receive postnatal steroids to prevent or treat BPD
- A decreased incidence of BPD at 36 weeks using the physiologic definition of BPD
- A decreased incidence of ROP
- A decreased incidence of necrotizing enterocolitis (NEC)
- A decreased incidence of IVH and severe IVH (grade 3 or 4)
- A decreased incidence of periventricular leukomalacia (PVL)

Characteristic	Ventilation Arm		Oxygen Saturation Arm	
	Treatment A (N=258)	Treatment B (N=233)	Treatment A (N=239)	Treatment B (N=252)
Surfactant in the DR or NICU	164 ( 94.3%)	224 ( 98.2%)	192 ( 95.5%)	196 ( 97.5%)
Air leak at any time	22 ( 10.8%)	6 ( 3.2%)	11 ( 5.7%)	17 ( 8.6%)
Postnatal steroids for BPD	15 ( 7.4%)	25 ( 13.4%)	21 ( 10.9%)	19 ( 9.7%)
BPD	58 ( 33.7%)	65 ( 43.9%)	72 ( 43.4%)	51 ( 33.1%)
ROP in one or both eyes	21 ( 16.4%)	24 ( 21.2%)	28 ( 22.8%)	17 ( 14.4%)
NEC	17 ( 8.5%)	20 ( 10.8%)	19 ( 10.0%)	18 ( 9.2%)
Any IVH	68 ( 32.9%)	45 ( 24.1%)	55 ( 28.2%)	58 ( 29.1%)
IVH grade 3 or 4	31 ( 15.0%)	18 ( 9.6%)	21 ( 10.8%)	28 ( 14.1%)
PVL	9 ( 4.4%)	9 ( 4.9%)	9 ( 4.7%)	9 ( 4.6%)

**Table 5. Secondary Outcomes for Ventilation and Oxygen Saturation Arms**

Aside from certain expected differences because of the nature of the interventions, the ventilation arm has suggestive trends in favor of treatment A for steroids and BPD, and for treatment B for any IVH. In the oxygen saturation arm there are trends in favor of treatment B for BPD and ROP. However, none of these approach statistical significance at this point.

### Death and other Adverse Events

Safety monitoring for death and other severe adverse events in the SUPPORT trial is done using Pocock bounds. To adjust for the increased Type-I error rate associated with sequential testing, Pocock bounds are calculated using the Lan-DeMets spending function. The Pocock bounds provide appropriate criteria for judging the significance of differences between treatments at each interim analysis. The p-values associated with the bounds are two-sided, with an overall cumulative significance of 0.025 to account for the fact that we are testing for differences within each of the two treatment factors.

**Deaths** As of January 24, 2007, there were 400 SUPPORT patients who had either died or who had survived to discharge, transfer, or 120 days. Information on deaths is collected from both the SUPPORT trial forms (for the first 14 days of life) and the GDB forms (beyond 14 days of life). Within this group, Table 6 below shows the percent of infants in each treatment group who died during the course of the SUPPORT Trial. The table also displays p-values for statistical tests comparing the percent of infants who died in each level of the two treatment factors. The test for the oxygen saturation arm is adjusted for familial clustering due to multiple births and for stratification by center and GA group. Due to constraints on model convergence, the test for the effect of the ventilation treatment is only adjusted for the effect of multiple births, and not for the effect of center. Pocock bounds were calculated for planned analysis at 19% (January 2006), 30% (January 2007), 50%, 75%, and 100% of enrollment. The p-value associated with the Pocock bound for the significance of this interim analysis is 0.0033, which is not reached by either arm here, though there is some suggestion of a trend in the oxygen saturation arm.

Ventilation Arm				Oxygen Saturation Arm			
Treatment A (N=207)	Treatment B (N=193)	Test p-value	Pocock bound p-value	Treatment A (N=196)	Treatment B (N=204)	Test p-value	Pocock bound p-value
39 ( 19%)	42 (22%)	0.4473	0.0033	33 (17%)	48 ( 24%)	0.0694	0.0033

**Table 6. Deaths, by Treatment**

Gestational age was a significant predictor of death in the tests presented in Table 6 (p=0.0004 and p=0.0003, respectively). Table 7 below accordingly presents the above mortality information by gestational age strata.

Gestational Age Stratum	Ventilation Arm		Oxygen Saturation Arm	
	Treatment A (N=207)	Treatment B (N=193)	Treatment A (N=196)	Treatment B (N=204)
24-25 weeks	21 ( 24%)	27 (35%)	22 (26%)	26 ( 33%)
26-27* weeks	18 ( 15%)	15 (13%)	11 (10%)	22 ( 18%)

**Table 7. Deaths, by Treatment and GA strata**

\*Includes one infant with a GA of 28 weeks

**All Adverse Events** As of January 24, 2007, there were 462 infants enrolled in the SUPPORT Trial who had either reached 14 days of life or experienced an adverse event (AE), including death. AEs occurring during the first 14 days of life are recorded on a designated SUPPORT form. Additional events occurring afterwards are identified using other SUPPORT and Generic Database (GDB) forms. Specific AEs monitored for the SUPPORT Trial are listed below.

- Air leak
- Need for chest compressions or epinephrine in the delivery room or NICU
- Severe IVH (Grades 3-4, Papile)
- Pulmonary hemorrhage
- Nasal breakdown requiring discontinuation of nasal prongs
- Death

Table 8 below shows the percent of infants in each treatment group who had experienced an AE, as well as p-values for statistical tests comparing the percent of infants experiencing AEs in each level of the two treatment factors. The test for the oxygen saturation arm is adjusted for familial clustering due to multiple births and for stratification by center and GA group. Due to constraints on model convergence, the test for the effect of the ventilation treatment is only adjusted for the effect of multiple births, and not for center. Pocock bounds were calculated for planned analysis at 19% (January 2006), 35% (January 2007), 50%, 75%, and 100% of enrollment. The p-value associated with the Pocock bound for the significance of this interim analysis is 0.0047. Neither the test for the ventilation arm nor the test for the oxygen saturation arm reaches that level of significance.

Ventilation Arm				Oxygen Saturation Arm			
Treatment A (N=250)	Treatment B (N=212)	Test p-value	Pocock bound p-value	Treatment A (N=229)	Treatment B (N=233)	Test p-value	Pocock bound p-value
98 (39%)	73 (34%)	0.3738	0.0047	84 (37%)	87 (37%)	0.7324	0.0047

**Table 8. All AEs, by Treatment**

Table 9 below shows the number of each type of AE, by treatment group combinations. Note that, if a patient experienced more than one AE, each event is included in Table 9.

Adverse event type	Ventilation A, Oxygen saturation A	Ventilation A, Oxygen saturation B	Ventilation B, Oxygen saturation A	Ventilation B, Oxygen saturation B	Total
	A	B	A	B	
Air leak	10	12	1	5	28
Chest compressions or drugs in delivery room	6	4	10	7	27
Severe IVH (grades III-IV)	14	17	7	11	49
Pulmonary hemorrhage	6	8	4	5	23
Nasal breakdown	6	7	2	0	15
Death	16	23	17	25	81
Other	7	7	6	3	23
<b>Total</b>	<b>65</b>	<b>78</b>	<b>47</b>	<b>56</b>	<b>246</b>

**Table 9. Type of AE, by Treatment**

Historic AE Rates in the Neonatal Research Network

In order to provide comparable prevalence rates for the AEs experienced by this severely ill population, Table 10 below displays rates of AEs among infants born at Neonatal Research Network (NRN) centers between 2002 and 2004, and Table 11 thereafter shows the same for the SUPPORT trial. Table 10 shows the percent of infants experiencing AEs for all centers combined, as well as ranges across the individual centers. These tables show that death and overall AE rates in the SUPPORT Trial appear to be comparable to, and fall within the plausible ranges of such events in the NRN population.

Type of adverse event	All infants: 24-27 weeks		24-25 weeks		26-27 weeks	
	Percent	Range	Percent	Range	Percent	Range
Chest compressions/epinephrine	11.2	3.2 - 31.8	13.9	2.8 - 42.1	9.1	3.2 - 23.2
Air leak	8.2	1.9 - 16.1	11.0	2.9 - 20.6	6.1	1.1 - 13.0
Pulmonary hemorrhage	9.0	3.4 - 29.3	12.3	2.5 - 32.0	6.5	1.1 - 26.9
Severe IVH (grades III-IV)	16.9	8.4 - 26.4	24.2	14.0 - 38.9	11.7	2.3 - 20.8
Death	23.1	12.1 - 46.4	35.5	19.9 - 66.1	13.3	4.4 - 26.8
Any AE listed above	42.9	23.3 - 66.1	57.4	42.0 - 78.6	31.5	20.8 - 53.6

**Table 10. Adverse Event Rates in the NRN: Births in 2002-2004**

Type of adverse event	All Infants	24-25 wks	26-27 wks*
Chest compressions/epinephrine in DR	5.8	9.0	3.6
Air leak	6.2	7.2	5.6
Pulmonary hemorrhage	5.1	7.2	3.7
Severe IVH (grades III-IV)	12.4	17.2	9.3
Death	20.3	29.3	14.0
Any AE	37.0	47.9	29.6

**Table 11. Adverse Event Rates in the SUPPORT Trial**

Note: Table contains data on some infants still at risk for adverse event

\*The 26-27 week GA group includes one infant with a GA of 28 weeks

### Protocol Deviations

Table 12 summarizes protocol deviations reported by Network centers through January 24, 2007. A total of 108 protocol violations were reported during this period. Most of these were related to failure to use study oximeter as required or use of high flow nasal cannula within first 14 days of life. Except for certain expected differences because of the nature of the interventions, distribution of the other categories of violation do not appear substantially skewed between the two groups in either arm.

Type of protocol deviation	Ventilation Arm		Oxygen Saturation Arm	
	Treatment A	Treatment B	Treatment A	Treatment B
Assigned arm not implemented within required amount of time	4	10	7	7
Infant placed on study oximeter for incorrect treatment	6	2	6	2
Failure to use study oximeter at times required by protocol	19	7	14	12
Non-study oximeter used at same time as study oximeter	3	1	3	1
NSIMV initiated in infant not previously intubated	4	0	1	3
Extubation (excluding unplanned) for other than study criteria	0	4	2	2
Failure to extubate infant if all criteria met	4	2	5	1
High flow nasal cannula used within first 14 days of life	12	6	7	11
Infant received postnatal steroids in first 21 days of life	4	6	5	5
Head ultrasound done outside 4-21 day window	1	0	0	1
Consent errors	0	1	1	0
Randomization errors	4	5	2	7
Other	3	0	1	2
<b>Total</b>	<b>64</b>	<b>44</b>	<b>54</b>	<b>54</b>

**Table 12. SUPPORT Protocol Deviations**

- 
- 1 O'Brien, P. C. and Fleming, T. R. (1979), A multiple testing procedure for clinical trials. *Biometrics*, 35, 549-556.
  - 2 Reboussin, D. M., DeMets, D. L., Kim, K. and Lan, K. K. G. (2000), Computations for group sequential boundaries using the Lan-DeMets spending function method. *Controlled Clinical Trials*, 21, 190-207.
  - 3 Pocock, S. J. (1977), Group sequential methods in the design and analysis of clinical trials. *Biometrika*, 64, 191-199.

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "adas@rti.org"; "nfiner@ucsd.edu"; "wcarlo@peds.uab.edu"; "mgantz@rti.org"  
**Cc:** "wrich@ucsd.edu"  
**Subject:** Re: new NEJM question  
**Date:** Thursday, April 15, 2010 6:01:43 PM

---

The MOP changes were in a technical memo re: the ROP outcomes

----- Original Message -----

**From:** Das, Abhik <adas@rti.org>  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu <nfiner@ucsd.edu>; wcarlo@peds.uab.edu <wcarlo@peds.uab.edu>; Gantz, Marie <mgantz@rti.org>  
**Cc:** wrich@ucsd.edu <wrich@ucsd.edu>  
**Sent:** Thu Apr 15 17:57:33 2010  
**Subject:** RE: new NEJM question

We used any death for the ROP composite because using ROP or death at 36 weeks did not make sense given that definitive ROP could not be determined until much after that time.

Thanks  
Abhik

Abhik Das  
Senior Research Statistician  
RTI International

-----Original Message-----

**From:** Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]  
**Sent:** Thursday, April 15, 2010 05:45 PM Eastern Standard Time  
**To:** 'nfiner@ucsd.edu'; 'wcarlo@peds.uab.edu'; Gantz, Marie  
**Cc:** 'wrich@ucsd.edu'; Das, Abhik  
**Subject:** Re: new NEJM question

No

The ROP was tracked later due to immature rop or active disease present at 36 weeks.

We need to know how marie classified "death" (by which age).

---

**From:** Finer, Neil <nfiner@ucsd.edu>  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; 'wcarlo@peds.uab.edu' <wcarlo@peds.uab.edu>; 'mgantz@rti.org' <mgantz@rti.org>  
**Cc:** Rich, Wade <wrich@ucsd.edu>; 'adas@rti.org' <adas@rti.org>  
**Sent:** Thu Apr 15 17:45:51 2010  
**Subject:** RE: new NEJM question

Rose

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Would this not have had to be in the protocol or some official document?

Thanks  
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Neil N. Finer, M.D.  
Professor of Pediatrics  
Director, Division of Neonatology  
Department of Pediatrics

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UC San Diego Medical Center  
402 Dickinson Street, MPF 1-140  
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Telephone: 619-543-3759  
Facsimile: 619-543-3812

From: Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]  
Sent: Thursday, April 15, 2010 2:34 PM  
To: 'wcarlo@peds.uab.edu'; 'mgantz@rti.org'; Finer, Neil  
Cc: Rich, Wade; 'adas@rti.org'  
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This could possibly be in SC meeting minutes?? Or tech memo dated oct 26, 2007 with the 55 week outcomes - though this is a bit of a stretch.

Marie/Abhik - is death for the sat study death by 36 weeks or hosp discharge

---

From: Wally Carlo, M.D. <WCarlo@peds.uab.edu>  
To: Gantz, Marie <mgantz@rti.org>; Finer, Neil <nfiner@ucsd.edu>; Higgins, Rosemary (NIH/NICHD) [E]  
Cc: Rich, Wade <wrich@ucsd.edu>; Das, Abhik <adas@rti.org>  
Sent: Thu Apr 15 16:15:11 2010  
Subject: new NEJM question  
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Do you know if we do and if so, can you send it to me?

Wally

---

From: Gantz, Marie [<mailto:mgantz@rti.org>]  
Sent: Tue 4/13/2010 8:58 AM  
To: Wally Carlo, M.D.; Finer, Neil; Rosemary Higgins  
Cc: Rich, Wade; Das, Abhik  
Subject: RE: O2 sat talk final 4/12/10  
Wally,

On slide 10, the statement "severe retinopathy was defined as threshold retinopathy if any of the following were present..." is somewhat misleading. The first two sub-bullets define threshold ROP. The third, surgery, is not part of the definition of threshold ROP, but is part of the definition of severe ROP.

Also, if you are planning to include the CONSORT figure, please note my corrections in the previous version of the presentation. The errors remain in the current version.

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: Monday, April 12, 2010 4:37 PM  
To: Finer, Neil; Rosemary Higgins  
Cc: Rich, Wade; Gantz, Marie; Das, Abhik  
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Wally

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From: Finer, Neil [mailto:nfiner@ucsd.edu]  
Sent: Mon 4/12/2010 2:41 PM  
To: Rosemary Higgins; Wally Carlo, M.D.  
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Here is the final SUPPORT Presentation  
Let me know if you see any problems  
Neil

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**To:** "adas@rti.org"; "wcarlo@peds.uab.edu"; "mgantz@rti.org"; "nfiner@ucsd.edu"  
**Cc:** "wrich@ucsd.edu"  
**Subject:** Re: new NEJM question  
**Date:** Thursday, April 15, 2010 5:57:24 PM

---

It is not in the sc meeting minutes that i could find

----- Original Message -----

**From:** Das, Abhik <adas@rti.org>  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; wcarlo@peds.uab.edu <wcarlo@peds.uab.edu>; Gantz, Marie <mgantz@rti.org>; nfiner@ucsd.edu <nfiner@ucsd.edu>  
**Cc:** wrich@ucsd.edu <wrich@ucsd.edu>  
**Sent:** Thu Apr 15 17:53:59 2010  
**Subject:** RE: new NEJM question

We are searching through all possible documentation. We did discuss this in the subcommittee before our first planned 25% DSMC look in early 2007 because Marie wanted this nailed down before she could do the efficacy analysis for them.

Thanks  
Abhik

Abhik Das  
Senior Research Statistician  
RTI International

-----Original Message-----

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**Sent:** Thursday, April 15, 2010 05:34 PM Eastern Standard Time  
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**Subject:** Re: new NEJM question

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Marie/Abhik - is death for the sat study death by 36 weeks or hosp discharge

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Do you know if we do and if so, can you send it to me?

Wally

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Sent: Tue 4/13/2010 8:58 AM  
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---

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]  
Sent: Monday, April 12, 2010 4:37 PM  
To: Finer, Neil; Rosemary Higgins  
Cc: Rich, Wade; Gantz, Marie; Das, Abhik  
Subject: O2 sat talk final 4/12/10

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## **Higgins, Rosemary (NIH/NICHD) [E]**

---

**From:** Finer, Neil <nfiner@ucsd.edu>  
**Sent:** Thursday, April 15, 2010 5:57 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; 'wcarlo@peds.uab.edu'; 'mgantz@rti.org'  
**Cc:** Rich, Wade; 'adas@rti.org'  
**Subject:** RE: new NEJM question

Interestingly enough

The Tables on The Protocol state the secondary outcomes as death at 36 weeks and Death before discharge  
Can we use this as evidence  
Neil

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**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Thursday, April 15, 2010 2:46 PM  
**To:** Finer, Neil; 'wcarlo@peds.uab.edu'; 'mgantz@rti.org'  
**Cc:** Rich, Wade; 'adas@rti.org'  
**Subject:** Re: new NEJM question

No  
The ROP was tracked later due to immature rop or active disease present at 36 weeks.

We need to know how marie classified "death" (by which age).

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**From:** Finer, Neil <nfiner@ucsd.edu>  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; 'wcarlo@peds.uab.edu' <wcarlo@peds.uab.edu>; 'mgantz@rti.org' <mgantz@rti.org>  
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**To:** Gantz, Marie <mgantz@rti.org>; Finer, Neil <finer@ucsd.edu>; Higgins, Rosemary (NIH/NICHD) [E]  
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## Higgins, Rosemary (NIH/NICHD) [E]

---

**From:** Finer, Neil <nfiner@ucsd.edu>  
**Sent:** Thursday, April 15, 2010 5:26 PM  
**To:** Wally Carlo, M.D.; Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Rich, Wade; Das, Abhik  
**Subject:** RE: new NEJM question

I have no recollection of doing this  
Neil

Neil N. Finer, M.D.  
Professor of Pediatrics  
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**From:** Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]  
**Sent:** Thursday, April 15, 2010 1:15 PM  
**To:** Gantz, Marie; Finer, Neil; Rosemary Higgins  
**Cc:** Rich, Wade; Das, Abhik  
**Subject:** new NEJM question

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**From:** Solomon, Caren, M.D.  
**To:** "Wally Carlo, M.D."  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]; Abel, Brendan  
**Subject:** RE: NEJM more questions  
**Date:** Thursday, April 15, 2010 10:28:33 AM

---

Thanks for your continued attention to these questions. This will be helpful in making final changes. However, what we were actually requesting was the original statistical analysis plan so we fully understand what was prespecified. THANKS,

Caren

-----Original Message-----

**From:** Wally Carlo, M.D. [<mailto:WCarlo@peds.uab.edu>]  
**Sent:** Thursday, April 15, 2010 10:22 AM  
**To:** Solomon, Caren, M.D.  
**Cc:** M.D.Wally Carlo; Rose Higgins  
**Subject:** FW: NEJM more questions

Caren:

Enclosed is the text suggested by our statistician. I am on my way to Greece so will not be available after 4 pm today but will have email access tomorrow.

wally

Sent from my Windows Mobile phone

This email message is a private communication. The information transmitted, including attachments, is intended only for the person or entity to which it is addressed and may contain confidential, privileged, and/or proprietary material. Any review, duplication, retransmission, distribution, or other use of, or taking of any action in reliance upon, this information by persons or entities other than the intended recipient is unauthorized by the sender and is prohibited. If you have received this message in error, please contact the sender immediately by return email and delete the original message from all computer systems. Thank you.

**From:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**To:** [Archer, Stephanie \(NIH/NICHD\) \[E\]](#)  
**Subject:** Fw: SUPPORT\_NEUROcohort\_StateOfArtPAS.ppt  
**Date:** Wednesday, April 14, 2010 2:09:19 PM

---

---

**From:** Kristi Watterberg <KWatterberg@salud.unm.edu>  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Wed Apr 14 14:07:32 2010  
**Subject:** Re: SUPPORT\_NEUROcohort\_StateOfArtPAS.ppt

yes - Kristi

>>> "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> 4/12/2010 8:55 AM >>>

Hi

Susan Hintz is presenting in a Neuroimaging for Prognosis in Preterms: Ultrasound and MRI State of the Art Plenary (5/4) at PAS and is requesting permission from the steering committee to use the attached slides in her presentation. This is a nice venue to lay the groundwork for the school age outcome study from SUPPORT. **Please send me a YES/NO vote by April 15.**

**THANKS**  
**ROSE**

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "srhintz@stanford.edu"  
**Subject:** Re: Fwd: Extended SUPPORT follow up question  
**Date:** Wednesday, April 14, 2010 1:53:52 PM

---

This is the first i have heard of this - i am happy to join on on call if needed. This protocol was approved quite awhile ago

Rose

---

**From:** Susan Hintz <srhintz@stanford.edu>  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Wed Apr 14 13:38:30 2010  
**Subject:** Fwd: Extended SUPPORT follow up question

Hi Rose

Below is an email stream from the Houston folks about a follow-up study they are doing after the Nehal Parikh volumetric MRI study, and questions they have about how we chose the Extended SUPPORT NEURO follow-up battery. I am trying to be nice, but firm, that we have chosen our battery of tests. I am hoping you agree that at this point we do not have much wiggle room to make major changes - correct? I did not get much detail from them yet about the specific areas of conflict between the SUPPORT and their proposed battery, but just giving you a heads up.

Susan

Begin forwarded message:

**From:** Susan Hintz <srhintz@stanford.edu>  
**Date:** April 14, 2010 10:22:27 AM PDT  
**To:** "Jimenez, Margarita" <Margarita.Jimenez@uth.tmc.edu>  
**Cc:** "Evans, Patricia W" <Patricia.W.Evans@uth.tmc.edu>  
**Subject:** Re: Extended SUPPORT follow up question

Hi Maggie and Patricia

It is great to hear from you and to hear about the extended VMRI follow-up. That sounds great!

Can you let me know a bit more about the differences - for instance, the battery you are putting together vs. SUPPORT? We tried to choose each of the tests and questionnaires after a lot of consideration and discussion - but of course nothing is perfect, and there are downsides to every assessment. I realize there are many different options for a battery at early school age, that each area we are trying to assess has *many* different possible instruments, and of course we are all concerned about the time in clinic issues! Our multidisciplinary subcommittee that made the final recommendations for the visit battery included Gerry Taylor, Maureen Hack, Betty Vohr, Jane Hammond, Seetha Shankaran, and others; we also had input from the gold standard psychologists in the Network, and also from

international colleagues including Lex Doyle and Peter Anderson, and investigators in the EPICure group. For social-behavioral issues and questionnaires, I also got input from colleagues in developmental psychology here at Stanford including Heidi Feldman. Before the protocol was finalized, we sent also sent it to all the follow-up PI's for comments and input.

I am happy to discuss with you anytime, and I am sorry if the SUPPORT Extended follow-up is causing challenges for the VMRI study (which I think is a really important study!) I am sure we can find a way to work around any major issues. I am on clinical duties right now, and also trying to finish preparations for PAS talks and presentations - so maybe we can start the process by email?

Thanks again, and looking forward to hearing from you

Susan

On Apr 14, 2010, at 9:53 AM, Jimenez, Margarita wrote:

Dear Susan,

It was nice to have met you this past October at the NRN meeting. Patricia Evans and I are working on a long term follow up component to a VMRI study started by Nehal Parikh here at UT Houston. We plan to test preschool and school age children in the areas of cognitive, social, motor, verbal skills etc (similar to other long term follow up studies in the network). Some of our patients are in both the VMRI cohort and the Extended SUPPORT cohort. As such, we have tried to select our assessments based partially on the SUPPORT extended follow up trial. We are working with an independent group of school psychologists to select what we believe to be a very solid battery of testing (best answers the questions while not being an unfeasible amount of time for the families). Some of the tests are different from what is planned for Extended SUPPORT. As we are still trying to finalize our selection of tests, would it be possible to discuss with you some of the thoughts behind choosing the particular tests used for Extended SUPPORT? If so, please let us know some times that would be convenient for you.

Thank you in advance,  
Maggie Jimenez and Patricia Evans.

---

*Maggie Jimenez MD MPH FAAP  
Assistant Professor of Pediatrics, Division of Neonatology  
University of Texas Health Science Center at Houston  
Office: MSB 3.218, 713-500-6331*

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*E-mail: [margarita.jimenez@uth.tmc.edu](mailto:margarita.jimenez@uth.tmc.edu)*

**From:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**To:** [Archer, Stephanie \(NIH/NICHD\) \[E\]](#)  
**Subject:** Fw: SUPPORT\_NEUROcohort\_StateOfArtPAS.ppt  
**Date:** Wednesday, April 14, 2010 11:04:08 AM

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----- Original Message -----

From: Kurt Schibler <Kurt.Schibler@cchmc.org>  
To: Higgins, Rosemary (NIH/NICHD) [E]  
Sent: Wed Apr 14 10:52:51 2010  
Subject: Re: SUPPORT\_NEUROcohort\_StateOfArtPAS.ppt

Hi Rose,  
Yes,  
Kurt

>>> "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> 4/12/2010 10:55 AM >>>

Hi

Susan Hintz is presenting in a Neuroimaging for Prognosis in Preterms: Ultrasound and MRI State of the Art Plenary (5/4) at PAS and is requesting permission from the steering committee to use the attached slides in her presentation. This is a nice venue to lay the groundwork for the school age outcome study from SUPPORT. Please send me a YES/NO vote by April 15.

THANKS  
ROSE

**From:** Archer, Stephanie (NIH/NICHD) [E]  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: SUPPORT\_NEUROcohort\_StateOfArtPAS.ppt  
**Date:** Wednesday, April 14, 2010 9:04:01 AM

---

We have 13 Yes's for this already.

-----Original Message-----

From: Higgins, Rosemary (NIH/NICHD) [E]  
Sent: Wednesday, April 14, 2010 5:54 AM  
To: Archer, Stephanie (NIH/NICHD) [E]  
Subject: Fw: SUPPORT\_NEUROcohort\_StateOfArtPAS.ppt

----- Original Message -----

From: Pablo Sanchez <Pablo.Sanchez@UTSouthwestern.edu>  
To: Higgins, Rosemary (NIH/NICHD) [E]  
Sent: Tue Apr 13 23:34:13 2010  
Subject: Re: SUPPORT\_NEUROcohort\_StateOfArtPAS.ppt

yes--pablo

>>> "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> 4/12/10 9:55 AM >>>

Hi

Susan Hintz is presenting in a Neuroimaging for Prognosis in Preterms: Ultrasound and MRI State of the Art Plenary (5/4) at PAS and is requesting permission from the steering committee to use the attached slides in her presentation. This is a nice venue to lay the groundwork for the school age outcome study from SUPPORT. Please send me a YES/NO vote by April 15.

THANKS  
ROSE



**From:** Susan Hintz  
**To:** Shankaran, Seetha  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** Re: SUPPORT\_NEUROcohort\_StateOfArtPAS.ppt  
**Date:** Tuesday, April 13, 2010 7:04:14 PM

---

Thanks Seetha. Yes, I have the Horsch article (online ahead of print), and refer to the results in the talk.

See you soon

Susan

On Apr 13, 2010, at 12:51 PM, Shankaran, Seetha wrote:

Rose  
Ok with me

Susan  
Please see Horsh et al: Cranial Ultrasound and MRI at term age in extremely preterm infants BMJ—downloaded today 77 infants  
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](mailto:sshankar@med.wayne.edu)

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]  
**Sent:** Monday, April 12, 2010 10:56 AM  
**To:** (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Matthew Bizzarro; Michelle Walsh; Mickey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOLdberg; Shankaran, Seetha; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; 'kzaterka@rti.org'; Gantz, Marie; Neil Finer; 'Susan Hintz'  
**Subject:** SUPPORT\_NEUROcohort\_StateOfArtPAS.ppt

Hi

Susan Hintz is presenting in a Neuroimaging for Prognosis in Preterms: Ultrasound and MRI State of the Art Plenary (5/4) at PAS and is requesting permission from the steering committee to use the attached

slides in her presentation. This is a nice venue to lay the groundwork for the school age outcome study from SUPPORT. **Please send me a YES/NO vote by April 15.**

**THANKS  
ROSE**

## **Higgins, Rosemary (NIH/NICHD) [E]**

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**From:** Finer, Neil <nfiner@ucsd.edu>  
**Sent:** Tuesday, April 13, 2010 3:57 PM  
**To:** Walsh, Michele; Higgins, Rosemary (NIH/NICHD) [E]; Carlo Waldemar (E-mail)  
**Subject:** RE: Confidential PAS PResentation Finer SUPPORT 2010-04-06.ppt  
**Attachments:** SUPPORT Final rev PAS-ATS April 13.ppt

Thanks Michele  
Have a quick look  
I think I made all the fixes  
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:** Walsh, Michele [mailto:Michele.Walsh@UHhospitals.org]  
**Sent:** Tuesday, April 13, 2010 8:03 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; Carlo Waldemar (E-mail)  
**Subject:** RE: Confidential PAS PResentation Finer SUPPORT 2010-04-06.ppt

Sorry hit send accidently: continuing

5. Demographics- can reduce the size of some font to reduce clutter on slide  
(eg mean +- SD)
6. Slide 20- would just put % instead of N to decrease clutter
7. Slide 21- can you put in table like slide 20?
8. Slide 22: Why is there an X in the box next to reduced death for CPAP?  
Makes it seem like that is a bad thing.
9. Slide 23: Font goes off the bottom. Does this need to be 2 slides? Or could reduce to phrases to get all on one slide.

Michele Walsh  
beeper (b) (6)  
Ph 216 844 3759

---

**From:** Walsh, Michele  
**Sent:** Tuesday, April 13, 2010 10:56 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Neil Finer  
**Subject:** RE: Confidential PAS PResentation Finer SUPPORT 2010-04-06.ppt

HI: Few comments

1. Too many background slides- do you need the detail on the COIN trial?
2. Can you reduce the text on all the slides to make shorter- they are a bit overwhelming.
3. Intervention slides: could use one of your slides from earlier presentation with approach placed in a table. Would be more clear.
4. Pt flow: suggest not put the oxygen intervention, just put the cpap/surf intervention to reduce the complexity of the slide... not needed for this 10 min presentation. Could save the big one for questions.

Michele Walsh

beeper (b) (6)

Ph 216 844 3759

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]

**Sent:** Tuesday, April 06, 2010 12:19 PM

**To:** (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Matthew Bizzarro; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOLDBERG; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa

**Cc:** Finer, Neil; Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Cunningham, Meg; Huitema, Carolyn Petrie

**Subject:** Confidential PAS PResentation Finer SUPPORT 2010-04-06.ppt

**Importance:** High

Hi,

Attached is Neil's presentation for PAS. If you have any comments, please send them to Neil.

Please keep this information confidential. **We are not to discuss the fact that the papers have been reviewed or accepted by NEJM.** PI's - please insure that all of your staff with the confidential knowledge regarding the SUPPORT papers are aware of the NEJM rules!!

In addition, since the papers are not yet published in NEJM, we need to respect their embargo policy. This means that we are requested to follow the guidelines at <http://authors.nejm.org/Help/Embargo.asp>.

Specifically, the guidelines state:

- Please do not discuss the fact that the research has been submitted or accepted for publication in the *New England Journal of Medicine*.
- Please do not distribute any copies of the manuscript, tables, or figures. (It is acceptable to use the materials in a presentation, but they should not be distributed.)

Meeting organizers may promote an author's presentation in a press release, plan a press conference, publish the abstract in a meeting proceedings, and/or post the presentation on their Web site. We ask that authors, their institutions, and other organizations sponsoring the research not do any further promotion of the presentation

Visit us at [www.UHhospitals.org](http://www.UHhospitals.org).

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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:** Kennedy, Kathleen A  
**To:** Phelps, Dale; Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: ROP Natural History Observational Study  
**Date:** Tuesday, April 13, 2010 2:59:17 PM

---

More great suggestions. I'll working on incorporating the comments from both of you into a "final" document that Rose can forward to the subcommittee. Thank you both for your work on 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  
UT-Houston Medical School  
6431 Fannin, Suite 2.106  
Houston, TX 77030  
713 500-6708

-----Original Message-----

From: Phelps, Dale [mailto:Dale\_Phelps@URMC.Rochester.edu]  
Sent: Tuesday, April 13, 2010 1:51 PM  
To: Kennedy, Kathleen A; 'higginsr@mail.nih.gov'  
Subject: Re: ROP Natural History Observational Study

Hi Kathleen and Rose,

I've reviewed the abstract for the subcommittee. You've done a nice job on this. It is a testing of the Reynolds' paper on onset and resolution in a more current dataset. I agree with all of your "cautions". I would also add that SUPPORT had no upper limit on BW, but CRYO and LIGHT cut them off at 1250g, irrespective of gestation.

On your page 2, you are correct about the "55 weeks". That is NOT "1 year". More like 6 months from birth (55-25 weeks = 25 weeks = "6" months).

We have to start with a flow sheet to be sure we know who to tell the statisticians to include in which tables. I have found this to be invaluable. Whenever it get skipped, we always end up going back to making one part way through, and then having to repeat all the analyses.

I would consider for your Baseline Characteristics Table, subgroups among the infants with known outcomes: BW, GA Gender, etc. For

Never ROP  
ROP, never "threshold"  
"Threshold" ROP

Or alternatively a separate table for these. Include M  $\pm$ sd, ranges

Something to watch out for is falsely increasing the "age" for knowing a regressed outcome.

Example: last examination showed ROP stage 1 in Zone III at 38 weeks PMA -- first time in Zone III. The infant was lost and not seen again until a 6 month follow up visit at 50 weeks PMA where the ophthalmologist nabbed him and found a good retinal outcome (whew!)

By our study definition, we did not declare him a good outcome until 50 weeks PMA. However, the ROP was certainly regressed and the retinae fully vascularized well before that.

Because the protocol did not insist on every two week exams, there are some very large windows at the end for good outcome babies.

Or...

Maybe we just plot the distribution of those that get treated, as you suggested in replicating the figure that shows accumulated event rate by PMA (and/or postnatal age).

Finally:

My great interest in this analysis was to learn how many kids go to treatment after discharge home. or or after transfer.

We should probably do this analysis at the same time, since the thought processes are similar. However, if it does not fit in, I would work on a separate paper. If it comes out too lean for a separate paper, I would be grateful to be able to fold it in here.

Your thoughts?

Dale

----- Original Message -----

From: Kennedy, Kathleen A <Kathleen.A.Kennedy@uth.tmc.edu>  
To: Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov>  
Cc: Phelps, Dale  
Sent: Thu Apr 08 07:29:16 2010  
Subject: RE: ROP Natural History Observational Study

Thanks for your comments. All good ones. They will add more meat to the paper. I'll incorporate them when I get a response from Dale and then we should be ready to submit to the subcommittee.

---

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]  
Sent: Wednesday, April 07, 2010 3:31 PM  
To: Kennedy, Kathleen A  
Cc: Phelps, Dale  
Subject: RE: ROP Natural History Observational Study

Kathleen

I made a stab at a couple of tables. I also think we should create graphs of gestational age on the x-axis and "most severe" exam and "Timing of intervention" on the y-axis to see if the course of ROP (especially severe ROP) has changed since the CRYO-ROP study.

We may also want to look at progression of disease over time (Do the more immature children, i.e. 24 and 25 week infants still get the worst disease between 36-36 weeks post concept age?). We can look at presence of plus disease and zone 1 exams/disease to see if these factors are still predictive of the most serious disease.

Perhaps this is too much, but we have nice exam data on a very large number of children in a contemporary cohort.

Rose

---

From: Kennedy, Kathleen A [mailto:Kathleen.A.Kennedy@uth.tmc.edu]  
Sent: Tuesday, April 06, 2010 12:22 PM  
To: Higgins, Rosemary (NIH/NICHD) [E]  
Cc: Phelps, Dale  
Subject: RE: ROP Natural History Observational Study

I've updated this based on the information I have. I think it's almost ready to go to the SUPPORT subcommittee.

There are a couple of questions in red about the details of the eye exams. There wasn't complete agreement between what's in the manuscript and the manual, but I think Dale probably knows what really happened. I'd really appreciate input from you and Dale on this. I'm not sure we need to include ophthalmologists if the two of you are involved.

Kathleen A. Kennedy, MD, MPH  
Richard W. Mithoff Professor of Pediatrics

Director, Division of Neonatal-Perinatal Medicine  
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, April 05, 2010 8:42 AM  
To: Kennedy, Kathleen A  
Subject: RE: ROP Natural History Observational Study

Kathleen

1. – Submit to subcommittee (send it to me and I can send it out) – Wally is the Vice chair of SUPPORT so will have significant input.
2. The papers are accepted, so please send us the proposal
3. Generally subcommittee members are co-authors on secondary studies. You may include anyone who can add to the science of the paper. I am happy to be included in this one as I did some ROP work prior to joining the network. Dale would likely be an asset and can be included.

Let me know if you have other questions

Rose

---

From: Kennedy, Kathleen A [mailto:Kathleen.A.Kennedy@uth.tmc.edu]  
Sent: Thursday, April 01, 2010 6:04 PM  
To: Higgins, Rosemary (NIH/NICHD) [E]  
Subject: ROP Natural History Observational Study

I'm trying to revise this proposal to turn it into something that can be submitted as a secondary study. I have a few procedural questions (not entirely clear to me from the Network policy).

- 1) It looks like this needs to be submitted to the Subcommittee chairman. This proposal is logically a secondary study of the Oximetry arm of the SUPPORT study (for which we did the careful ROP assessments). Do I send this to Neil (the official subcommittee chairman) or Wally (the lead author on the Oximetry study arm)?
- 2) Do I really need to wait for 3 months after the papers are submitted to give subcommittee members the first shot at this? That doesn't seem to be how Ed Bell understands it.
- 3) Dale is really the only other person who's expressed some interest after I brought it up at a meeting. I haven't contacted any of the ophthalmologists yet. Are there any restrictions on who can be included on the writing/planning group for the proposal? None of us is on the subcommittee and Dale isn't even in the Network anymore. Would everyone in this group be included as an author?

Kathleen A. Kennedy, MD, MPH  
Richard W. Mithoff Professor of Pediatrics  
Director, Division of Neonatal-Perinatal Medicine  
Director, MS in Clinical Research Degree Program  
UT-Houston Medical School  
6431 Fannin, Suite 2.106  
Houston, TX 77030  
713 500-6708



**From:** [Krisa Van Meurs](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\)](#) [E]  
**Subject:** Re: SUPPORT\_NEUROcohort\_StateOfArtPAS.ppt  
**Date:** Tuesday, April 13, 2010 12:24:17 AM

---

Yes.  
Krisa

>Hi  
>Susan Hintz is presenting in a Neuroimaging for  
>Prognosis in Preterms: Ultrasound and MRI State  
>of the Art Plenary (5/4) at PAS and is  
>requesting permission from the steering  
>committee to use the attached slides in her  
>presentation. This is a nice venue to lay the  
>groundwork for the school age outcome study from  
>SUPPORT. Please send me a YES/NO vote by April  
>15.  
>  
>  
>THANKS  
>ROSE  
>  
>Content-Type: application/vnd.ms-powerpoint;  
> name="SUPPORT\_NEUROcohort\_StateOfArtPAS.ppt"  
>Content-Description: SUPPORT\_NEUROcohort\_StateOfArtPAS.ppt  
>Content-Disposition: attachment;  
> filename="SUPPORT\_NEUROcohort\_StateOfArtPAS.ppt"; size=389120;  
> creation-date="Mon, 12 Apr 2010 10:52:19 GMT";  
> modification-date="Mon, 12 Apr 2010 10:55:39 GMT"  
>  
>Attachment converted: Macintosh  
>HD:SUPPORT\_NEUROcohort\_#56F86A.ppt (SLD3/«IC»)  
>(0056F86A)

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Wally Carlo, M.D."  
**Subject:** RE: Confidential PAS PResentation Finer SUPPORT 2010-04-06.ppt  
**Date:** Tuesday, April 13, 2010 12:22:00 PM

---

He is going to call you -he thinks we should offer to remove the survival curve and be done with it. The survival curve adds very little (these are more often used in adult medicine and surgery)

---

**From:** Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]  
**Sent:** Tuesday, April 13, 2010 12:21 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Confidential PAS PResentation Finer SUPPORT 2010-04-06.ppt

Should I call him?

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: 205 266 (b)

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Tuesday, April 13, 2010 11:18 AM  
**To:** Wally Carlo, M.D.  
**Subject:** RE: Confidential PAS PResentation Finer SUPPORT 2010-04-06.ppt

Wally  
DID Abhik call you about the NEJM?

---

**From:** Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]  
**Sent:** Tuesday, April 13, 2010 12:17 PM  
**To:** Walsh, Michele; Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Confidential PAS PResentation Finer SUPPORT 2010-04-06.ppt

THANKS, Michele.  
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: 205 266 (b)

---

**From:** Walsh, Michele [mailto:Michele.Walsh@UHHospitals.org]  
**Sent:** Tuesday, April 13, 2010 9:51 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.  
**Subject:** RE: Confidential PAS PResentation Finer SUPPORT 2010-04-06.ppt

Hi: Overall looks terrific.

Some comments by slide number.

Slide 7: sat skew: this is always tricky to explain- so take extra time.

11- Do not understand the 3 different ROP outcome grps:

How can they have an ROP outcome if lost to FU. May need the slide at the end with the study pop flow to proceed this one.

Do you really mean Severe ROP or LOSt (with lost assumed to have severe ROP?)- a sensitivity analysis?

16: Survival Curve. Change title- to Survival Curve: (delete for Mortality) confusing to have Survival Curve for Mortality

17: Are you going to comment on challenge and study oximeter issues- I assume not.

Optional Slides:

25- Other causes of death. Were any differences significant? Interesting that there is more RDS in high sat and less NEC.

Slides 27 and 28: would pick one or other. I think median is more clear.

29: Cant see points and curves- needs to be different background and more bold lines/symbols.

Michele Walsh  
beeper (b) (6)  
Ph 216 844 3759

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Tuesday, April 06, 2010 12:45 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; 'Abhik Das'; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); 'Brenda Poindexter'; 'Carlo Waldemar (E-mail)'; cotte010@mc.duke.edu; 'Dennis Wallace'; 'Ed Bell'; 'Ed Donovan'; 'Ehrenkranz Richard (E-mail)'; Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; 'Kristi Watterberg'; Kurt Schibler [kurt.schibler@cchmc.org]; 'Matthew Bizzarro'; 'Michelle Walsh'; 'Mickey Caplan'; 'Oh William (E-mail)'; 'Pablo Sanchez'; 'Poole Kenneth (E-mail)'; 'Roger Faix'; 'Ronald Goldberg'; 'Seetha Shankaran'; 'Stevenson David (E-mail)'; 'Stoll Barbara (E-mail)'; 'Tyson Jon (E-mail)'; VanMeurs, Krisa  
**Cc:** 'Finer, Neil'; Archer, Stephanie (NIH/NICHD) [E]; 'Zaterka-Baxter, Kristin'; 'Cunningham, Meg'; 'Huitema, Carolyn Petrie'  
**Subject:** RE: Confidential PAS PResentation Finer SUPPORT 2010-04-06.ppt

Here is Wally's presentation for PAS. Please send comments directly to Wally

Rose

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Tuesday, April 06, 2010 12:19 PM  
**To:** (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Matthew Bizzarro; Michelle Walsh; Mickey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOLDBERG; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa  
**Cc:** Finer, Neil; Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Cunningham, Meg; Huitema, Carolyn Petrie  
**Subject:** Confidential PAS PResentation Finer SUPPORT 2010-04-06.ppt  
**Importance:** High

Hi,

Attached is Neil's presentation for PAS. If you have any comments, please send them to Neil.

Please keep this information confidential. **We are not to discuss the fact that the papers have been reviewed or accepted by NEJM.** PI's - please insure that all of your staff with the confidential knowledge regarding the SUPPORT papers are aware of the NEJM rules!!

In addition, since the papers are not yet published in NEJM, we need to respect their embargo policy. This means that we are requested to follow the guidelines at <http://authors.nejm.org/Help/Embargo.asp>.

Specifically, the guidelines state:

- Please do not discuss the fact that the research has been submitted or accepted for publication in the *New England Journal of Medicine*.
- Please do not distribute any copies of the manuscript, tables, or figures. (It is acceptable to use the materials in a presentation, but they should not be distributed.)

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**From:** Walsh, Michele  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Neil Finer; Carlo Waldemar (E-mail)  
**Subject:** RE: Confidential PAS Presentation Finer SUPPORT 2010-04-06.ppt  
**Date:** Tuesday, April 13, 2010 11:03:45 AM

---

Sorry hit send accidentally: continuing

5. Demographics- can reduce the size of some font to reduce clutter on slide  
(eg mean +/- SD)
6. Slide 20- would just put % instead of N to decrease clutter
7. Slide 21- can you put in table like slide 20?
8. Slide 22: Why is there an X in the box next to reduced death for CPAP?  
Makes it seem like that is a bad thing.
9. Slide 23: Font goes off the bottom. Does this need to be 2 slides? Or could reduce to phrases to get all on one slide.

Michele Walsh  
beeper (b) (6)  
Ph 216 844 3759

---

**From:** Walsh, Michele  
**Sent:** Tuesday, April 13, 2010 10:56 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Neil Finer  
**Subject:** RE: Confidential PAS Presentation Finer SUPPORT 2010-04-06.ppt

HI: Few comments

1. Too many background slides- do you need the detail on the COIN trial?
2. Can you reduce the text on all the slides to make shorter- they are a bit overwhelming.
3. Intervention slides: could use one of your slides from earlier presentation with approach placed in a table. Would be more clear.
4. Pt flow: suggest not put the oxygen intervention, just put the cpap/surf intervention to reduce the complexity of the slide... not needed for this 10 min presentation. Could save the big one for questions.

Michele Walsh  
beeper (b) (6)  
Ph 216 844 3759

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Tuesday, April 06, 2010 12:19 PM  
**To:** (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Matthew Bizzarro; Michelle Walsh; Mickey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald Goldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa  
**Cc:** Finer, Neil; Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Cunningham, Meg; Huitema, Carolyn Petrie  
**Subject:** Confidential PAS Presentation Finer SUPPORT 2010-04-06.ppt

**Importance:** High

Hi,

Attached is Neil's presentation for PAS. If you have any comments, please send them to Neil.

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Meeting organizers may promote an author's presentation in a press release, plan a press conference, publish the abstract in a meeting proceedings, and/or post the presentation on their Web site. We ask that authors, their institutions, and other organizations sponsoring the research not do any further promotion of the presentation

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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:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: SUPPORT\_NEUROcohort\_StateOfArtPAS.ppt  
**Date:** Tuesday, April 13, 2010 9:50:00 AM

---

Absolutely yes!!

-----Original Message-----

From: Archer, Stephanie (NIH/NICHD) [E]  
Sent: Tuesday, April 13, 2010 9:50 AM  
To: Higgins, Rosemary (NIH/NICHD) [E]  
Subject: RE: SUPPORT\_NEUROcohort\_StateOfArtPAS.ppt

I assume you are a Yes, correct?

-----Original Message-----

From: Higgins, Rosemary (NIH/NICHD) [E]  
Sent: Tuesday, April 13, 2010 6:19 AM  
To: Archer, Stephanie (NIH/NICHD) [E]  
Subject: Fw: SUPPORT\_NEUROcohort\_StateOfArtPAS.ppt

----- Original Message -----

From: Krisa Van Meurs <vanmeurs@stanford.edu>  
To: Higgins, Rosemary (NIH/NICHD) [E]  
Sent: Mon Apr 12 23:54:46 2010  
Subject: Re: SUPPORT\_NEUROcohort\_StateOfArtPAS.ppt

Yes.  
Krisa

>Hi

>Susan Hintz is presenting in a Neuroimaging for  
>Prognosis in Preterms: Ultrasound and MRI State  
>of the Art Plenary (5/4) at PAS and is  
>requesting permission from the steering  
>committee to use the attached slides in her  
>presentation. This is a nice venue to lay the  
>groundwork for the school age outcome study from  
>SUPPORT. Please send me a YES/NO vote by April  
>15.

>

>

>THANKS

>ROSE

>

>Content-Type: application/vnd.ms-powerpoint;  
> name="SUPPORT\_NEUROcohort\_StateOfArtPAS.ppt"  
>Content-Description: SUPPORT\_NEUROcohort\_StateOfArtPAS.ppt  
>Content-Disposition: attachment;  
> filename="SUPPORT\_NEUROcohort\_StateOfArtPAS.ppt"; size=389120;  
> creation-date="Mon, 12 Apr 2010 10:52:19 GMT";  
> modification-date="Mon, 12 Apr 2010 10:55:39 GMT"  
>



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>Attachment converted: Macintosh  
>HD:SUPPORT\_NEUROcohort\_#56F86A.ppt (SLD3/«IC»)  
>(0056F86A)

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** Fw: SUPPORT\_NEUROcohort\_StateOfArtPAS.ppt  
**Date:** Monday, April 12, 2010 6:56:07 PM

---

**From:** Walsh, Michele <Michele.Walsh@UHHospitals.org>  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Luc.Brion@UTSouthwestern.edu <Luc.Brion@UTSouthwestern.edu>; rohls@unm.edu <rohls@unm.edu>; aaf2@po.cwru.edu <aaf2@po.cwru.edu>; Abhik Das <adas@rti.org>; alaptook@WIHRI.org <alaptook@WIHRI.org>; ambal@uab.edu <ambal@uab.edu>; Bradley.yoder@hsc.utah.edu <Bradley.yoder@hsc.utah.edu>; Brenda Poindexter <bpoindex@iupui.edu>; Carlo Waldemar (E-mail) <wcarlo@peds.uab.edu>; cotte010@mc.duke.edu <cotte010@mc.duke.edu>; Dennis Wallace <dwallace@rti.org>; Ed Bell <Edward-bell@uiowa.edu>; Ed Donovan <edward.donovan@cchmc.org>; Ehrenkranz Richard (E-mail) <richard.ehrenkranz@yale.edu>; ifrantz@tuftsmedicalcenter.org <ifrantz@tuftsmedicalcenter.org>; Kennedy, Kathleen A <Kathleen.A.Kennedy@uth.tmc.edu>; Kristi Watterberg <kwatterberg@salud.unm.edu>; kurt.schibler@cchmc.org <kurt.schibler@cchmc.org>; Matthew Bizzarro <matthew.bizzarro@yale.edu>; Michelle Walsh <mcw3@po.cwru.edu>; Mickey Caplan <mcaplan@northshore.org>; Oh William (E-mail) <william\_oh@brown.edu>; Pablo Sanchez <Pablo.Sanchez@UTSouthwestern.edu>; Poole Kenneth (E-mail) <poo@rti.org>; Roger Faix <Roger.Faix@hsc.utah.edu>; Ronald GOLdberg <goldb008@mc.duke.edu>; Seetha Shankaran <sshankar@med.wayne.edu>; Stevenson David (E-mail) <dstevenson@stanford.edu>; Stoll Barbara (E-mail) <barbara\_stoll@oz.ped.emory.edu>; Tyson Jon (E-mail) <Jon.E.Tyson@uth.tmc.edu>; VanMeurs, Krisa <vanmeurs@leland.stanford.edu>  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; kzaterka@rti.org <kzaterka@rti.org>; Gantz, Marie <mgantz@rti.org>; Neil Finer <nfiner@ucsd.edu>; Susan Hintz <srhintz@stanford.edu>  
**Sent:** Mon Apr 12 18:45:07 2010  
**Subject:** RE: SUPPORT\_NEUROcohort\_StateOfArtPAS.ppt

Yes.

Michele Walsh  
beeper (b) (6)  
Ph 216 844 3759

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Monday, April 12, 2010 10:56 AM  
**To:** (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Matthew Bizzarro; Michelle Walsh; Mickey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOLdberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; 'kzaterka@rti.org'; Gantz, Marie; Neil Finer; 'Susan Hintz'  
**Subject:** SUPPORT\_NEUROcohort\_StateOfArtPAS.ppt

Hi

Susan Hintz is presenting in a Neuroimaging for Prognosis in Preterms: Ultrasound and MRI State of the Art Plenary (5/4) at PAS and is requesting permission from the steering committee to use the attached slides in her presentation. This is a nice venue to lay the groundwork for the school age outcome study from SUPPORT. **Please send me a YES/NO vote by April 15.**

**THANKS  
ROSE**

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**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** Fw: SUPPORT\_NEUROcohort\_StateOfArtPAS.ppt  
**Date:** Monday, April 12, 2010 6:55:58 PM

---

**From:** Laptook, Abbot <ALaptook@WIHRI.org>  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Mon Apr 12 18:43:42 2010  
**Subject:** RE: SUPPORT\_NEUROcohort\_StateOfArtPAS.ppt

yes

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Monday, April 12, 2010 10:56 AM  
**To:** (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; Laptook, Abbot; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Matthew Bizzarro; Michelle Walsh; Mickey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOLdberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; 'kzaterka@rti.org'; Gantz, Marie; Neil Finer; 'Susan Hintz'  
**Subject:** SUPPORT\_NEUROcohort\_StateOfArtPAS.ppt

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**THANKS  
ROSE**

---

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## **Higgins, Rosemary (NIH/NICHD) [E]**

---

**From:** Finer, Neil <nfiner@ucsd.edu>  
**Sent:** Monday, April 12, 2010 6:05 PM  
**To:** Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.  
**Cc:** Rich, Wade; Das, Abhik  
**Subject:** RE: PAS presentation  
**Attachments:** SUPPORT Final rev PAS-ATS April 12.ppt

Thanks Marie  
The first slide has been replaced and is fixed  
I made all the other corrections  
Abbot suggested the use of comparable  
I think I will leave it  
This is not the NEJM  
Many thanks for your detailed review  
You picked up a lot!!!  
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:** Gantz, Marie [mailto:mgantz@rti.org]  
**Sent:** Monday, April 12, 2010 2:46 PM  
**To:** Finer, Neil; Rosemary Higgins; Wally Carlo, M.D.  
**Cc:** Rich, Wade; Das, Abhik  
**Subject:** PAS presentation

Neil,

Here are my edits. Sorry there are so many – this is the first time I've seen this presentation.

- 1) It appears that the first N in "Neonatal" is missing from the bottom of the first slide.
- 2) On slide 15, should "If FiO2 <.30, oxygen withdrawal performed" be a separate bullet?
- 3) On slides 17, 18 and 20, the Ns for the CPAP and Surfactant groups are 663 and 653 (not 664 and 652).
- 4) On slide 17, percent Hispanic in the CPAP group is 20.8 (not 20.3).
- 5) On slide 18, I would note that "Death" is actually "Death by 36 weeks PMA."
- 6) On slide 20, BPD (O2 use)/Death was 48.7% in the CPAP group and 54.1% in the Surfactant group (RR is correct).
- 7) On slide 20, Days on mechanical vent is among survivors.
- 8) On slide 21, the numbers presented for death in the 24-25 GA group are incorrect. The correct numbers are CPAP 23.9% vs. Surfactant 32.1%, Relative Risk 0.74 (0.57, 0.98).
- 9) On slide 22, there is a comma instead of a period in the p value for intubation in the second bullet.

- 10) On slide 23, I wonder if we should say something other than that CPAP and surfactant are "comparable" since we were not doing an equivalence study. We could say that infants with CPAP experienced some significant benefits without additional morbidities.

Marie

Marie Gantz, Ph.D.  
Research Statistician  
RTI International  
mgantz@rti.org  
828-254-6255

---

**From:** Finer, Neil [mailto:nfiner@ucsd.edu]  
**Sent:** Monday, April 12, 2010 3:41 PM  
**To:** Rosemary Higgins; Wally Carlo, M.D.  
**Cc:** Rich, Wade; Gantz, Marie; Das, Abhik  
**Subject:**

Hi Everyone  
Here is the final SUPPORT Presentation  
Let me know if you see any problems  
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

## **Higgins, Rosemary (NIH/NICHD) [E]**

---

**From:** Finer, Neil <nfiner@ucsd.edu>  
**Sent:** Monday, April 12, 2010 4:59 PM  
**To:** Wally Carlo, M.D.  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE:

Hi Wally

Thanks

I was going to show the Consort and let it sit for 10 seconds \_ I don't expect anyone to follow all the numbers but presenting it shows that we have followed all the rules

I will look for the new slide and include it when I upload

I'm anxious to resolve the death story for your paper

Be well

Neilh

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:** Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]  
**Sent:** Monday, April 12, 2010 1:07 PM  
**To:** Finer, Neil; Rosemary Higgins  
**Cc:** Rich, Wade; Gantz, Marie; Das, Abhik  
**Subject:** RE:

Neil:

Great job. A few suggestions:

The CONSORT diagram (slide 16) is so crowded that I was going to leave it in the reserve in case someone asks. If you decide to keep it in the slides you will show, I can do the same.

I got a picture of a SUPPORT baby at birth on CPAP and another at 18 month follow up. The picture I had put in (slide 24) is a bit dated as it shows a scalp IV which many do not like.

Rose got a better slide to replace 25 and 26 which I will include in my set which I will send shortly.

Wally

---

**From:** Finer, Neil [mailto:nfiner@ucsd.edu]  
**Sent:** Mon 4/12/2010 2:41 PM

**To:** Rosemary Higgins; Wally Carlo, M.D.  
**Cc:** Rich, Wade; Gantz, Marie; Das, Abhik  
**Subject:**

Hi Everyone  
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Let me know if you see any problems  
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:** Roger Faix  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: SUPPORT\_NEUROcohort\_StateOfArtPAS.ppt  
**Date:** Monday, April 12, 2010 2:53:10 PM

---

Yes

Roger

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]  
**Sent:** Monday, April 12, 2010 8:55 AM  
**To:** (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Bradley Yoder; Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Matthew Bizzarro; Michelle Walsh; Mickey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOLdberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; 'kzaterka@rti.org'; Gantz, Marie; Neil Finer; 'Susan Hintz'  
**Subject:** SUPPORT\_NEUROcohort\_StateOfArtPAS.ppt

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**THANKS  
ROSE**

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** FW: SUPPORT\_NEUROcohort\_StateOfArtPAS.ppt  
**Date:** Monday, April 12, 2010 1:19:00 PM

---

Michele was on vacation so use Av's vote

---

**From:** Avroy Fanaroff [mailto:aaf2@case.edu]  
**Sent:** Monday, April 12, 2010 1:09 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** Re: SUPPORT\_NEUROcohort\_StateOfArtPAS.ppt

Fine by me  
Av

On 4/12/10, **Higgins, Rosemary (NIH/NICHD) [E]** <[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)> wrote:  
Hi

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**THANKS  
ROSE**

--

Avroy A. Fanaroff, M.D.  
Eliza Henry Barnes Professor of Neonatology  
Rainbow Babies & Children's Hospital  
Professor of Pediatrics  
Case Western Reserve University School of Medicine  
11100 Euclid Avenue  
Cleveland, Ohio 44106  
(216) 844-3387  
[aaf2@case.edu](mailto:aaf2@case.edu)

**From:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**To:** [Archer, Stephanie \(NIH/NICHD\) \[E\]](#)  
**Subject:** FW: SUPPORT\_NEUROcohort\_StateOfArtPAS.ppt  
**Date:** Monday, April 12, 2010 1:15:00 PM

---

---

**From:** Barbara Stoll [<mailto:Barbara.Stoll@oz.ped.emory.edu>]  
**Sent:** Monday, April 12, 2010 1:15 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** Re: SUPPORT\_NEUROcohort\_StateOfArtPAS.ppt

AOK  
BJS

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](mailto:barbara_stoll@oz.ped.emory.edu)

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**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** FW: SUPPORT\_NEUROcohort\_StateOfArtPAS.ppt  
**Date:** Monday, April 12, 2010 11:48:00 AM

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**From:** Frantz, Ivan [mailto:ifrantz@tuftsmedicalcenter.org]  
**Sent:** Monday, April 12, 2010 11:31 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: SUPPORT\_NEUROcohort\_StateOfArtPAS.ppt

yes

Ivan D. Frantz, III, M.D.  
Professor of Pediatrics  
Tufts University School of Medicine

Tufts Medical Center Box 44  
800 Washington St.  
Boston, MA 02111

617 636 5322

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Monday, April 12, 2010 10:56 AM  
**To:** (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Frantz, Ivan; Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Matthew Bizzarro; Michelle Walsh; Mickey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald Goldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; 'kzaterka@rti.org'; Gantz, Marie; Neil Finer; 'Susan Hintz'  
**Subject:** SUPPORT\_NEUROcohort\_StateOfArtPAS.ppt

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**THANKS  
ROSE**

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Matthew Bizzarro"  
**Subject:** RE: SUPPORT\_NEUROcohort\_StateOfArtPAS.ppt  
**Date:** Monday, April 12, 2010 11:19:00 AM

---

Thanks and thanks for the update

Rose

---

**From:** Matthew Bizzarro [mailto:matthew.bizzarro@yale.edu]  
**Sent:** Monday, April 12, 2010 11:18 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: SUPPORT\_NEUROcohort\_StateOfArtPAS.ppt

Hi Rose,

Yes on using the slides.

Rich had his surgery on Friday which went very well. He is still in the hospital recovering, but in good spirits (as usual).

Thanks

Matt

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Monday, April 12, 2010 10:56 AM  
**To:** (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Matthew Bizzarro; Michelle Walsh; Mickey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOLDBERG; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; 'kzaterka@rti.org'; Gantz, Marie; Neil Finer; 'Susan Hintz'  
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**Please send me a YES/NO vote by April 15.**

**THANKS  
ROSE**

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** FW: SUPPORT\_NEUROcohort\_StateOfArtPAS.ppt  
**Date:** Monday, April 12, 2010 11:08:00 AM

---

-----Original Message-----

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]  
Sent: Monday, April 12, 2010 11:04 AM  
To: Higgins, Rosemary (NIH/NICHD) [E]  
Subject: RE: SUPPORT\_NEUROcohort\_StateOfArtPAS.ppt

Yes.

Sent from my Windows Mobile phone

-----Original Message-----

From: Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov>  
Sent: Monday, April 12, 2010 8:55 AM  
To: (Luc.Brion@UTSouthwestern.edu) <Luc.Brion@UTSouthwestern.edu>; (rohls@unm.edu) <rohls@unm.edu>; aaf2@po.cwru.edu <aaf2@po.cwru.edu>; Abhik Das <adas@rti.org>; alaptook@WIHRI.org <alaptook@WIHRI.org>; Ambal (ambal@uab.edu) <ambal@uab.edu>; Brad Yoder (Bradley.yoder@hsc.utah.edu) <Bradley.yoder@hsc.utah.edu>; Brenda Poindexter <bpoindex@iupui.edu>; Carlo Waldemar (E-mail) <wcarlo@peds.uab.edu>; cotte010@mc.duke.edu <cotte010@mc.duke.edu>; Dennis Wallace <dwallace@rti.org>; Ed Bell <Edward-bell@uiowa.edu>; Ed Donovan <edward.donovan@cchmc.org>; Ehrenkranz Richard (E-mail) <richard.ehrenkranz@yale.edu>; Ivan Frantz (ifrantz@tuftsmedicalcenter.org) <ifrantz@tuftsmedicalcenter.org>; Kennedy, Kathleen A <Kathleen.A.Kennedy@uth.tmc.edu>; Kristi Watterberg <kwatterberg@salud.unm.edu>; Kurt Schibler [kurt.schibler@cchmc.org] <kurt.schibler@cchmc.org>; Matthew Bizzarro <matthew.bizzarro@yale.edu>; Michelle Walsh <mcw3@po.cwru.edu>; Mickey Caplan <mcaplan@northshore.org>; Oh William (E-mail) <william\_oh@brown.edu>; Pablo Sanchez <Pablo.Sanchez@UTSouthwestern.edu>; Poole Kenneth (E-mail) <poo@rti.org>; Roger Faix <Roger.Faix@hsc.utah.edu>; Ronald GOLDBERG <goldb008@mc.duke.edu>; Seetha Shankaran <sshankar@med.wayne.edu>; Stevenson David (E-mail) <dstevenson@stanford.edu>; Stoll Barbara (E-mail) <barbara\_stoll@oz.ped.emory.edu>; Tyson Jon (E-mail) <Jon.E.Tyson@uth.tmc.edu>; VanMeurs, Krisa <vanmeurs@leland.stanford.edu>  
Cc: Archer, Stephanie (NIH/NICHD) [E] <archerst@mail.nih.gov>; 'kzaterka@rti.org' <kzaterka@rti.org>; Gantz, Marie <mgantz@rti.org>; Neil Finer <nfiner@ucsd.edu>; 'Susan Hintz' <srhintz@stanford.edu>  
Subject: SUPPORT\_NEUROcohort\_StateOfArtPAS.ppt

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THANKS  
ROSE

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** FW: SUPPORT\_NEUROcohort\_StateOfArtPAS.ppt  
**Date:** Monday, April 12, 2010 11:08:00 AM

---

**From:** Bell, Edward [mailto:edward-bell@uiowa.edu]  
**Sent:** Monday, April 12, 2010 11:06 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: SUPPORT\_NEUROcohort\_StateOfArtPAS.ppt

Yes

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Monday, April 12, 2010 9:56 AM  
**Subject:** SUPPORT\_NEUROcohort\_StateOfArtPAS.ppt

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**THANKS  
ROSE**

## **Higgins, Rosemary (NIH/NICHD) [E]**

---

**From:** Finer, Neil <nfiner@ucsd.edu>  
**Sent:** Saturday, April 10, 2010 7:12 PM  
**To:** Shankaran, Seetha; Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Confidential PAS PResentation Finer SUPPORT 2010-04-06.ppt

Thanks Seetha  
I will make the changes  
Neil

---

**From:** Shankaran, Seetha [mailto:sshankar@med.wayne.edu]  
**Sent:** Saturday, April 10, 2010 12:56 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil  
**Cc:** Shankaran, Seetha  
**Subject:** RE: Confidential PAS PResentation Finer SUPPORT 2010-04-06.ppt

Hi Neil  
Sorry for not getting back earlier  
Some minor comments:  
N is missing in first slide for Neonatal at bottom of slide  
My feeling is that Background slides are too many---you many want to reduce them  
expand SUPPORT in slide 7  
add antennal re consent slide 9????  
slides 11 to 14 are very "busy"--can you reduce---i.e not define terms like hemodynamic stability?  
Consort also busy, move to slides at back for if needed only?  
Results in 18-21, I think you can just give % and take out numerator denominator so less rows for audience to focus on???

Hope this helps  
Seetha

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]  
**Sent:** Tuesday, April 06, 2010 12:19 PM  
**To:** (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Matthew Bizzarro; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOLdberg; Shankaran, Seetha; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa  
**Cc:** Finer, Neil; Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Cunningham, Meg; Huitema, Carolyn Petrie  
**Subject:** Confidential PAS PResentation Finer SUPPORT 2010-04-06.ppt

Hi,  
Attached is Neil's presentation for PAS. If you have any comments, please send them to Neil.

Please keep this information confidential. **We are not to discuss the fact that the papers have been reviewed or accepted by NEJM.** PI's - please insure that all of your staff with the confidential knowledge regarding the SUPPORT papers are aware of the NEJM rules!!



In addition, since the papers are not yet published in NEJM, we need to respect their embargo policy. This means that we are requested to follow the guidelines at <http://authors.nejm.org/Help/Embargo.asp>.

Specifically, the guidelines state:

- Please do not discuss the fact that the research has been submitted or accepted for publication in the *New England Journal of Medicine*.
- Please do not distribute any copies of the manuscript, tables, or figures. (It is acceptable to use the materials in a presentation, but they should not be distributed.)

Meeting organizers may promote an author's presentation in a press release, plan a press conference, publish the abstract in a meeting proceedings, and/or post the presentation on their Web site. We ask that authors, their institutions, and other organizations sponsoring the research not do any further promotion of the presentation

**From:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**To:** [Archer, Stephanie \(NIH/NICHD\) \[E\]](#)  
**Subject:** FW: SUPPORT\_NEUROcohort\_StateOfArtPAS.ppt  
**Date:** Monday, April 12, 2010 11:07:00 AM

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**From:** Kennedy, Kathleen A [mailto:Kathleen.A.Kennedy@uth.tmc.edu]  
**Sent:** Monday, April 12, 2010 11:00 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: SUPPORT\_NEUROcohort\_StateOfArtPAS.ppt

Yes

Kathleen A. Kennedy, MD, MPH  
Richard W. Mithoff Professor of Pediatrics  
Director, Division of Neonatal-Perinatal Medicine  
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, April 12, 2010 9:56 AM  
**To:** (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Matthew Bizarro; Michelle Walsh; Mickey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald Goldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson, Jon E; VanMeurs, Krisa  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; 'kzaterka@rti.org'; Gantz, Marie; Neil Finer; 'Susan Hintz'  
**Subject:** SUPPORT\_NEUROcohort\_StateOfArtPAS.ppt

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**THANKS  
ROSE**

**From:** [Bell, Edward](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Subject:** RE: SUPPORT\_NEUROcohort\_StateOfArtPAS.ppt  
**Date:** Monday, April 12, 2010 11:06:22 AM

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Yes

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**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)]  
**Sent:** Monday, April 12, 2010 9:56 AM  
**Subject:** SUPPORT\_NEUROcohort\_StateOfArtPAS.ppt

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**From:** Kennedy, Kathleen A  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: SUPPORT\_NEUROcohort\_StateOfArtPAS.ppt  
**Date:** Monday, April 12, 2010 10:59:48 AM

---

Yes

Kathleen A. Kennedy, MD, MPH  
Richard W. Mithoff Professor of Pediatrics  
Director, Division of Neonatal-Perinatal Medicine  
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, April 12, 2010 9:56 AM  
**To:** (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Matthew Bizzarro; Michelle Walsh; Mickey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald Goldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson, Jon E; VanMeurs, Krisa  
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**Cc:** Archer, Stephanie (NIH/NICHD) [E]; "kzaterka@rti.org"; "Gantz, Marie"; "Neil Finer"; "Susan Hintz"  
**Subject:** SUPPORT\_NEUROcohort\_StateOfArtPAS.ppt  
**Date:** Monday, April 12, 2010 10:55:00 AM  
**Attachments:** SUPPORT\_NEUROcohort\_StateOfArtPAS.ppt

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**THANKS  
ROSE**



NICHD



# NICHD Neonatal Research Network: The SUPPORT NEURO Study

- **Neuroimaging and Neurodevelopmental Outcomes (NEURO) Study**
  - Prospective study of “early” CUS (4-14 days), “late” CUS (35-42 weeks PMA), and brain MRI (within 5 days of late CUS) to predict neurodevelopmental outcomes at 18-22 months and early school age in a subcohort of extremely preterm infants enrolled in the NICHD NRN SUPPORT study



# NICHD Neonatal Research Network: The SUPPORT NEURO Study

## SUBJECTS

- The NEURO study is a secondary to SUPPORT
  - The SUPPORT study was a multicenter, randomized, 2x2 factorial trial of ventilation and oxygenation strategies among infants **24 to 27+6/7 weeks EGA**
- 16 centers participated in the NEURO secondary
- **The NEURO study cohort includes ~530 infants with early and late CUS and MRI**
  - Largest extremely preterm neuroimaging cohort with early childhood and later follow-up to date





# NICHD Neonatal Research Network: The SUPPORT NEURO Study

## IMAGING

- CUS performed per standard procedures at site; brain MRI with protocol-specified sequences
  - MRI's obtained *preferentially without* sedation; only ~7% of MRIs performed with sedation
  - CUS and MRI interpreted by central readers; local site interpretations also collected

## DATA COLLECTION

- Substantial maternal, perinatal, neonatal, sociodemographic data; detailed respiratory data; further services and supports data at follow-up



# NICHD Neonatal Research Network: The SUPPORT NEURO Study

## NEURODEVELOPMENTAL FOLLOW-UP

- 18-22 months, corrected for prematurity
  - Bayley III, neurologic exam, growth measures; medical and social history, supports and services
  - Ongoing: **Final window closes April 2011**
- 6 ½-7 ½ years
  - Child assessments: WISC-IV, executive function, neurologic, movement/coordination, achievement
  - Parent questionnaires: executive function, behavior and attention, chronic conditions, medical and social history
  - Visits begin 2012; **final window closes August 2016**



# NICHD Neonatal Research Network: The SUPPORT NEURO Study

- **Primary Objective:**
  - To assess the absolute and relative value of early and late CUS, and near-term MRI, alone and in combination with other risk factors, to predict death or adverse neurodevelopmental outcomes in early childhood and school age
  - ***What is the predictive capability of MRI over and above CUS and clinical and sociodemographic risk factors?***



# NICHD Neonatal Research Network: The SUPPORT NEURO Study

- But, the NEURO study will also allow us to explore:
  - Links between ***specific clinical morbidities with brain injury patterns***
  - Neonatal neuroimaging to predict school-age ***emotional and behavioral problems, executive function and achievement delays***
  - Association of neonatal neuroimaging findings with ***longitudinal changes*** in cognitive impairment and other disabilities



# NICHD Neonatal Research Network Centers (1996-2006)

- Brown University
- Case Western Reserve University
- Duke University
- Emory University
- Indiana University
- Research Triangle Institute
- Stanford University
- University of Alabama – Birmingham
- University of California – San Diego
- University of Cincinnati
- University of Miami
- University of New Mexico
- University of Rochester
- University of Tennessee – Memphis
- University of Texas, Southwestern – Dallas
- University of Texas – Houston
- Wake Forest University
- Wayne State University
- Yale University



NICHD



# NICHD Neonatal Research Network Centers (2006-2011)

- Brown University
- Case Western Reserve University
- Duke University
- Emory University
- Indiana University
- Research Triangle Institute
- Stanford University
- Tufts Medical Center
- University of Cincinnati
- University of Alabama – Birmingham
- University of Iowa
- University of New Mexico
- University of Texas, Southwestern – Dallas
- University of Texas – Houston
- University of Utah
- Wayne State University
- Yale University



NICHD



**From:** Susan Hintz  
**To:** das.Das  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** Fwd: SUPPORT form ng03  
**Date:** Saturday, April 10, 2010 10:36:02 PM

---

FYI - Helen's email to Marie re: missing data

Susan

Begin forwarded message:

**From:** "Cheng, Helen" <hcheng@rti.org>  
**Date:** April 10, 2010 5:57:36 PM PDT  
**To:** "Gantz, Marie" <mgantz@rti.org>  
**Cc:** "Susan Hintz" <srhintz@stanford.edu>  
**Subject:** SUPPORT form ng03

Hi Marie,

Susan would like to determine which SUPPORT ppts survived to 36 weeks PMA. To identify those ppts, I'm taking all who were randomized per the SUPP02 and looking at the ng03 form, section K variable named OCTST36 and declaring anyone who did not die (OCGST36=5) a 'survivor'. All SUPPORT ppts (n=1316) have a NG03 form, but 67 of them have a blank on this status variable. And several of the blanks belong to ppts who are in our cohort of ppts who have an early and a late CUS, so I assume they made it to 36 weeks PMA. Am I using the correct variable to determine 36 weeks PMA? Do you know why a ppt would skip out of the OCGST36 variable? I don't see any skip pattern on the paper forms that indicate so.

Thanks! And please let me know if there's someone more appropriate to ask my question to.

Helen

**From:** Susan Hintz  
**To:** Helen Cheng  
**Cc:** das.Das; Higgins, Rosemary (NIH/NICHD) [E]; vanmeurs Meurs  
**Subject:** Fwd: PAS platform  
**Date:** Saturday, April 10, 2010 10:35:07 PM

---

Hi Helen

This is the email stream from our previous discussions of the mock table - in case you cannot put your fingers on it

Susan

Begin forwarded message:

**From:** "Das, Abhik" <adas@rti.org>  
**Date:** April 1, 2010 10:25:09 AM PDT  
**To:** "Susan Hintz" <srhintz@stanford.edu>  
**Cc:** "Cheng, Helen" <hcheng@rti.org>  
**Subject:** RE: PAS platform

Thinking about this again, it seems to make most sense to just have the baseline variables in the propensity analysis. We can have two sets of analyses – one for the whole trial and one restricted to the neuro cohort sites. Center does need to be included in these models.

Thanks

Abhik

---

**From:** Susan Hintz [<mailto:srhintz@stanford.edu>]  
**Sent:** Thursday, April 01, 2010 1:22 PM  
**To:** Das, Abhik  
**Cc:** Cheng, Helen  
**Subject:** Re: PAS platform

Hi again

Well...the first table I sent in the MOCK tables included only BASELINE variables, not the BPD and other variables. So are you saying put EVERYTHING from both tables in? (Attaching again)

Depending on your response (maybe you will say two models in stepwise fashion? First the baseline, then the neonatal variables?) I will need to slim down the variables, particularly from the second table, because some would be duplicative (i.e, 2 different BPD definitions)

Next, would you suggest running 2 sets of models - one with ALL overall SUPPORT cohort in, and another with just the centers that participated in the NEURO secondary?



I suppose the other variable that would need to be added would be "In NEURO Cohort" (yes/no) - sort of goes without saying, so forget I did.

I am not sure that early deaths should be adjusted for - I assumed we would just have patients that survived to 36 weeks in this group, correct?

What about NRN center? I KNOW that that will be different because I KNOW that NRN centers had different approaches to enrolling, and also centers came "on line" with this secondary at different times. For instance, as you see, Emory enrolled very few - they came on board very late. So what do you think?

I am worried about the number of variables we are looking including.

Susan

On Apr 1, 2010, at 5:55 AM, Das, Abhik wrote:

I would put all the variables you have in the 1<sup>st</sup> table into the propensity analysis model as well (using only one of the BPD definitions, preferably physiologic?). This will essentially be a multivariable logistic regression model for the entire trial cohort, with the outcome being membership in the neuro cohort. Please let us know what else we may need to adjust for (early deaths?).

Thanks

Abhik

---

**From:** Susan Hintz [<mailto:srhintz@stanford.edu>]  
**Sent:** Wednesday, March 31, 2010 8:01 PM  
**To:** Cheng, Helen  
**Cc:** Das, Abhik  
**Subject:** Re: PAS platform

Thanks Helen. It is not a horse I have decided - it is a mule. A big, spitting, ugly mule.

The propensity analysis - Abhik and I talked in broad terms, but maybe he can weigh in on more specific terms at this point. **Help me Abhik!**

As for the overall sample: Obvious for the CUS SUPPORT NEURO cohort - should just be the 572 with early and late CUS that you did all the analyses on. For the comparison (SUPPORT main trial), I would say SURVIVORS to 36 weeks PMA. Also - we may need to look at 2 comparisons - the OVERALL main trial, and the LIMITED SUPPORT main trial group = only the centers that participated in this secondary.

I am attaching a MOCK TABLE to that effect with variables to compare - these

are the SAME as Tables 1 a and 1 b from our bunch of tables. It may be ridiculous to start this way - so many variables - but at least we can see in broad terms what we have. **Also - the idea of p values for comparing may ALSO be crazy (see final columns in the tables.) Feel free to tell me I am crazy and multiply comparing. Help me statisticians!**

I am also attaching the table from Abhik that has some basic numbers of our cohort and the centers that participated.

**From:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**To:** [Blaisdell, Carol \(NIH/NHLBI\) \[E\]](#)  
**Subject:** RE: SUPPORT overview for ATS  
**Date:** Friday, April 09, 2010 12:07:00 PM

---

Yes  
301-435-7909

---

**From:** Blaisdell, Carol (NIH/NHLBI) [E]  
**Sent:** Friday, April 09, 2010 12:04 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: SUPPORT overview for ATS

How about 3 today?

Carol J. Blaisdell, M.D.  
Medical Officer  
Lung Developmental Biology and  
Pediatric Pulmonary Diseases  
Division of Lung Diseases, NHLBI/NIH  
(301) 435-0222 phone

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Friday, April 09, 2010 12:02 PM  
**To:** Blaisdell, Carol (NIH/NHLBI) [E]  
**Subject:** RE: SUPPORT overview for ATS

Thanks  
I still wanted to talk to you re:NEJM and ATS

Do you have nay time before 1 or after 2 PM today??

---

**From:** Blaisdell, Carol (NIH/NHLBI) [E]  
**Sent:** Friday, April 09, 2010 11:37 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: SUPPORT overview for ATS

Hi Rose, sorry I missed your call.  
I have a series of meetings/calls today.

Here are some comments (look for small yellow boxes at top of slides usually)  
Let me know if you have more questions.  
This will be a really great session for ATS.

Carol

Carol J. Blaisdell, M.D.  
Medical Officer  
Lung Developmental Biology and

Pediatric Pulmonary Diseases  
Division of Lung Diseases, NHLBI/NIH  
(301) 435-0222 phone

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Friday, April 09, 2010 9:03 AM  
**To:** Blaisdell, Carol (NIH/NHLBI) [E]  
**Subject:** RE: SUPPORT overview for ATS

Tell me what you think of this – I can cover it in about 5 minutes. I added some NRN background information

Thanks for your help  
Rose

---

**From:** Blaisdell, Carol (NIH/NHLBI) [E]  
**Sent:** Friday, April 09, 2010 8:42 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: SUPPORT overview for ATS

Sounds good!

Carol

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Friday, April 09, 2010 8:28 AM  
**To:** Blaisdell, Carol (NIH/NHLBI) [E]  
**Subject:** RE: SUPPORT overview for ATS

Neil and Wally will give the background for each of the arms of the study. I can add a little bit about the network and explain the current practice at the time (essentially shifting towards more CPAP and lower sats with small reports of “success” depending on how you define success)

Thanks for your help. I have never presented to an audience like this.

Rose

---

**From:** Blaisdell, Carol (NIH/NHLBI) [E]  
**Sent:** Friday, April 09, 2010 8:10 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: SUPPORT overview for ATS

Dear Rose,

This is good.

I wonder if the audience needs to know a little bit about the network first, then why the questions were proposed for SUPPORT (what was going on in practice that suggested these questions and study should be done?) for your 2 research questions, what is the outcome that is being measured to answer these? I think you need to say that too.

Would Neil and Wally be giving the background on the SUPPORT hypotheses for each of their sections, or could you state that in the set up to their report of the outcomes?

Carol

Carol J. Blaisdell, M.D.  
Medical Officer  
Lung Developmental Biology and  
Pediatric Pulmonary Diseases  
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(301) 435-0222 phone

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Wednesday, April 07, 2010 4:02 PM  
**To:** Blaisdell, Carol (NIH/NHLBI) [E]  
**Subject:** SUPPORT overview for ATS

Carol

I have not participated previously in ATS or one of these lunch sessions. Does this small set of slides seem appropriate to introduce the trial??

Let me know  
Thanks  
Rose

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network  
Pregnancy and Perinatology Branch  
Center for Developmental Biology and Perinatal Medicine  
Eunice Kennedy Shriver National Institute of Child Health and Human Development  
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6100 Executive Blvd., Room 4B03  
MSC 7510  
Bethesda, MD 20892  
For overnight delivery use Rockville, MD 20852  
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: SUPPORT overview for ATS  
**Date:** Friday, April 09, 2010 9:02:00 AM  
**Attachments:** [SUPPORT TRAIL OVERVIEW FOR ATS.ppt](#)

---

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Thanks for your help  
Rose

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**From:** [Blaisdell, Carol \(NIH/NHLBI\) \[E\]](#)  
**Sent:** Friday, April 09, 2010 8:42 AM  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Subject:** RE: SUPPORT overview for ATS

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Rose

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**From:** [Blaisdell, Carol \(NIH/NHLBI\) \[E\]](#)  
**Sent:** Friday, April 09, 2010 8:10 AM  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Subject:** RE: SUPPORT overview for ATS

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Medical Officer  
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Pediatric Pulmonary Diseases  
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(301) 435-0222 phone

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**Sent:** Wednesday, April 07, 2010 4:02 PM  
**To:** Blaisdell, Carol (NIH/NHLBI) [E]  
**Subject:** SUPPORT overview for ATS

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Let me know

Thanks

Rose

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network  
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higginsr@mail.nih.gov

NICHD



# SUPPORT TRIAL

## NICHD Neonatal Research Network





# NICHD NRN Mission

The Neonatal Research Network is designed to conduct studies to investigate the safety and efficacy of treatment and management strategies to care for newborn infants.



# Origins of Neonatal Research Network (NRN)

- Neonatal management, especially for high-risk term and preterm infants, has often adopted practices without objective evaluation
- NICHD established the Neonatal Research Network in 1986 to address the need for well-designed clinical trials in Neonatal Medicine



# NICHD NRN Aims

- Identify priority issues for research in the promotion of infant health and prevention of disease
- Evaluate interventions for efficacy, safety, and cost-effectiveness, including:
  - Translational research
  - Genetics
  - New technologies



# Background NRN

- Collaborative participation on common protocols
- Cooperative agreements
- Competitively peer-reviewed
  - Open competition
  - Content of grant, concept proposal, depth of faculty and institution
  - Priority score
  - Diversity in population

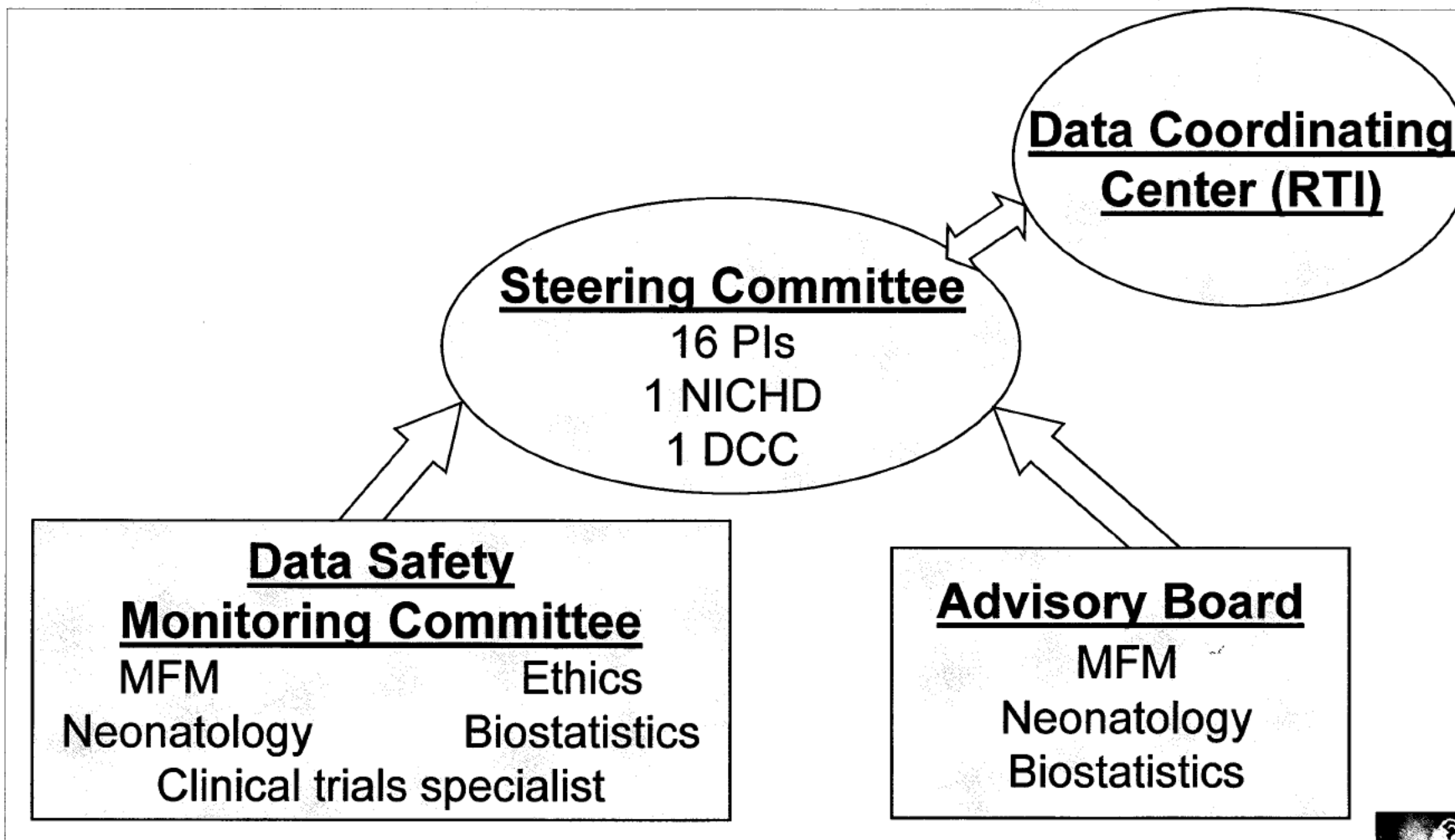


# NICHD NRN

- **25<sup>th</sup> award year (beginning 5th cycle)**
  - **1986 - 1991: 7 centers**
  - **1991 - 1996: 12 centers**
  - **1996 - 2001: 14 centers**
  - **2001 - 2006: 16 centers**
  - **2006 - 2011: 16 centers**
- **Data Coordinating Center**
- **Funding from:**
  - **NICHD**
  - **Other NIH Institutes and Agencies (NHLBI, NEI, NIDA, CDC) for specific studies**



# NRN Organization



# Neonatal Practice 2003-2004

- Trend towards more use of CPAP
- Trend towards use of lower oxygen saturation targets



# SUPPORT RESEARCH QUESTIONS

- Where do we target saturations for optimal outcome?
  - Low 90's
  - Mid-high 80's
- What's better?
  - Early Surfactant
  - CPAP



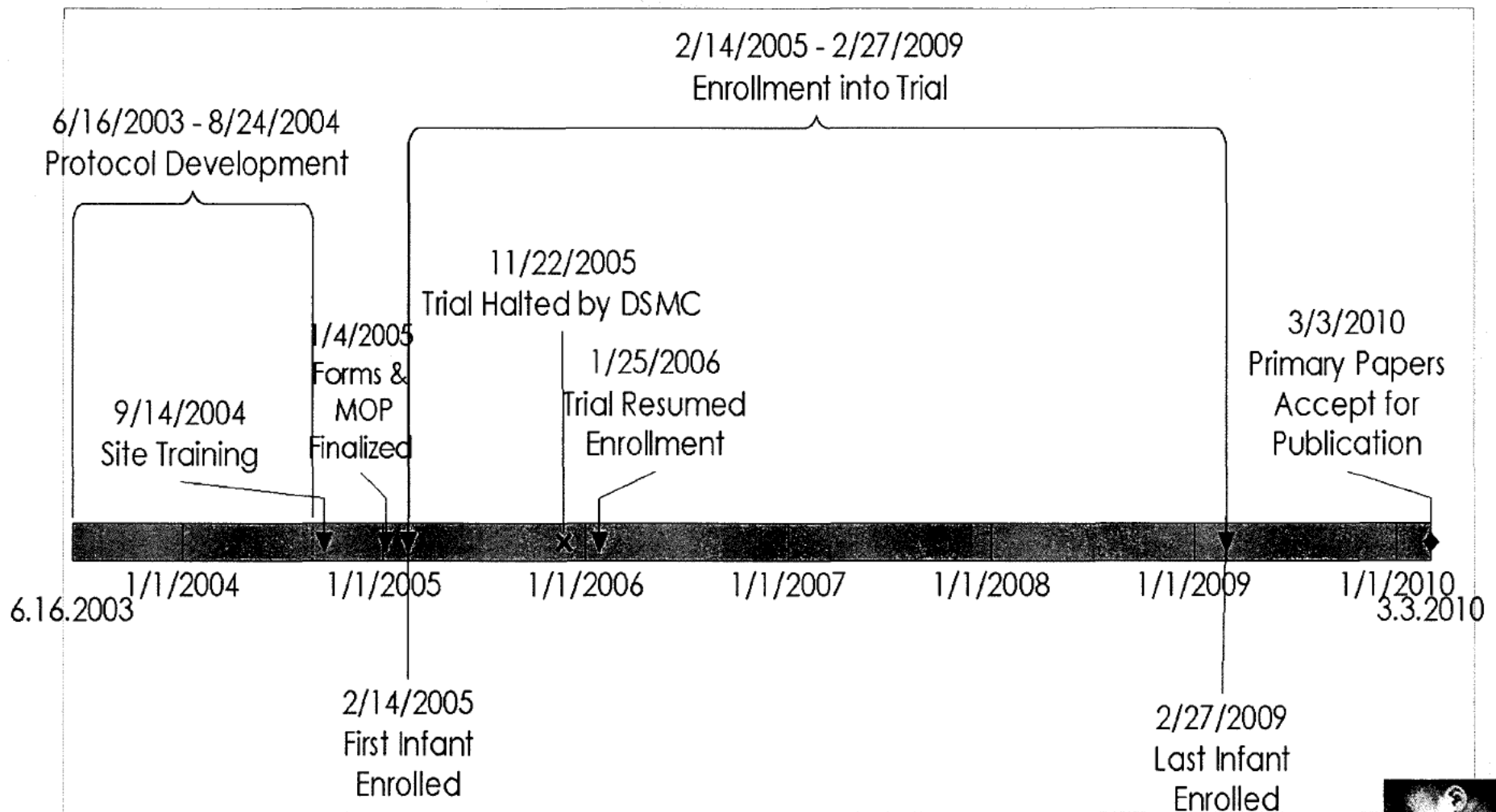


# 4-arms for study

<b>Randomized Intervention</b>	<b>Low SpO2 85% to 89%</b>	<b>High SpO2 91 to 95%</b>
<b>Treatment Early CPAP</b>	<b>Early CPAP + Low SpO2</b>	<b>Early CPAP + High SpO2</b>
<b>Control Prophylactic/Early Surfactant</b>	<b>Control + Low SpO2</b>	<b>Control + High SpO2</b>



# SUPPORT TIMELINE



# NICHD Neonatal Research Network SUPPORT Trial Centers (2004-2009)

- Brown University
- Case Western Reserve University
- Duke University
- Emory University
- Indiana University
- Research Triangle Institute
- Stanford University
- Tufts Medical Center
- University of Alabama – Birmingham
- University of Cincinnati
- University of California – San Diego
- 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
- Wayne State University
- Wake Forest University
- Yale University



NICHD



**From:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**To:** [Bock, Robert \(NIH/NICHD\) \[E\]](#)  
**Cc:** [Spong, Catherine \(NIH/NICHD\) \[E\]](#)  
**Subject:** SUPPORT news release 6cys  
**Date:** Friday, April 09, 2010 8:32:00 AM  
**Attachments:** [SUPPORT news release 6cys.docx](#)

---

Bob - see my comments to Cathy's comments - I agree with all her suggestions. Up to you regarding the web links - this may be good for lay folks/parents who might read this

Thanks  
Rose

**From:** [Spong, Catherine \(NIH/NICHD\) \[E\]](#)  
**To:** [Bock, Robert \(NIH/NICHD\) \[E\]](#)  
**Cc:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Subject:** RE: Preterm oxygen studies release  
**Date:** Thursday, April 08, 2010 8:53:06 PM  
**Attachments:** [SUPPORT news release 6cys.docx](#)

---

Thanks Bob and Rose for all of your help on these! Attached are my comments and suggestions  
Xoxoxoc  
athy

Catherine Y Spong MD  
Chief, Pregnancy and Perinatology Branch  
Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health  
6100 Executive Blvd, Rm 4B03, MSC 7510  
Bethesda MD 20892 (express mail: Rockville MD 20852)  
Phone 301 435 6894 or 301 496 5575  
Fax 301 496 3790  
email [spongcy@mail.nih.gov](mailto:spongcy@mail.nih.gov)

---

**From:** Bock, Robert (NIH/NICHD) [E]  
**Sent:** Thursday, April 08, 2010 4:26 PM  
**To:** Spong, Catherine (NIH/NICHD) [E]  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** Preterm oxygen studies release

Hi Cathy. Please see attached and let me know what you think. Rose has reviewed. After I hear from you, I'll share with NHLBI.

Thanks.

**From:** [Kennedy, Kathleen A](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Cc:** [dale\\_phelps@urmc.rochester.edu](mailto:dale_phelps@urmc.rochester.edu)  
**Subject:** RE: ROP Natural History Observational Study  
**Date:** Thursday, April 08, 2010 7:31:11 AM

---

Thanks for your comments. All good ones. They will add more meat to the paper. I'll incorporate them when I get a response from Dale and then we should be ready to submit to the subcommittee.

---

From: Higgins, Rosemary (NIH/NICHD) [E] [[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)]  
Sent: Wednesday, April 07, 2010 3:31 PM  
To: Kennedy, Kathleen A  
Cc: Phelps, Dale  
Subject: RE: ROP Natural History Observational Study

Kathleen

I made a stab at a couple of tables. I also think we should create graphs of gestational age on the x-axis and "most severe" exam and "Timing of intervention" on the y-axis to see if the course of ROP (especially severe ROP) has changed since the CRYO-ROP study.

We may also want to look at progression of disease over time (Do the more immature children, i.e. 24 and 25 week infants still get the worst disease between 36-36 weeks post concept age?). We can look at presence of plus disease and zone 1 exams/disease to see if these factors are still predictive of the most serious disease.

Perhaps this is too much, but we have nice exam data on a very large number of children in a contemporary cohort.

Rose

---

From: Kennedy, Kathleen A [<mailto:Kathleen.A.Kennedy@uth.tmc.edu>]  
Sent: Tuesday, April 06, 2010 12:22 PM  
To: Higgins, Rosemary (NIH/NICHD) [E]  
Cc: Phelps, Dale  
Subject: RE: ROP Natural History Observational Study

I've updated this based on the information I have. I think it's almost ready to go to the SUPPORT subcommittee. There are a couple of questions in red about the details of the eye exams. There wasn't complete agreement between what's in the manuscript and the manual, but I think Dale probably knows what really happened. I'd really appreciate input from you and Dale on this. I'm not sure we need to include ophthalmologists if the two of you are involved.

Kathleen A. Kennedy, MD, MPH  
Richard W. Mithoff Professor of Pediatrics  
Director, Division of Neonatal-Perinatal Medicine  
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, April 05, 2010 8:42 AM  
To: Kennedy, Kathleen A  
Subject: RE: ROP Natural History Observational Study

Kathleen

1. – Submit to subcommittee (send it to me and I can send it out) – Wally is the Vice chair of SUPPORT so will have significant input.
2. The papers are accepted, so please send us the proposal
3. Generally subcommittee members are co-authors on secondary studies. You may include anyone who can add to the science of the paper. I am happy to be included in this one as I did some ROP work prior to joining the network. Dale would likely be an asset and can be included.

Let me know if you have other questions

Rose

---

From: Kennedy, Kathleen A [<mailto:Kathleen.A.Kennedy@uth.tmc.edu>]  
Sent: Thursday, April 01, 2010 6:04 PM  
To: Higgins, Rosemary (NIH/NICHD) [E]  
Subject: ROP Natural History Observational Study

I'm trying to revise this proposal to turn it into something that can be submitted as a secondary study. I have a few procedural questions (not entirely clear to me from the Network policy).

- 1) It looks like this needs to be submitted to the Subcommittee chairman. This proposal is logically a secondary study of the Oximetry arm of the SUPPORT study (for which we did the careful ROP assessments). Do I send this to Neil (the official subcommittee chairman) or Wally (the lead author on the Oximetry study arm)?
- 2) Do I really need to wait for 3 months after the papers are submitted to give subcommittee members the first shot at this? That doesn't seem to be how Ed Bell understands it.
- 3) Dale is really the only other person who's expressed some interest after I brought it up at a meeting. I haven't contacted any of the ophthalmologists yet. Are there any restrictions on who can be included on the writing/planning group for the proposal? None of us is on the subcommittee and Dale isn't even in the Network anymore. Would everyone in this group be included as an author?

Kathleen A. Kennedy, MD, MPH  
Richard W. Mithoff Professor of Pediatrics  
Director, Division of Neonatal-Perinatal Medicine  
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 \(NIH/NICHD\) \[E\]](#)  
**To:** [Blaisdell, Carol \(NIH/NHLBI\) \[E\]](#)  
**Subject:** SUPPORT overview for ATS  
**Date:** Wednesday, April 07, 2010 4:02:00 PM  
**Attachments:** [SUPPORT TRAIL OVERVIEW FOR ATS.ppt](#)

---

Carol

I have not participated previously in ATS or one of these lunch sessions. Does this small set of slides seem appropriate to introduce the trial??

Let me know

Thanks

Rose

Rosemary D. Higgins, MD  
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NICHD



# SUPPORT TRIAL

## NICHD Neonatal Research Network



# SUPPORT RESEARCH QUESTIONS

- Where do we target saturations for optimal outcome?
  - Low 90's
  - Mid-high 80's
- What's better?
  - Early Surfactant
  - CPAP

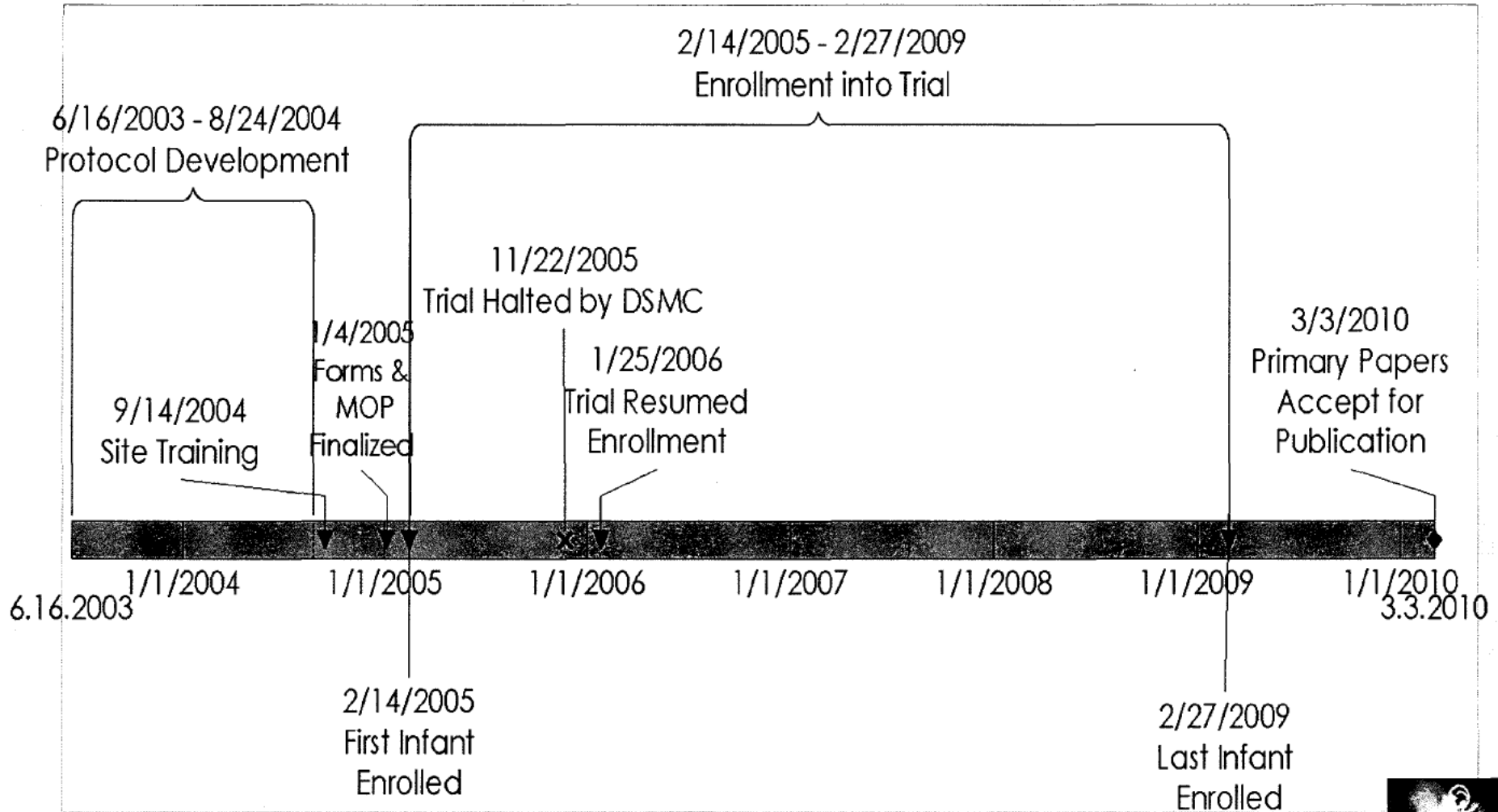


# 4-arms for study

<b>Randomized Intervention</b>	<b>Low SpO2 85% to 89%</b>	<b>High SpO2 91 to 95%</b>
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# SUPPORT TIMELINE



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- University of Texas – Houston
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- Wayne State University
- Wake Forest University
- Yale University



NICHD



**From:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**To:** ["Finer, Neil"; "wacarlo@uab.edu"](#)  
**Subject:** SUPPORT TRial introduction for ATS  
**Date:** Wednesday, April 07, 2010 4:00:00 PM  
**Attachments:** [SUPPORT TRAIL OVERVIEW FOR ATS.ppt](#)

---

Hi,

I have a couple of minutes to introduce the SUPPORT Trial at ATS – can you let me know what you think of this draft presentation? I know that I need to take out “accepted for publication” on the timeline slide.

Thanks for your help

Rose

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network  
Pregnancy and Perinatology Branch  
Center for Developmental Biology and Perinatal Medicine  
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NICHD



# SUPPORT TRIAL

## NICHD Neonatal Research Network



# SUPPORT RESEARCH QUESTIONS

- Where do we target saturations for optimal outcome?
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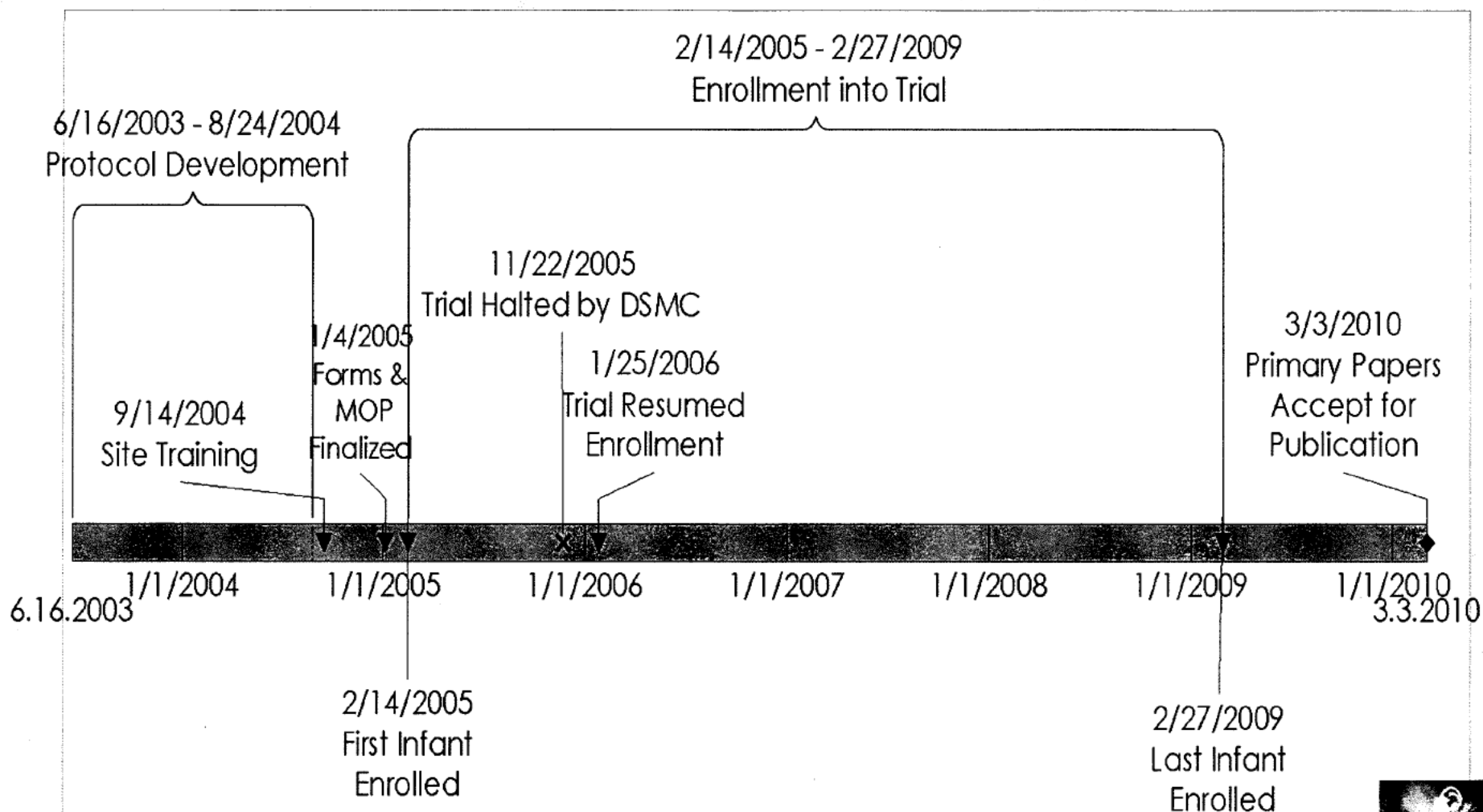


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- University of Texas – Houston
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- Wayne State University
- Wake Forest University
- Yale University



NICHD



**From:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**To:** [Bock, Robert \(NIH/NICHD\) \[E\]](#)  
**Subject:** SUPPORT news release 4  
**Date:** Wednesday, April 07, 2010 11:32:00 AM  
**Attachments:** [SUPPORT news release 4.docx](#)

---

I shortened the Guttmacher quote - and yes, the canula is what the older folks with COPD/emphysema use. Let me know when this goes over to NHLBI (they may want to insert a quote also)

Rose

**From:** [Bock, Robert \(NIH/NICHD\) \[E\]](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Subject:** More fine tuning  
**Date:** Wednesday, April 07, 2010 10:22:40 AM  
**Attachments:** [SUPPORT news release 4.docx](#)

---

Slight modifications on your modifications and some questions with the comment feature.

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Wednesday, April 07, 2010 9:50 AM  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Subject:** SUPPORT news release 3

Some word smithing mainly. (b) (5) [REDACTED]  
[REDACTED] rather more questions will be asked so I feel strongly about the changes in this first section. Otherwise the issues are minor.

Rose

**From:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**To:** [Bock, Robert \(NIH/NICHD\) \[E\]](#)  
**Subject:** SUPPORT news release 3  
**Date:** Wednesday, April 07, 2010 9:50:00 AM  
**Attachments:** [SUPPORT news release 3.doc](#)

---

Some word smithing mainly. (b) (5) [REDACTED]  
[REDACTED] rather more questions will be asked so I feel strongly about the changes in this first section. Otherwise the issues are minor.

Rose

**May 3 (1-3 PM). Are you able to attend? If not, can you designate someone to do the update for the study??**

**Let me know by Monday March 29 as we are finalizing the agenda**

**Thanks**

**Rose**

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network  
Pregnancy and Perinatology Branch  
Center for Developmental Biology and Perinatal Medicine  
Eunice Kennedy Shriver National Institute of Child Health and Human Development  
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**From:** [Bock, Robert \(NIH/NICHD\) \[E\]](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Subject:** Oxygen studies release  
**Date:** Tuesday, April 06, 2010 6:16:56 PM  
**Attachments:** [SUPPORT news release 3.doc](#)

---

Hi Rose. Please let me know what you think. Thanks.



**From:** Archer, Stephanie (NIH/NICHD) [E]  
**To:** Wally Carlo (wcarlo@peds.uab.edu)  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Confidential PAS PResentation Finer SUPPORT 2010-04-06.ppt  
**Date:** Tuesday, April 06, 2010 2:41:29 PM  
**Attachments:** Carlo, SUPPORT, 2010-04-06 swa.ppt

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Hi Wally,

I made a few changes to Slides 15 (some words were off the side of the slide), 22 (added the picture from Neil's thank-you slide), and combined the acknowledgement slides into one.

Stephanie

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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

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, April 06, 2010 12:45 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; 'Abhik Das'; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); 'Brenda Poindexter'; 'Carlo Waldemar (E-mail)'; cotte010@mc.duke.edu; 'Dennis Wallace'; 'Ed Bell'; 'Ed Donovan'; 'Ehrenkranz Richard (E-mail)'; Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; 'Kristi Watterberg'; Kurt Schibler [kurt.schibler@cchmc.org]; 'Matthew Bizzarro'; 'Michelle Walsh'; 'MIckey Caplan'; 'Oh William (E-mail)'; 'Pablo Sanchez'; 'Poole Kenneth (E-mail)'; 'Roger Faix'; 'Ronald GOLdberg'; 'Seetha Shankaran'; 'Stevenson David (E-mail)'; 'Stoll Barbara (E-mail)'; 'Tyson Jon (E-mail)'; VanMeurs, Krisa  
**Cc:** 'Finer, Neil'; Archer, Stephanie (NIH/NICHD) [E]; 'Zaterka-Baxter, Kristin'; 'Cunningham, Meg'; 'Huitema, Carolyn Petrie'  
**Subject:** RE: Confidential PAS PResentation Finer SUPPORT 2010-04-06.ppt

Here is Wally's presentation for PAS. Please send comments directly to Wally

Rose

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**To:** (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Matthew Bizzarro; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOLdberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa  
**Cc:** Finer, Neil; Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Cunningham, Meg; Huitema, Carolyn Petrie  
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**Importance:** High

Hi,

Attached is Neil's presentation for PAS. If you have any comments, please send them to Neil.

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NICHD



# Randomized Trial of Oxygen Saturation Targets in Premature Infants - the SUPPORT Trial

The SUPPORT Trial Group of the  
NICHD Neonatal Research Network



# Disclosure Statement

Dr. Carlo has documented that he has no relevant financial relationships to disclose or COIs to resolve

# Background

- 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<sub>2</sub> saturation target range (85 to 89%)  
compared to  
a higher O<sub>2</sub> saturation target range (91 to 95%)  
reduces  
the incidence of the composite outcome of  
severe ROP or death  
among  
infants of 24<sup>0/7</sup> to 27<sup>6/7</sup> weeks gestational age

# Method – Patients

- Inborn infants of 24<sup>0/7</sup> to 27<sup>6/7</sup> weeks gestation for whom a decision had been made to provide full resuscitation were eligible
- Parental consent was obtained antenatally
- Enrollment from February 2005 to February 2009
- Randomization was stratified by center and by gestational age:
  - 24 and 25 weeks
  - 26 and 27 weeks

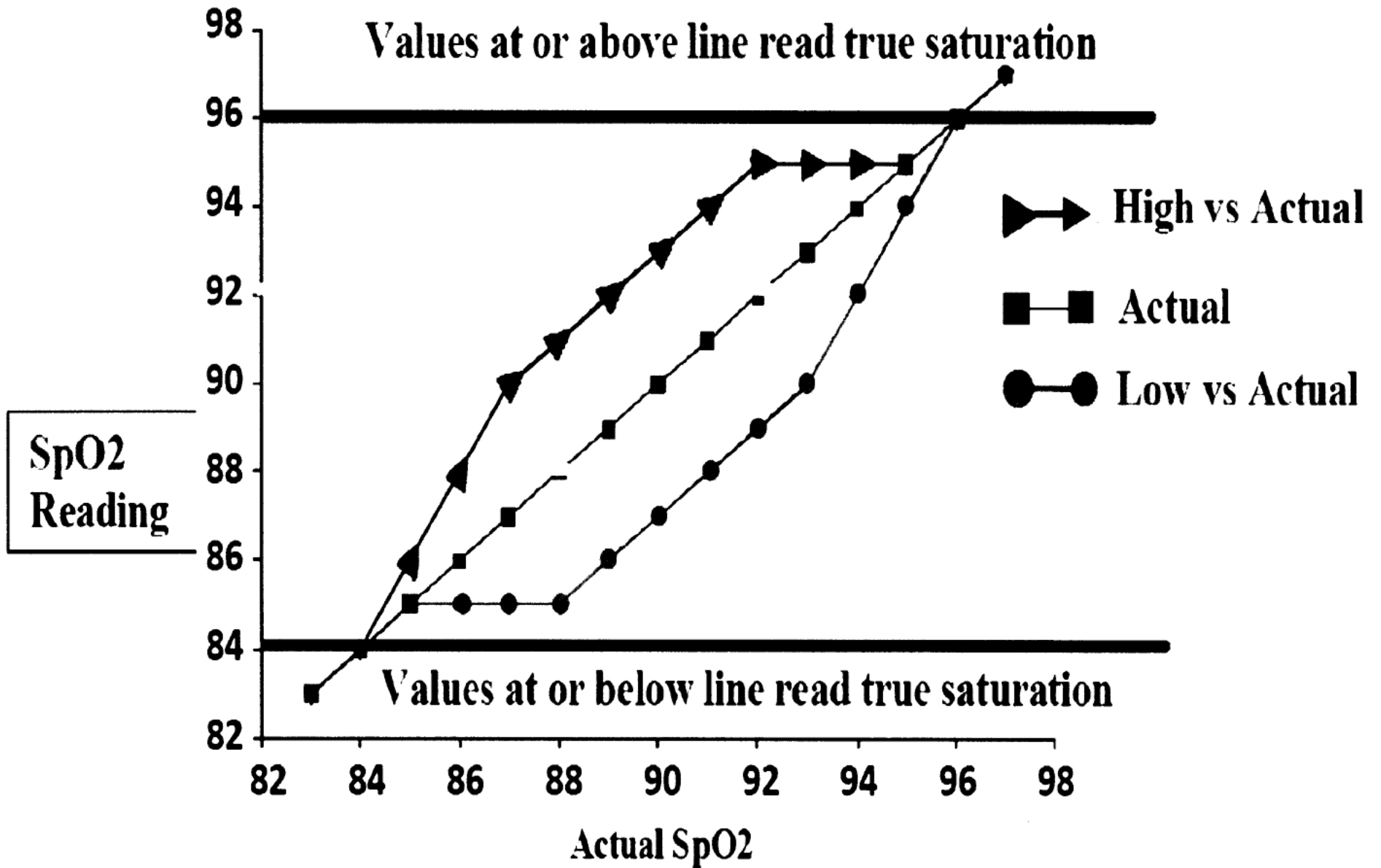
# Methods – Intervention (1)

- 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 Oximeter

<b>SpO2 Group</b>	<b>Displayed Target</b>	<b>Actual Target</b>	<b>Alarm Values</b>
Low SpO2	88-92%	85-89%	<85 and >95%
High SpO2	88-92%	91-95%	<85 and >95%



## Actual vs Low and Hi Reading SaO2



## Methods – Intervention (2)

- Oxygen saturation targeting was initiated within the first two hours after birth and was continued until 36 weeks post-menstrual age or until the infant remained 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
- Results of the CPAP/surfactant Trial were presented by Dr. Finer at the Clinical Trials session

# Methods – ROP Assessments

- Trained ophthalmologists followed the infants until the study endpoint *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
  - In zone II: plus disease with stage 2 or 3 ROP
  - If ophthalmologic surgery and/or bevacizumab ROP treatment was used

# Methods – Sample Size Monitoring and Analysis

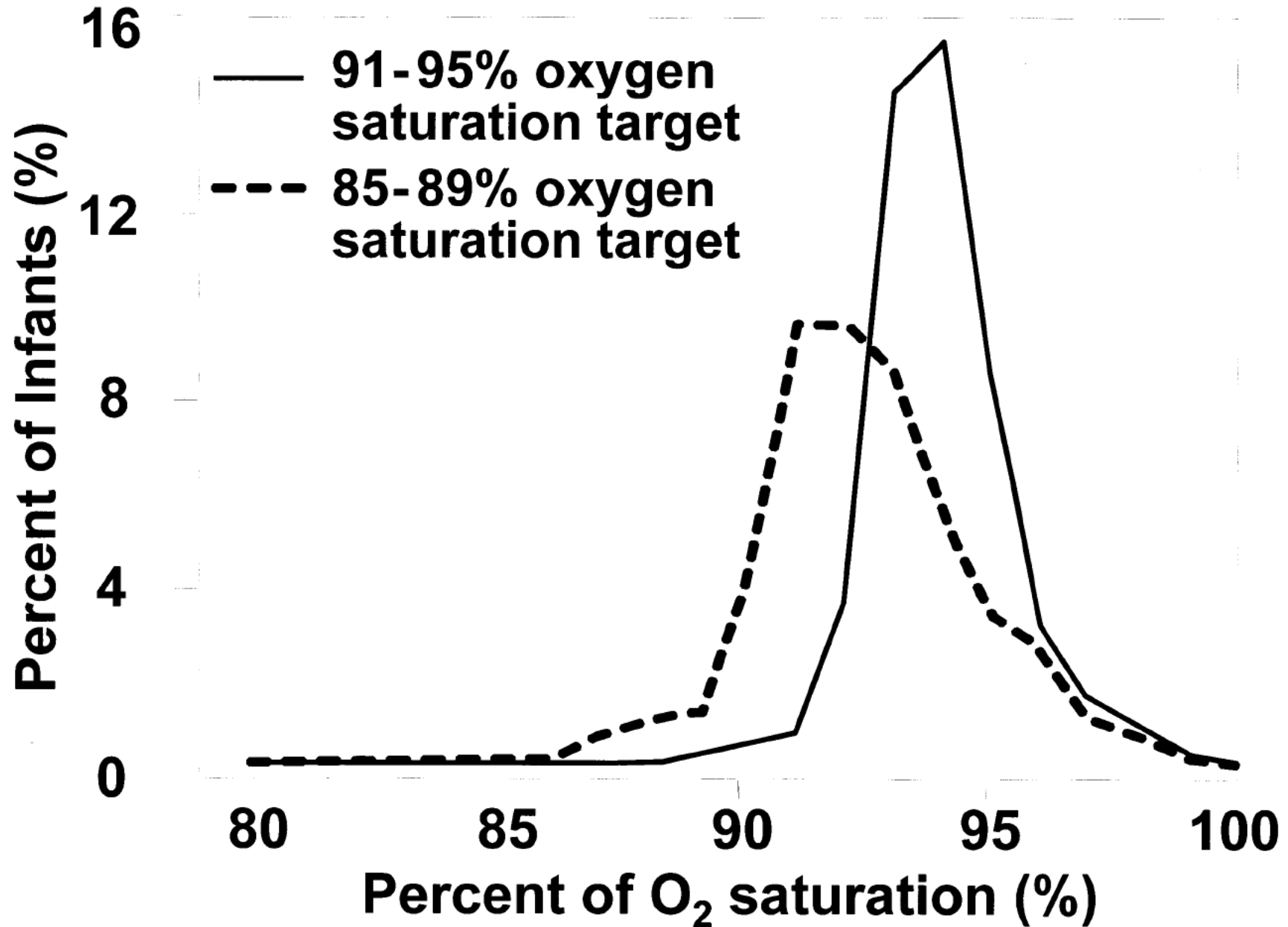
- Based on an absolute difference of 10% in the primary outcome, sample size was 1310
- An independent DSMC reviewed primary outcomes and adverse events at 25%, 50%, and 75% of outcome assessment
- The DSMC evaluated compliance with oxygen saturation targeting
- Adjustment was performed for pre-specified 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±193g	825±193g
Gestational age	26±1w	26±1w
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 (%)



# Results – Primary Outcome

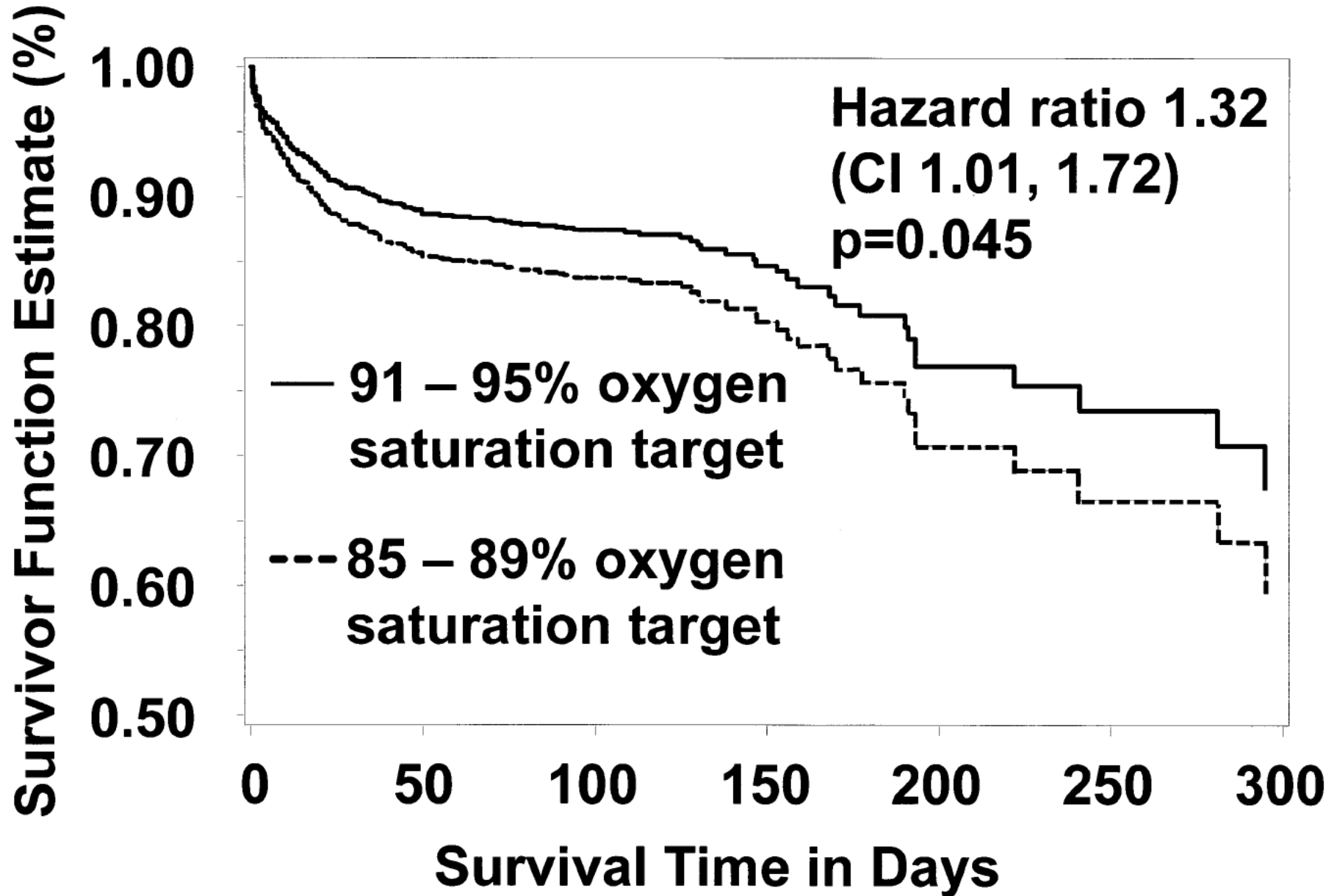
	Lower Saturation Group N=654	Higher Saturation Group N=662	Adjusted Relative Risk (95% CI)	
Severe ROP/death	28.3%	32.1%	0.90 (0.76, 1.06)	
Severe ROP	8.6%	17.9%	0.52 (0.37, 0.73)	NNT=11
Death	19.9%	16.2%	1.27 (1.01, 1.60)	NNH=27



# Results – ROP Adjudication Analysis

	Lower Saturation Group N=654	Higher Saturation Group N=662	Relative Risk for Low SpO <sub>2</sub> vs. High SpO <sub>2</sub> (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 for Mortality



# Results – BPD and other pulmonary outcomes

	Lower Saturation Group N=654	Higher Saturation Group N=662	Adjusted Relative Risk (95% CI)
BPD (O <sub>2</sub> use at 36 w)	37.6%	46.7%	0.82 (0.72, 0.93)
BPD (O <sub>2</sub> 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 <sub>x</sub> for PDA	34.5%	36.1%	0.95 (0.82, 1.09)
Surgical R <sub>x</sub> 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 $\geq$ 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<sub>2</sub> saturation targeting in the range of 85-89% did not affect severe ROP/death
- O<sub>2</sub> 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
- The potential to reduce the risk of severe ROP must be carefully weighed against the possibility of increased risk of death
- Follow up of these infants and data from the similarly designed ongoing trials will be important

**Thanks to the many parents,  
infants, 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



# Results – Causes of Death

	Lower Saturation Group (N = 130)	Higher Saturation Group (N = 107)
Respiratory distress syndrome	23.8%	29.0%
Infection	19.2%	19.6%
Necrotizing enterocolitis	17.7%	13.1%
Bronchopulmonary dysplasia	10.8%	9.3%
Central nervous system insult	9.2%	8.4%
Immaturity	5.4%	2.8%
Other	13.8%	17.8%

# Other Outcomes

	Lower Saturation Group	Higher Saturation Group	Adjusted p value
Length of stay (days) m+SE	104 ± 2.0	106 ± 2.0	0.45
Duration of MV (days) m+SE	26 ± 1	27 ± 1	0.30
Duration of O <sub>2</sub> suppl (days) m+SE	60 ± 2	67 ± 2	0.0002
CPAP (days) m+SE	17 ± 1	17 ± 1	0.94
Nasal SIMV (days) m+SE	3 ± 0.3	4 ± 0.3	0.14

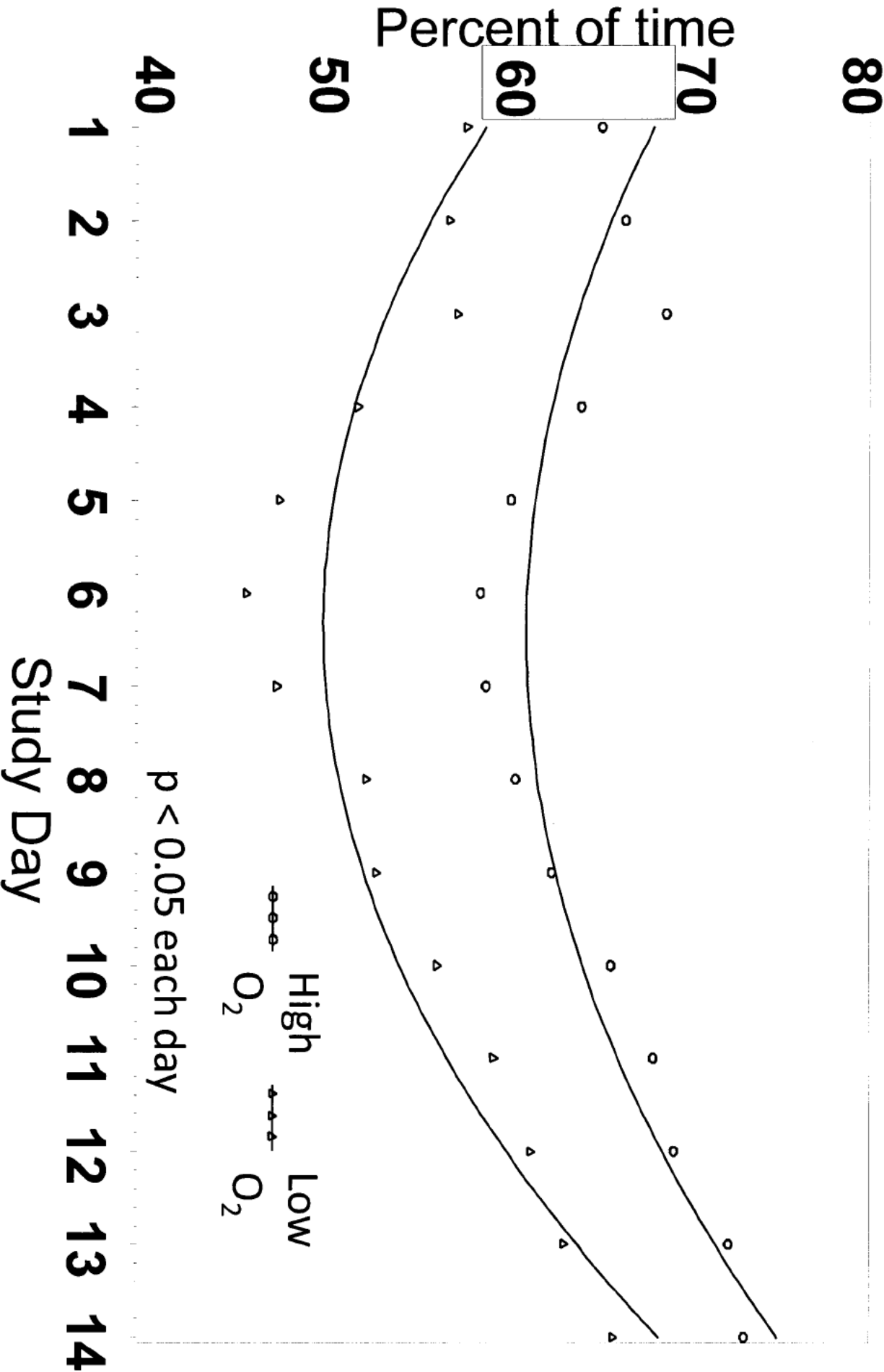
# Mean percent of time spent in SpO<sub>2</sub> ranges while on supplemental oxygen

SpO <sub>2</sub> 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)	0.0001
<80%	7.3 (6.6, 8.1)	5.5 (4.8, 6.3)	0.0002
<75%	4.5 (3.8, 5.2)	3.6 (2.9, 4.3)	0.0486
<70%	2.5 (1.9, 3.1)	2.1 (1.5, 2.7)	0.4090

# Median percent of time spent in SpO<sub>2</sub> ranges while on supplemental oxygen

SpO <sub>2</sub> range	Lower Saturation Group Median % of time in range	Higher Saturation Group Median % of time in range	p value
>96%	16.0	19.6	<0.0001
<80%	5.9	3.9	<0.0001
<75%	3.3	2.1	<0.0001
<70%	1.5	0.9	<0.0001

# Percent of time on oxygen by day and group



3546 Infants were assessed for eligibility (3127 pregnancies)\*

235 Did not meet eligibility criteria  
125 Personnel/Equipment not available  
699 Eligible but consent not sought  
•Parent unavailable for consent  
•Consent denied by parent or guardian  
11 Excluded for other reasons  
68 Consented but not randomized

1316 Underwent randomization

654 Were assigned to oxygen saturation targeting 85-89%

662 Were assigned to oxygen saturation targeting 91-95%

130 Died before discharge

524 Survived to discharge, transfer one year of life

107 Died before discharge

555 Survived to discharge, transfer or one year of life

41 Severe ROP

434 No severe ROP

49 Final ROP outcome missing

91 Severe ROP

418 No severe ROP

46 Final ROP outcome missing

# Methods – Data Analysis

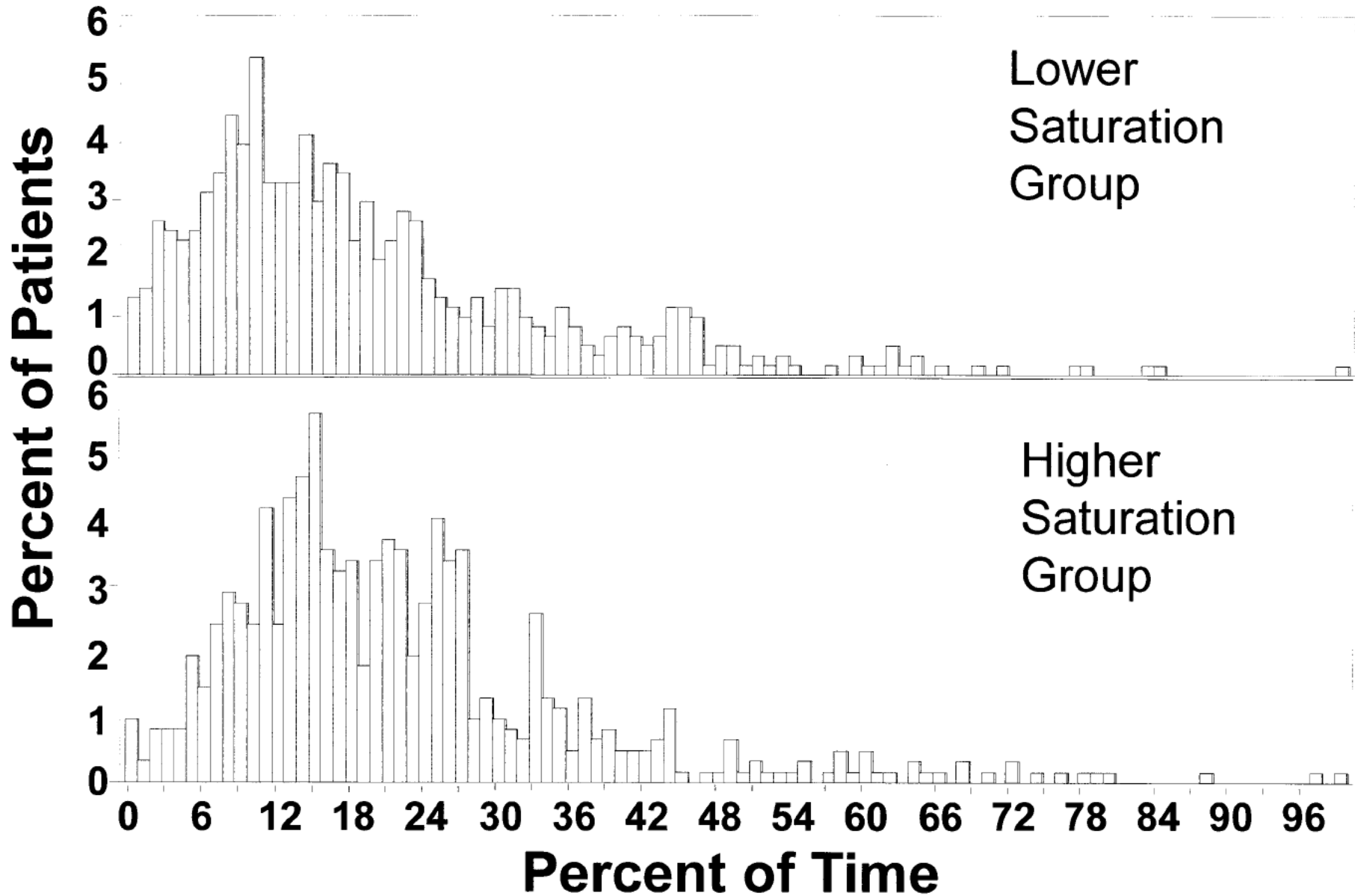
- The primary and categorical outcomes were analyzed using Poisson regression implemented in a Generalized Estimating Equation (GEE) model to obtain adjusted relative risk and 95% CI
- Continuous outcomes were analyzed using mixed effects linear models to produce adjusted means and standard errors
- Adjustment was performed for pre-specified stratification (center and GA) and for familial clustering as multiple births were randomized to the same treatment arms



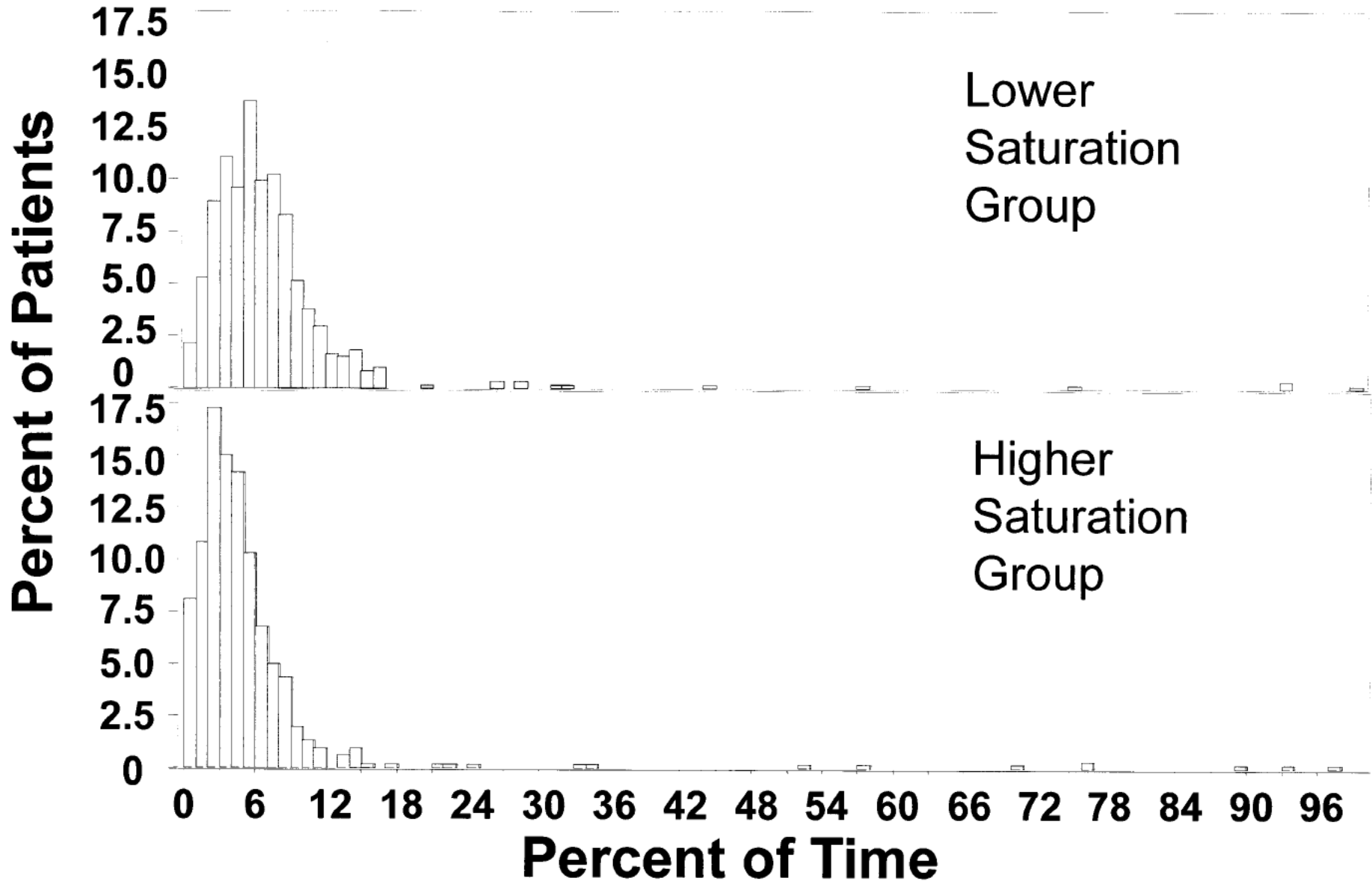
# Methods – Sample Size Estimate

- Baseline rate of severe ROP/Death of 50%
- Absolute risk difference of 10%
- Increased by 1.12 to allow for multiples randomized to same treatment
- Increased by 1.17 to adjust for attrition
- Increased further to minimize Type I error using a conservative 2% level of significance
- Final sample size was 1310 infants

# Percent of time with SpO<sub>2</sub> values >96% while on supplemental oxygen



# Percent of time with SpO<sub>2</sub> values <80% while on supplemental oxygen



**From:** [Fanaroff, Avroy](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Subject:** RE: Confidential PAS PRresentation Finer SUPPORT 2010-04-06.ppt  
**Date:** Tuesday, April 06, 2010 1:57:22 PM

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Hi Rose

It is not the length that I am concerned with – it is the delay in getting to the meat of the topic, but if you are all happy that is Ok

Wally's talk is fine, in fact very good

I wonder if he needs to spell out NNH – number needed to harm because as I first looked at it, I thought that he had a typo under the NNT

So if the abstracts are out there, it is OK to discuss, as long as we avoid mentioning where and when it will be published?

Hoping we will be successful with Dale's nomination – will be discussed Thursday – wiol keep you informed

Av

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]  
**Sent:** Tuesday, April 06, 2010 1:47 PM  
**To:** Fanaroff, Avroy  
**Subject:** RE: Confidential PAS PRresentation Finer SUPPORT 2010-04-06.ppt

The PAS abstract program is available on the website, so the abstracts are out there!!!

Thanks for looking this over (Neil will speak quickly so I am not too worried about the length)

Regards  
Rose

---

**From:** Fanaroff, Avroy [<mailto:Avroy.Fanaroff@UHhospitals.org>]  
**Sent:** Tuesday, April 06, 2010 1:45 PM  
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**Subject:** RE: Confidential PAS PRresentation Finer SUPPORT 2010-04-06.ppt

Hi Rose

Overall the presentation is excellent

The introduction is too long Need to reduce the number of slides in the intro

When can any of this data be released ie when do the PAS members have access to the abstracts?

Av

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]  
**Sent:** Tuesday, April 06, 2010 12:19 PM  
**To:** (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Matthew Bizzarro; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOLdberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa  
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**Importance:** High

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**To:** Higgins, Rosemary (NIH/NICHD) [E]; "(Luc.Brion@UTSouthwestern.edu)"; "(rohls@unm.edu)"; "aaf2@po.cwru.edu"; "Abhik Das"; "alaptook@WIHRI.org"; "Ambal (ambal@uab.edu)"; "Brad Yoder (Bradley.yoder@hsc.utah.edu)"; "Brenda Poindexter"; "Carlo Waldemar (E-mail)"; "cotte010@mc.duke.edu"; "Dennis Wallace"; "Ed Bell"; "Ed Donovan"; "Ehrenkranz Richard (E-mail)"; "Ivan Frantz (ifrantz@tuftsmedicalcenter.org)"; "Kennedy, Kathleen A"; "Kristi Watterberg"; "Kurt Schibler [kurt.schibler@cchmc.org]"; "Matthew Bizzarro"; "Michelle Walsh"; "MIckey Caplan"; "Oh William (E-mail)"; "Pablo Sanchez"; "Poole Kenneth (E-mail)"; "Roger Faix"; "Ronald GOLdberg"; "Seetha Shankaran"; "Stevenson David (E-mail)"; "Stoll Barbara (E-mail)"; "Tyson Jon (E-mail)"; "VanMeurs, Krisa"  
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**Subject:** RE: Confidential PAS PResentation Finer SUPPORT 2010-04-06.ppt  
**Date:** Tuesday, April 06, 2010 12:44:00 PM  
**Attachments:** Randomized Trial of Oxygen Saturation Targets 4-6-10.ppt

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Here is Wally's presentation for PAS. Please send comments directly to Wally

Rose

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Tuesday, April 06, 2010 12:19 PM  
**To:** (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Matthew Bizzarro; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOLdberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa  
**Cc:** Finer, Neil; Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Cunningham, Meg; Huitema, Carolyn Petrie  
**Subject:** Confidential PAS PResentation Finer SUPPORT 2010-04-06.ppt  
**Importance:** High

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NICHD



# Randomized Trial of Oxygen Saturation Targets in Premature Infants - the SUPPORT Trial

The SUPPORT Study Group of the  
Eunice Kennedy Shriver NICHD  
Neonatal Research Network



# Disclosure Statement

Dr. Carlo has documented that he has no relevant financial relationships to disclose or COIs to resolve

# Background

- 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<sub>2</sub> saturation target range (85 to 89%)  
compared to  
a higher O<sub>2</sub> saturation target range (91 to 95%)  
reduces  
the incidence of the composite outcome of  
severe ROP or death  
among  
infants of 24<sup>0/7</sup> to 27<sup>6/7</sup> weeks gestational age

# Method – Patients

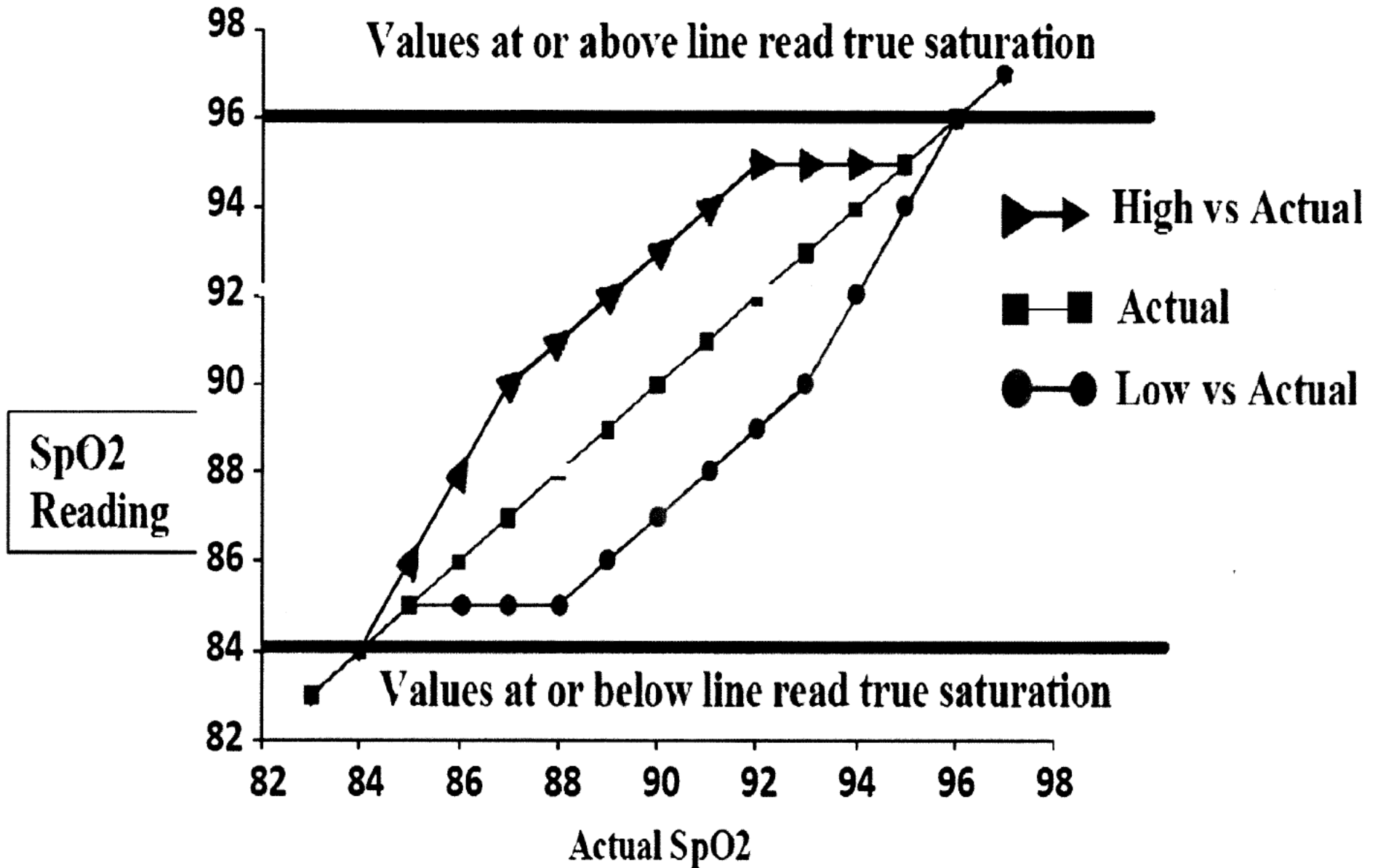
- Inborn infants of 24<sup>0/7</sup> to 27<sup>6/7</sup> weeks gestation for whom a decision had been made to provide full resuscitation were eligible
- Parental consent was obtained antenatally
- Enrollment from February 2005 to February 2009
- Randomization was stratified by center and by gestational 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 Oximeter

<b>SpO2 Group</b>	<b>Displayed Target</b>	<b>Actual Target</b>	<b>Alarm Values</b>
Low SpO2	88-92%	85-89%	<85 and >95%
High SpO2	88-92%	91-95%	<85 and >95%

## Actual vs Low and Hi Reading SaO2



## Methods – Intervention (2)

- Oxygen saturation targeting was initiated within the first two hours after birth and was continued until 36 weeks post-menstrual age or until the infant remained 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
- Results of the CPAP/surfactant Trial were presented by Dr. Finer at the Clinical Trials session

# Methods – ROP Assessments

- Trained ophthalmologists followed the infants until the study endpoint *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
  - In zone II: plus disease with stage 2 or 3 ROP
  - If ophthalmologic surgery and/or bevacizumab ROP treatment was used

# **Methods – Sample Size Monitoring and Analysis**

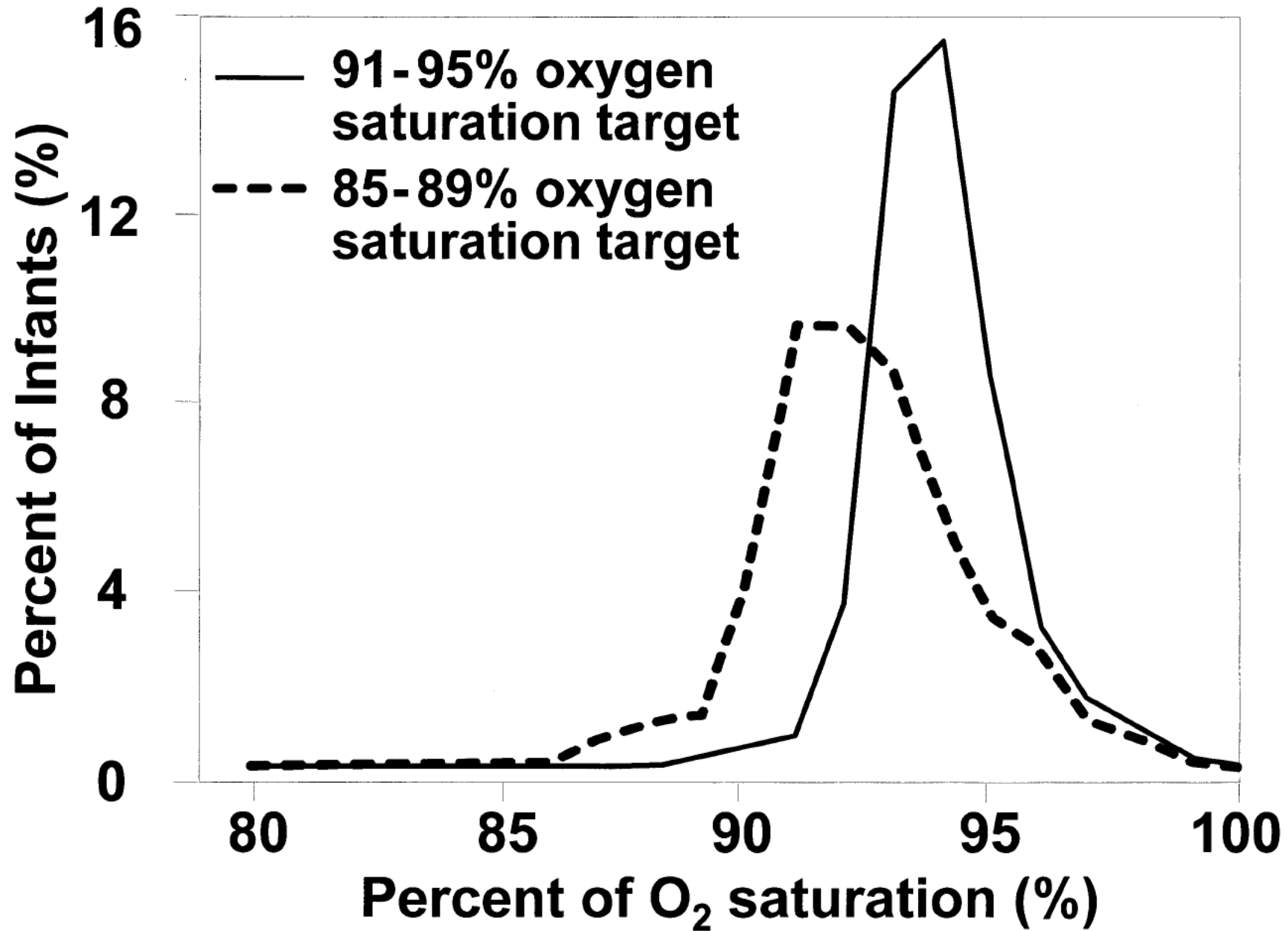
- Based on an absolute difference of 10% in the primary outcome, sample size was 1310
- An independent DSMC reviewed primary outcomes and adverse events at 25%, 50%, and 75% of outcome assessment
- The DSMC evaluated compliance with oxygen saturation targeting
- Adjustment was performed for pre-specified 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±193g	825±193g
Gestational age	26±1w	26±1w
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 (%)



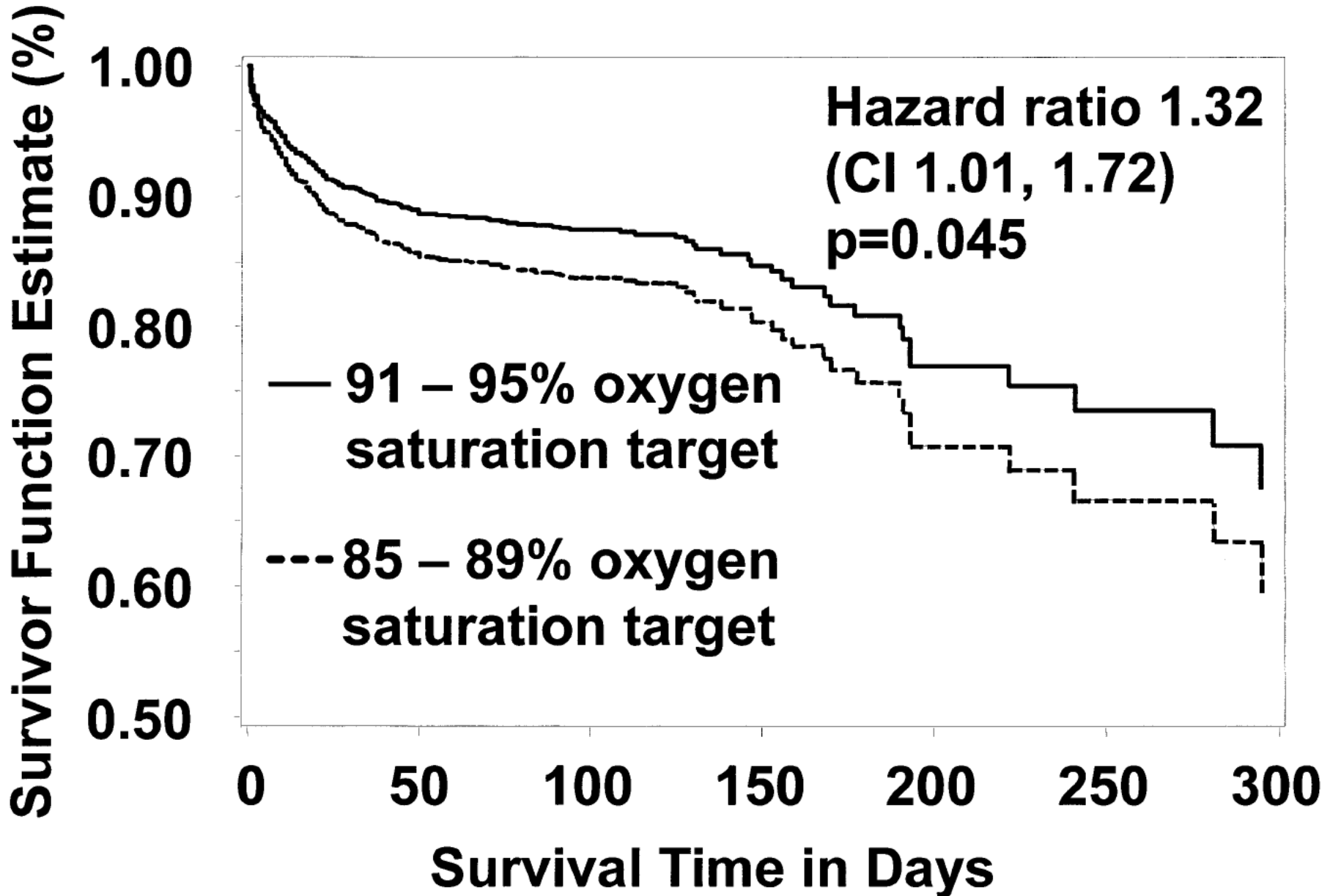
# Results – Primary Outcome

	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 <sub>2</sub> vs. High SpO <sub>2</sub> (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 for Mortality





# Results – BPD and other pulmonary outcomes

	Lower Saturation Group N=654	Higher Saturation Group N=662	Adjusted Relative Risk (95% CI)
BPD (O <sub>2</sub> use at 36 w)	37.6%	46.7%	0.82 (0.72, 0.93)
BPD (O <sub>2</sub> 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 <sub>x</sub> for PDA	34.5%	36.1%	0.95 (0.82, 1.09)
Surgical R <sub>x</sub> 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 $\geq$ 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<sub>2</sub> saturation targeting in the range of 85-89% did not affect severe ROP/death
- O<sub>2</sub> 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
- The potential to reduce the risk of severe ROP must be carefully weighed against the possibility of increased risk of death
- Follow up of these infants and data from the similarly designed ongoing trials will be important

**Thanks to the many parents,  
infants, and NICU staff**

**Thanks to the members of the  
Neonatal Research Network**

# NICHD Neonatal Research Network Centers (1996-2006)

- Brown University
- Case Western Reserve University
- Duke University
- Emory University
- Indiana University
- Research Triangle Institute
- Stanford University
- University of Alabama – Birmingham
- University of California – San Diego
- University of Cincinnati
- University of Miami
- University of New Mexico
- University of Rochester
- University of Tennessee – Memphis
- University of Texas, Southwestern – Dallas
- University of Texas – Houston
- Wake Forest University
- Wayne State University
- Yale University



# NICHD Neonatal Research Network Centers (2006-2011)

- Brown University
- Case Western Reserve University
- Duke University
- Emory University
- Indiana University
- Research Triangle Institute
- Stanford University
- Tufts Medical Center
- University of Cincinnati
- University of Alabama – Birmingham
- University of Iowa
- University of New Mexico
- University of Texas, Southwestern – Dallas
- University of Texas – Houston
- University of Utah
- Wayne State University
- Yale University





# Results – Causes of Death

	Lower Saturation Group (N = 130)	Higher Saturation Group (N = 107)
Respiratory distress syndrome	23.8%	29.0%
Infection	19.2%	19.6%
Necrotizing enterocolitis	17.7%	13.1%
Bronchopulmonary dysplasia	10.8%	9.3%
Central nervous system insult	9.2%	8.4%
Immaturity	5.4%	2.8%
Other	13.8%	17.8%

# Other Outcomes

	Lower Saturation Group	Higher Saturation Group	Adjusted p value
Length of stay (days) m+SE	104 ± 2.0	106 ± 2.0	0.45
Duration of MV (days) m+SE	26 ± 1	27 ± 1	0.30
Duration of O <sub>2</sub> suppl (days) m+SE	60 ± 2	67 ± 2	0.0002
CPAP (days) m+SE	17 ± 1	17 ± 1	0.94
Nasal SIMV (days) m+SE	3 ± 0.3	4 ± 0.3	0.14

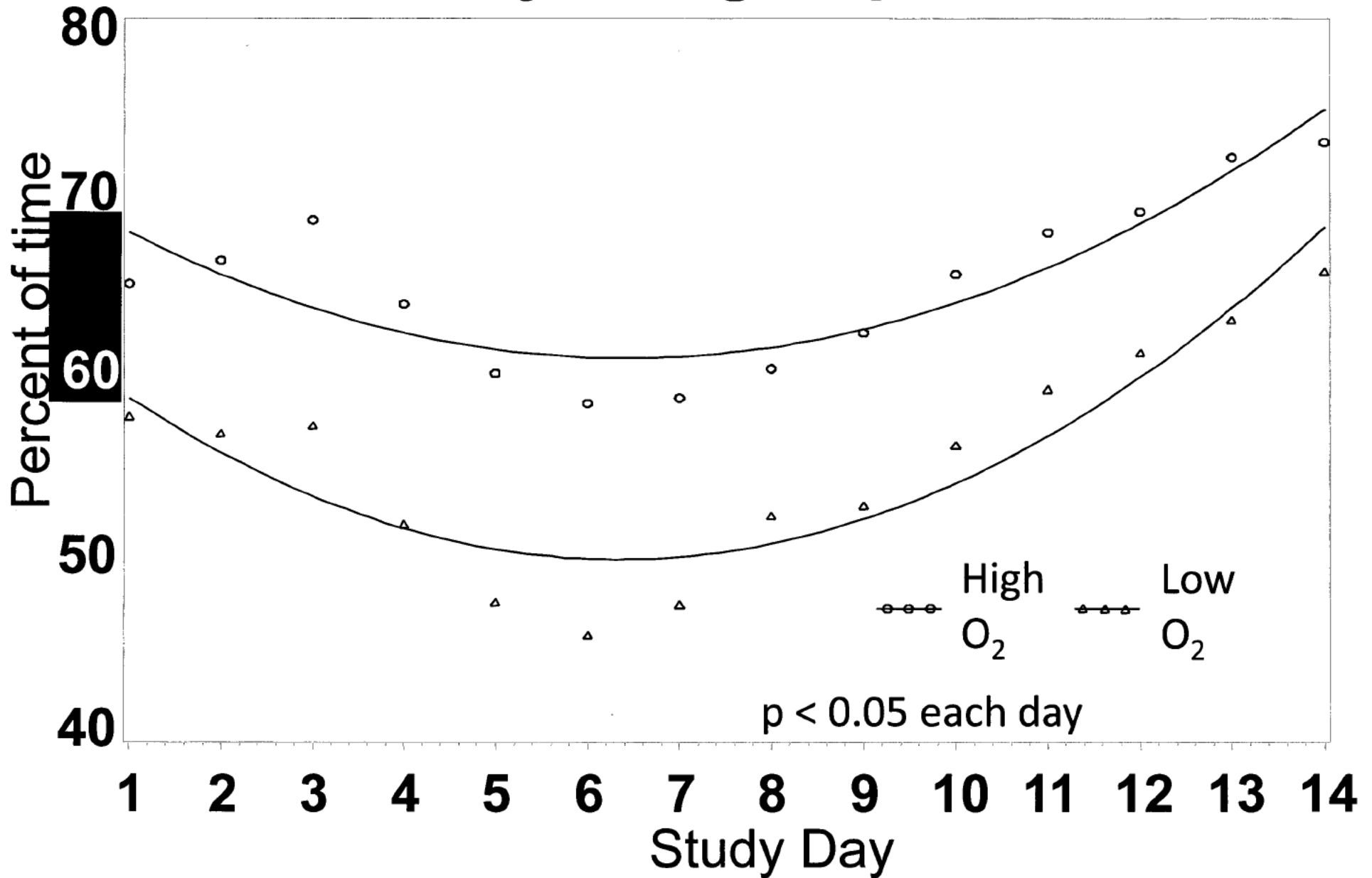
# Mean percent of time spent in SpO<sub>2</sub> ranges while on supplemental oxygen

SpO <sub>2</sub> 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)	0.0001
<80%	7.3 (6.6, 8.1)	5.5 (4.8, 6.3)	0.0002
<75%	4.5 (3.8, 5.2)	3.6 (2.9, 4.3)	0.0486
<70%	2.5 (1.9, 3.1)	2.1 (1.5, 2.7)	0.4090

# Median percent of time spent in SpO<sub>2</sub> ranges while on supplemental oxygen

SpO <sub>2</sub> range	Lower Saturation Group Median % of time in range	Higher Saturation Group Median % of time in range	p value
>96%	16.0	19.6	<0.0001
<80%	5.9	3.9	<0.0001
<75%	3.3	2.1	<0.0001
<70%	1.5	0.9	<0.0001

# Percent of time on oxygen by day and group



3546 Infants were assessed for eligibility (3127 pregnancies)\*

235 Did not meet eligibility criteria  
125 Personnel/Equipment not available  
699 Eligible but consent not sought  
•Parent unavailable for consent  
•Consent denied by parent or guardian  
11 Excluded for other reasons  
68 Consented but not randomized

1316 Underwent randomization

654 Were assigned to oxygen saturation targeting 85-89%

662 Were assigned to oxygen saturation targeting 91-95%

130 Died before discharge

524 Survived to discharge, transfer one year of life

107 Died before discharge

555 Survived to discharge, transfer or one year of life

41 Severe ROP

434 No severe ROP

49 Final ROP outcome missing

91 Severe ROP

418 No severe ROP

46 Final ROP outcome missing

# Methods – Data Analysis

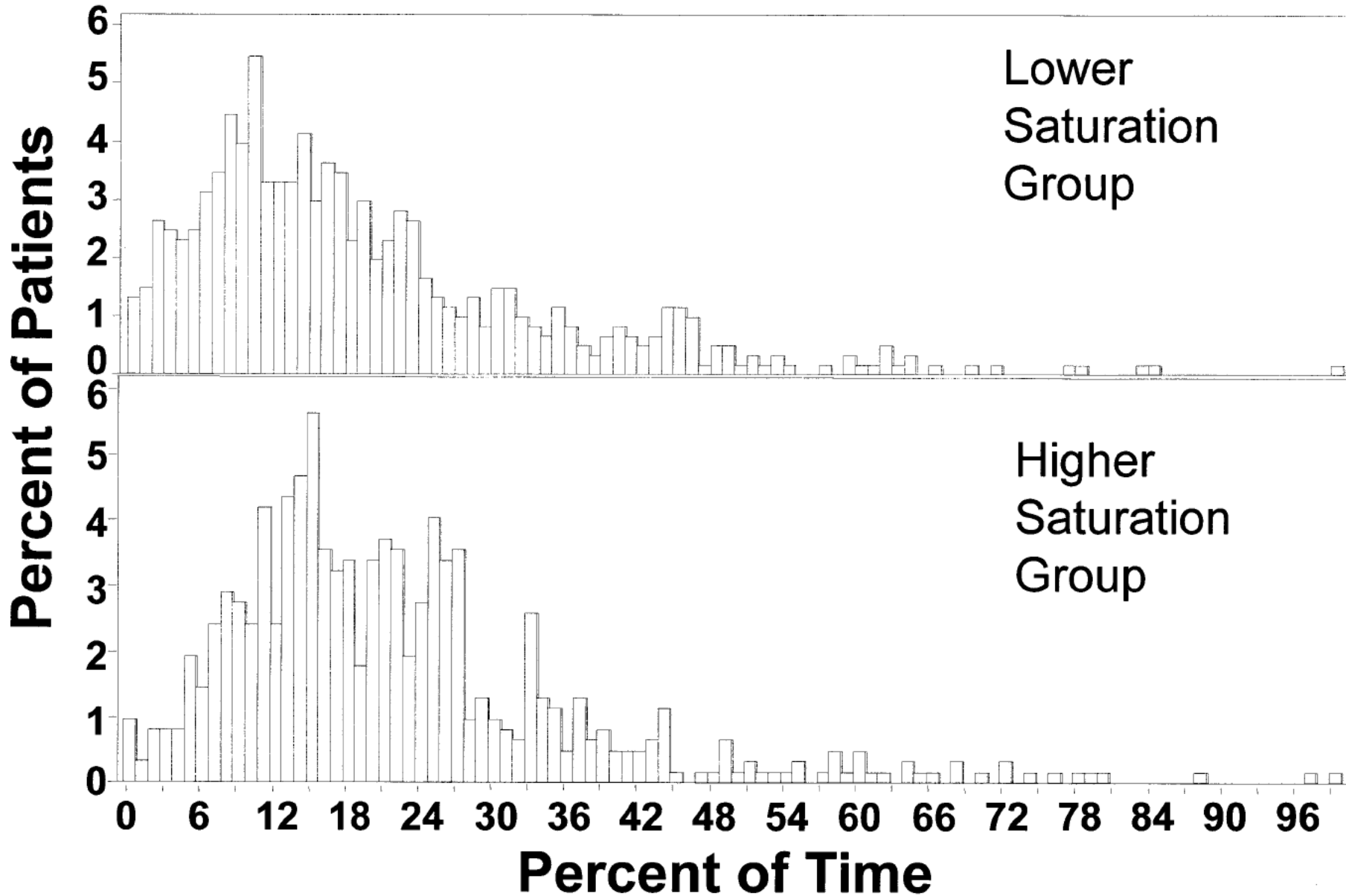
- The primary and categorical outcomes were analyzed using Poisson regression implemented in a Generalized Estimating Equation (GEE) model to obtain adjusted relative risk and 95% CI
- Continuous outcomes were analyzed using mixed effects linear models to produce adjusted means and standard errors
- Adjustment was performed for pre-specified stratification (center and GA) and for familial clustering as multiple births were randomized to the same treatment arms

# Methods – Sample Size Estimate

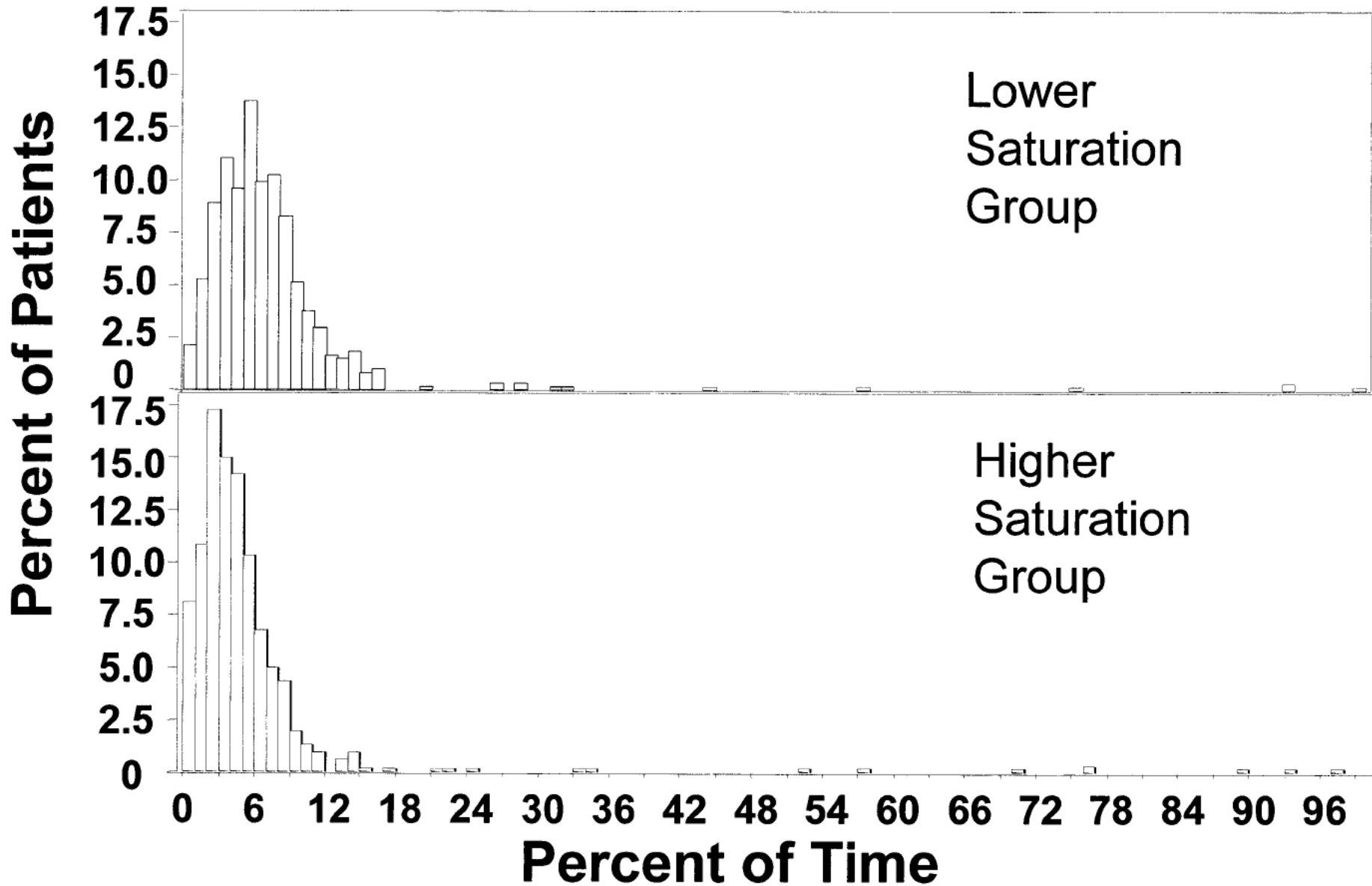
- Baseline rate of severe ROP/Death of 50%
- Absolute risk difference of 10%
- Increased by 1.12 to allow for multiples randomized to same treatment
- Increased by 1.17 to adjust for attrition
- Increased further to minimize Type I error using a conservative 2% level of significance
- Final sample size was 1310 infants



# Percent of time with SpO<sub>2</sub> values >96% while on supplemental oxygen



# Percent of time with SpO<sub>2</sub> values <80% while on supplemental oxygen



**From:** [Kennedy, Kathleen A](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Cc:** [Phelps, Dale](#)  
**Subject:** RE: ROP Natural History Observational Study  
**Date:** Tuesday, April 06, 2010 12:22:01 PM  
**Attachments:** [ROP Natural History Study.doc](#)

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I've updated this based on the information I have. I think it's almost ready to go to the SUPPORT subcommittee. There are a couple of questions in red about the details of the eye exams. There wasn't complete agreement between what's in the manuscript and the manual, but I think Dale probably knows what really happened. I'd really appreciate input from you and Dale on this. I'm not sure we need to include ophthalmologists if the two of you are involved.

Kathleen A. Kennedy, MD, MPH  
Richard W. Mithoff Professor of Pediatrics  
Director, Division of Neonatal-Perinatal Medicine  
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, April 05, 2010 8:42 AM  
**To:** Kennedy, Kathleen A  
**Subject:** RE: ROP Natural History Observational Study

Kathleen

1. – Submit to subcommittee (send it to me and I can send it out) – Wally is the Vice chair of SUPPORT so will have significant input.
2. The papers are accepted, so please send us the proposal
3. Generally subcommittee members are co-authors on secondary studies. You may include anyone who can add to the science of the paper. I am happy to be included in this one as I did some ROP work prior to joining the network. Dale would likely be an asset and can be included.

Let me know if you have other questions

Rose

---

**From:** Kennedy, Kathleen A [<mailto:Kathleen.A.Kennedy@uth.tmc.edu>]  
**Sent:** Thursday, April 01, 2010 6:04 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** ROP Natural History Observational Study

I'm trying to revise this proposal to turn it into something that can be submitted as a secondary study. I have a few procedural questions (not entirely clear to me from the Network policy).

- 1) It looks like this needs to be submitted to the Subcommittee chairman. This proposal is

logically a secondary study of the Oximetry arm of the SUPPORT study (for which we did the careful ROP assessments). Do I send this to Neil (the official subcommittee chairman) or Wally (the lead author on the Oximetry study arm)?

- 2) Do I really need to wait for 3 months after the papers are submitted to give subcommittee members the first shot at this? That doesn't seem to be how Ed Bell understands it.
- 3) Dale is really the only other person who's expressed some interest after I brought it up at a meeting. I haven't contacted any of the ophthalmologists yet. Are there any restrictions on who can be included on the writing/planning group for the proposal? None of us is on the subcommittee and Dale isn't even in the Network anymore. Would everyone in this group be included as an author?

**Kathleen A. Kennedy, MD, MPH**  
**Richard W. Mithoff Professor of Pediatrics**  
**Director, Division of Neonatal-Perinatal Medicine**  
**Director, MS in Clinical Research Degree Program**  
**UT-Houston Medical School**  
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**Houston, TX 77030**  
**713 500-6708**

## Retinopathy of Prematurity (ROP) Natural History Study Secondary Study for SUPPORT Trial

Kathleen A. Kennedy MD MPH, Rosemary D. Higgins MD, Dale L. Phelps MD

### Introduction and Rationale

Timely detection of treatable ROP is important to assure optimal outcomes for infants who meet the current criteria for treatment. The most recently published screening guidelines<sup>1</sup> are based on natural history data from the CRYO-ROP<sup>2</sup> and LIGHT-ROP<sup>3</sup> studies. The CRYO-ROP study<sup>4</sup> remains the most carefully conducted analysis of the incidence and timing of the onset of ROP, although it was conducted over 20 years ago (1986-1987). The LIGHT-ROP study enrolled infants from 1995-1997.<sup>5</sup> Over the past two decades, survival of lower gestational age infants has increased.<sup>6</sup> For infants ELBW infants (501-1000g birth weight), survival increased from 41% in 1990-1991 to 55% in 1997-2002. The timing of onset of ROP is related to both gestational age and postnatal age. The impact of increased survival of ELBW infants on the incidence and timing of the onset of ROP has not been systematically evaluated.

In the CRYO-ROP and LIGHT-ROP studies, treatment was initiated for threshold ROP (now termed "old threshold"). Based on the results of ET-ROP study, earlier treatment (termed "new threshold") is now recommended.<sup>7</sup> In the ET-ROP study, 60% of the infants with pre-threshold ROP (by the conventional definition used in the CRYO-ROP study) met the criteria for this earlier "new threshold" treatment. Based on these new treatment criteria, screening must now be initiated early enough to reliably identify infants with "new threshold", rather than "old threshold", ROP. In the CRYO-ROP study, for infants <750 g, ROP (any severity) occurred in 90% and reached pre-threshold in 39%. In 750-999 g infants ROP occurred in 78% and reached pre-threshold in 21%. In the <750 g infants, less than 5% of infants who reached pre-threshold ROP did so by 32.3 weeks postmenstrual age; in 750-999 g infants, <5% of those who reached pre-threshold ROP did so by 32.6 weeks postmenstrual age. In this study, <1% of infants who reached pre-threshold ROP did so by 30.9 weeks postmenstrual age.

In addition to information about when screening must begin, clinicians need information about when the baby is no longer at risk of treatable ROP so that appropriate follow-up can be arranged (particularly for infants who have been discharged from the hospital) or attempts to arrange follow-up can be curtailed. In the CRYO-ROP study, 99% of the infants who reached the threshold ROP criteria had done so by 45.9 weeks postmenstrual age.

In the NICHD Network SUPPORT trial, severe ROP ("new threshold" or treatment with laser, cryotherapy or bevacizumab) or death was the primary outcome for the O<sub>2</sub> saturation target arm of the factorial design. For this study, extensive ROP outcome data, in addition to the ROP outcome data routinely collected for the GDB, was prospectively collected for all enrolled infants. Infants 24 0/7 – 27 6/7 weeks gestation were eligible for this study. 1316 infants were enrolled. Ophthalmology exams began before 33 weeks post-menstrual age. For enrolled infants who survived until the first eye exam, the following data were recorded at each eye exam: the date of the eye exam, the highest stage and lowest zone of ROP, presence of plus disease, whether the infant met the criteria for "new threshold" ROP using the new ET-ROP definition, and whether treatment was administered. Examinations were continued according to current non-study screening recommendations. Study eye exam data was recorded until study endpoint (*I think it was really until treatment not untreated threshold disease but I'm not sure*), either full vascularization or vascularization in zone 3 in 2 consecutive exams, or the infant was 55 weeks postmenstrual age. *The manuscript says "until 1 year" but this is how I read the manual.*

These data will allow us to track the distribution of postnatal age and postmenstrual age at which treatable ROP occurs, using the new criteria for treatment and current survival demographics. We will use the data collected for this trial to generate tables and possibly figures, similar to those published from the CRYO-ROP and ET-ROP studies<sup>3</sup>, illustrating the distribution (with 1%, 5%, median, 95% and 99%iles) for the onset of ROP that meets the new threshold criteria for treatment.

### Methods

Postmenstrual age will be calculated as gestational age at birth in weeks + days, using the Best Obstetrical estimate, plus the postnatal age in days at the time of exam. In cases where the findings

differ between eyes, the age of onset will be recorded as the age at which the diagnostic criteria were met in the first eye.

Analytic Plan

A Baseline Characteristics Table will include the following summary statistics for all enrolled infants and for infants who survived until the first eye exam: birth weight (mean, SD), gestational age (mean, SD), race (% by category), sex (% by category), multiple birth (% by category)

The following Outcome Table will be generated:

ROP	n	Postmenstrual Age (weeks)					Postnatal Age (weeks)					
		1%	5%	Median	95%	99%	1%	5%	Median	95%	99%	
Any ROP												
New Threshold												

Separate tables will be generated for each of the trial strata (24 – 25 6/7 weeks and 26 – 26 6/7 weeks). If the data are indistinguishable, they will be combined and reported in a single table.

Limitations

We cannot generate incidence data because only consented inborn infants are included. The inclusion criteria will not allow us to generalize to infants < 24 weeks gestation. (NG03 form from the GDB does not include any dates of onset.)

We need to find out how much of a problem we have with missing data.  
A potential criticism is the lack of certified ROP examiners.

---

<sup>1</sup> Section on Ophthalmology American Academy of Pediatrics; American Academy of Ophthalmology; American Association for Pediatric Ophthalmology and Strabismus. Screening examination of premature infants for retinopathy of prematurity. *Pediatrics* 117: 572-6, 2006. Erratum (screen gestational age of 30 weeks or less) in: *Pediatrics* 118: 1324, 2006.

<sup>2</sup> Palmer EA et al. Incidence and early course of retinopathy of prematurity. *Ophthalmology* 98: 1628-1640, 1991.

<sup>3</sup> Reynolds JD, Dobson V, Quinn GE et al for the CRYO-ROP and LIGHT-ROP Cooperative Study Groups. Evidence-based screening criteria for retinopathy of prematurity: natural history data from the CRYO-ROP and LIGHT-ROP studies. *Arch Ophthalmol* 120: 1470-6, 2002.

<sup>4</sup> Cryotherapy for Retinopathy of Prematurity Cooperative Group. Multicenter trial of cryotherapy for retinopathy of prematurity; preliminary results. *Pediatrics* 81: 697-706, 1988 and *Arch Ophthalmol* 106: 471-479, 1988.

<sup>5</sup> Reynolds JD, Hardy RJ, Kennedy KA et al. Lack of efficacy of light reduction in preventing retinopathy of prematurity. Light Reduction in Retinopathy of Prematurity (LIGHT-ROP) Cooperative Group. *N Engl J Med* 338: 1572-6, 1998.

<sup>6</sup> Fanaroff AA, Stoll BJ, Wright LL et al for the NICHD Neonatal Research Network. Trends in neonatal morbidity and mortality for very low birthweight infants. *Am J Ob Gynecol* 196(2):147 e1-8, 2007.

<sup>7</sup> Good WV on behalf of the Early Treatment for Retinopathy of Prematurity Cooperative Group. Final results of the early treatment for retinopathy of prematurity (ETROP) randomized trial. *Trans Am Ophthalmol Soc* 102: 233-250, 2004.

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; "Abhik Das"; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); "Brenda Poindexter"; "Carlo Waldemar (E-mail)"; cotte010@mc.duke.edu; "Dennis Wallace"; "Ed Bell"; "Ed Donovan"; "Ehrenkranz Richard (E-mail)"; Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; "Kristi Watterberg"; Kurt Schibler [kurt.schibler@cchmc.org]; "Matthew Bizzarro"; "Michelle Walsh"; "Mickey Caplan"; "Oh William (E-mail)"; "Pablo Sanchez"; "Poole Kenneth (E-mail)"; "Roger Faix"; "Ronald GOLdberg"; "Seetha Shankaran"; "Stevenson David (E-mail)"; "Stoll Barbara (E-mail)"; "Tyson Jon (E-mail)"; VanMeurs, Krisa  
**Cc:** "Finer, Neil"; Archer, Stephanie (NIH/NICHD) [E]; "Zaterka-Baxter, Kristin"; "Cunningham, Meg"; "Huitema, Carolyn Petrie"  
**Subject:** Confidential PAS Presentation Finer SUPPORT 2010-04-06.ppt  
**Date:** Tuesday, April 06, 2010 12:19:00 PM  
**Attachments:** Finer SUPPORT 2010-04-06.ppt  
**Importance:** High

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Hi,

Attached is Neil's presentation for PAS. If you have any comments, please send them to Neil.

Please keep this information confidential. **We are not to discuss the fact that the papers have been reviewed or accepted by NEJM.** PI's - please insure that all of your staff with the confidential knowledge regarding the SUPPORT papers are aware of the NEJM rules!!

In addition, since the papers are not yet published in NEJM, we need to respect their embargo policy. This means that we are requested to follow the guidelines at <http://authors.nejm.org/Help/Embargo.asp>.

Specifically, the guidelines state:

- Please do not discuss the fact that the research has been submitted or accepted for publication in the *New England Journal of Medicine*.
- Please do not distribute any copies of the manuscript, tables, or figures. (It is acceptable to use the materials in a presentation, but they should not be distributed.)

Meeting organizers may promote an author's presentation in a press release, plan a press conference, publish the abstract in a meeting proceedings, and/or post the presentation on their Web site. We ask that authors, their institutions, and other organizations sponsoring the research not do any further promotion of the presentation

# Randomized Trial of Early CPAP versus Surfactant in Extremely Preterm Infants The SUPPORT Trial



The SUPPORT Study Group of the  
*Eunice Kennedy Shriver* NICHD  
Neonatal Research Network



NICHD





## **Disclosure Statement**

Dr. Finer has documented that he has no relevant financial relationships to disclose or COIs to resolve

Dr. Finer has documented that his presentation will not involve discussion of unapproved or off-label, experimental or investigational use agents.

## Background

- ✓ Surfactant treatment at less than 2 hours of life significantly decreases rates of death, air leak, and death or bronchopulmonary dysplasia (BPD) in preterm infants.
- ✓ Prophylactic surfactant has not been reported to significantly reduce the risk of BPD alone,
- ✓ Trials comparing early with later rescue use of surfactant have shown a decreased risk of chronic lung disease with early use
- ✓ Several studies have demonstrated that the use of surfactant does not significantly affect the risk of subsequent neurodevelopmental impairment



## Background

- ✓ No surfactant study had a comparison group who received early CPAP
- ✓ Follow-up from a randomized trial found that early ( mean 31 minutes of age) versus later ( mean 202 minutes of age) surfactant treatment was associated with significant increases in the frequency of infants with increased muscle tone and a delay in rolling from supine to prone (Hentschel et al, Acta Paediatr. 2009 Apr; 98:654-9)

## Background

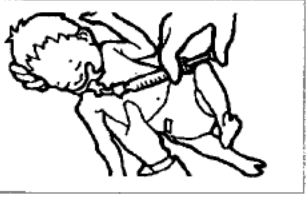


- ✓ Multiple reports from retrospective cohort studies have demonstrated that the early use of CPAP in very preterm infants with respiratory distress, not initially treated with surfactant, may decrease the need for mechanical ventilation without an increase in morbidity
- ✓ Morley et al reported the results of the COIN Trial of 610 infants between 25 0/7 to 28 6/7 weeks gestation at birth, who were able to breathe at 5 minutes of age and had evidence of respiratory distress

## **COIN Trial**

**Morley et al. NEJM2008; 358(7):700-708**

- ✓ Infants randomized to either intubation and ventilation, or CPAP at 8 cm H<sub>2</sub>O; CPAP infants were intubated if they met criteria for CPAP failure.
- ✓ No protocol requirement for surfactant administration
- ✓ As compared to the intubated group, the CPAP group had no significant reduction in the rate of death or need for oxygen at 36 weeks (the primary outcome), and a significantly higher rate of pneumothoraces (9.1% vs. 3.0%), most occurring within the first 2 days, consistent with the findings of an earlier meta analysis.



# Rationale

- ✓ Trials of ELBW infants randomized to early treatment with CPAP compared with early surfactant are needed to determine the optimal approach for such infants
- ✓ The SUPPORT Trial was designed to test such a comparison using early CPAP and a limited ventilator strategy and the administration of surfactant within 1 hour of birth

# Hypothesis

We hypothesized that early CPAP and a limited ventilator strategy compared to early Surfactant would reduce the incidence of death or survival with BPD at 36 weeks

## Method – Patients

- ✓ Inborn infants of 24<sup>0/7</sup> to 27<sup>6/7</sup> weeks gestation for whom a decision had been made to provide full resuscitation were eligible
- ✓ Parental consent was obtained
- ✓ Enrollment from February 2005 to February 2009
- ✓ Randomization was stratified by center and by gestational age (24 and 25 weeks; 26 and 27 weeks)



## **Factorial Design**

- Infants also randomized to 2 ranges of SpO<sub>2</sub> using purpose built blinded oximeters
- Ranges 85% to 89% vs 91% to 95%
- Below 84% and above 96% oximeters read actual SpO<sub>2</sub> values
- Results of this Trial presented by Dr Carlo at Clinical Epidemiology Session

## **Methods – Intervention - CPAP**

- ✓ In the delivery room, a T-piece resuscitator, a neonatal ventilator, or an equivalent CPAP methodology was used for the administration of CPAP. CPAP or ventilation with PEEP (at a recommended 5 cm H<sub>2</sub>O), was utilized if the infant received positive pressure during resuscitation. CPAP was continued until admission to the NICU
- ✓ Intubation was not performed for the sole purpose of surfactant administration in infants randomized to CPAP, but those infants who required intubation for resuscitation based on standard NRP indications were given surfactant within 60 minutes of birth

## Methods – Intervention - CPAP

In the NICU, infants randomized to CPAP could be intubated if they met any of the following criteria:

- ✓  $\text{FiO}_2$  greater than 0.50 required to maintain an indicated  $\text{SpO}_2$  at or above 88% for one hour,
- ✓ an arterial  $\text{PaCO}_2$  greater than 65 torr documented on a single blood gas within 1 hour prior to intubation
- ✓ hemodynamic instability defined as a low blood pressure for gestational age and/or poor perfusion, requiring volume and/or pressor support
- ✓ If intubated within the first 48 hours of life, infants were to receive surfactant.

## Methods – Intervention - CPAP

Extubation of infants in the CPAP arm was to be attempted within 24 hours of meeting all of the following criteria:

- ✓ a PaCO<sub>2</sub> below 65 torr with a pH greater than 7.20
- ✓ an SpO<sub>2</sub> greater than 88% with an FiO<sub>2</sub> below 50%
- ✓ a mean airway pressure (MAP) below 10 cm H<sub>2</sub>O, ventilator rate below 20 bpm, an amplitude below 2X MAP if on high frequency ventilation (HFV),
- ✓ hemodynamically stable, and without a clinically significant patent ductus arteriosus

## **Methods – Intervention - Surfactant**

- ✓ Infants were to receive surfactant within 1 hour of life,
- ✓ All infants were to be extubated within 24 hours of meeting all of the following criteria:
  - ✓ PaCO<sub>2</sub> below 50 torr and pH greater than 7.30
  - ✓ FiO<sub>2</sub>.35 or below with a SpO<sub>2</sub> 88% or higher, a MAP 8 cm H<sub>2</sub>O or lower , ventilator rate 20 bpm or less, an amplitude less than 2X MAP if on HFV, and hemodynamically stable without evidence of clinically significant PDA.
- ✓ Once extubated, infants were treated using NICU standard practice.

## **Methods – Duration of Intervention**

- ✓ The criteria for both arms were in effect for the first 14 days of life, following which the infant was treated as per NICU standard practice. For both arms, intubation could be performed at any time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery.

## **Methods – BPD Definitions**

- ✓ For the primary outcome, BPD was defined using the physiologic definition as the receipt of more than 30% oxygen at 36 weeks or the need for positive pressure support; or any oxygen dependence which was confirmed for infants requiring less than 30% oxygen at 36 weeks by attempted oxygen withdrawal.
- ✓ Pre-specified secondary outcomes included the evaluation of BPD defined by the receipt of oxygen at 36 weeks.

## Consort Diagram

3546 Infants were assessed for eligibility (3127 pregnancies)

235 Did not meet eligibility criteria  
125 Personnel/Equipment not available  
699 Eligible but consent not sought  
344 Parent or guardian unavailable  
748 Consent denied by parent or guardian  
11 Excluded for other reasons  
68 Consented but not randomized

1316 Underwent randomization

654 Randomized to oxygen saturation targeting 85-89%

662 Randomized to oxygen saturation targeting 91-95%

336 Randomized to early CPAP

318 Randomized to early surfactant

327 Randomized to early CPAP

335 Randomized to early surfactant

54 Died 282 Survived

60 Died 258 Survived

40 Died 287 Survived

54 Died 281 Survived

103 BPD 179 No BPD

102 BPD 156 No BPD

120 BPD 167 No BPD

117 BPD 164 No BPD



## Results – Patient Population

	Lower Saturation Group (N = 654)	Higher Saturation Group (N = 662)
Birthweight Overall (Mean ± StdDev)	835 ± 188.2	826 ± 198.1
Gestational Age (Mean ± StdDev)	26.2 ± 1.1	26.2 ± 1.1
Gestational Age --- 24 to 25 6/7ths	43% (285/663)	42.9% (280/653)
--- 26 to 27 6/7ths	57% (378/663)	57.1% (373/653)
Race, White/Black/Hispanic (%)	38.3 / 37.7 / 20.3	36 / 41.5/ 18.5
Antenatal corticosteroids	96.8%	95.6%
.....	96.8%	94.3%

## Results – Primary Outcome

	<b>CPAP N=654</b>	<b>Surfactant N=662</b>	<b>Adjusted Relative Risk (95% CI)</b>
<b>Death or BPD (Physiologic)</b>	<b>47.8% (317/663)</b>	<b>51.0% (333/653)</b>	<b>0.95 (0.85, 1.05)</b>
<b>BPD - Physiologic</b>	<b>39.2% (223/569)</b>	<b>40.6% (219/539)</b>	<b>0.99 (0.87, 1.14)</b>
<b>Death</b>	<b>14.2% (94/663)</b>	<b>17.5% (114/653)</b>	<b>0.81 (0.63, 1.03)</b>

## Results – Delivery Room

<b>Variable</b>	<b>CPAP (N=663)</b>	<b>Surfactant (N=653)</b>	<b>Relative Risk for CPAP vs. Surfactant (95% CI)</b>	<b>Adjusted P- value</b>
Apgar at 1 minute <3	23.3% (154/661)	25.6% (167/653)	0.92 (0.76, 1.11)	0.38
Apgar at 5 minutes <3	3.9% (26/663)	4.9% (32/653)	0.82 (0.5, 1.34)	0.43
PPV in the DR	65.7% (435/662)	92.9% (606/652)	0.71 (0.67, 0.75)	<0.0001
Intubated in DR	34.4% (227/660)	93.4% (609/652)	0.37 (0.34, 0.42)	<0.0001
DR intubation for resuscitation	32.6% (215/660)	27.0% (176/652)	1.21 (1.02, 1.43)	0.02
Surfactant in DR or NICU	67.1% (443/660)	98.9% (646/653)	0.67 (0.64, 0.71)	<0.0001
Epinephrine in DR	2.0% (13/660)	4.1% (27/653)	0.48 (0.25, 0.91)	0.02

## Results – Other Pre-specified Outcomes \* = p<0.05

	CPAP N=654	Surfactant N=662	Relative Risk or Difference in Means for CPAP vs. Surfactant
BPD (physiologic), 36 wks	39.2%	40.6%	0.99 (0.87, 1.14)
BPD (O <sub>2</sub> use at 36 wks)	40.2%	44.3%	0.94 (0.82, 1.06)
BPD (O <sub>2</sub> use) or death, 36 wks	48.5%	54.2%	0.91 (0.83, 1.01)
Severe ROP among survivors	13.1%	13.7%	0.94 (0.69, 1.28)
Any air leaks (14 days)	6.8%	7.4%	0.89 (0.6, 1.32)
Days on mechanical vent (HFV & CV)	24.8 ± 1.0	27.7 ± 1.1	-3.0 (-5.6, -0.3)*
Alive and off MV (HFV/CV) at 7 days	55.3% (362/655)	48.8% (318/652)	1.14 (1.03, 1.25)*
Postnatal steroids for BPD	7.2%	13.2%	0.57 (0.41, 0.78)*

## **SUPPORT – Other Results**

- ✓ There were no differences in the incidence of PDA, PDA requiring surgery, Medical or Surgical NEC
- ✓ There were no differences between the groups for Severe IVH/PVL
- For the 24 to 25 weeks strata there was a significant decrease in death for the CPAP infants :  
CPAP 20.0% vs Surfactant 29.3%  
Relative Risk difference 0.68 (0.5, 0.92)

## SUMMARY

- ✓ There was no significant difference for the primary outcome of death or BPD
- ✓ Fewer CPAP infants required intubation in the DR or overall,  $p < 0.001$ , and more were alive and off mechanical ventilation by day 7, ( $p = 0.011$ ) and they required fewer days of ventilation ( $p = 0.03$ ).
- ✓ The rate of use of postnatal steroids for BPD was lower in the CPAP group compared with the surfactant group ( $p < 0.001$ )
- ✓ Infants 24 to 25 6/7 weeks gestation randomized to CPAP had a significantly lower mortality rate while hospitalized

## Conclusions

- ✓ Early CPAP and a limited ventilator strategy is an effective alternative to early Surfactant for the initial stabilization and ongoing management of the extremely low birth weight infant
- ✓ CPAP was not associated with any increase in adverse neonatal outcomes including air leaks
- ✓ All surviving infants will have a full neurodevelopmental evaluation at 18 to 22 months

**Thanks to the many parents, infants,  
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



## 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,	80.8 ± 2.3	80.3 ± 2.4	0.5 (-5.8, 6.9)	0.86
Unadjusted Median (IQR) (N=421)	79.5 (51.5, 108.5)	79 (52, 110)		
Days on mechanical vent (HFV & CV) † Adjusted Mean ± StdErr, Unadjusted Median (IQR) (N=421)	35.8 ± 1.5	38.7 ± 1.6	-3.0 (-7.2, 1.3)	0.17
	29.5 (10, 48)	33 (14, 56)		
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

## 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

# Methods – Sample Size Estimate

- Baseline rate of BPD/Death of 50%
- Absolute risk difference of 10%
- Increased by 1.12 to allow for multiples randomized to same treatment
- Increased by 1.17 to adjust for attrition
- Increased further to minimize Type I error using a conservative 2% level of significance
- Final sample size was 1310 infants

# Methods – Data Analysis

- The primary and categorical outcomes were analyzed using Poisson regression implementation in a Generalized Estimating Equation (GEE) model to obtain adjusted relative risk and 95% CI
- Continuous outcomes were analyzed using mixed effects linear models to produce adjusted means and standard errors
- Adjustment was performed for pre-specified stratification (center and GA) and for familial clustering as multiple births were randomized to the same treatment arms

**From:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**To:** [Archer, Stephanie \(NIH/NICHD\) \[E\]](#)  
**Subject:** RE: Randomized Trial of CPAP vs Surfactant SUPPORT Trial PAS-ATS (2).ppt  
**Date:** Tuesday, April 06, 2010 11:54:00 AM

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Did he have all of the required elements on the original one? We need a better background in general as folks do not like the one on the website (If they liked it, they would consistently use it).

---

**From:** Archer, Stephanie (NIH/NICHD) [E]  
**Sent:** Tuesday, April 06, 2010 11:52 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Randomized Trial of CPAP vs Surfactant SUPPORT Trial PAS-ATS (2).ppt

What do you want me to do with it?

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Tuesday, April 06, 2010 11:51 AM  
**To:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** FW: Randomized Trial of CPAP vs Surfactant SUPPORT Trial PAS-ATS (2).ppt

They are wedded to the blue!!!

---

**From:** Finer, Neil [<mailto:nfiner@ucsd.edu>]  
**Sent:** Tuesday, April 06, 2010 11:48 AM  
**To:** Archer, Stephanie (NIH/NICHD) [E]; Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade  
**Subject:** RE: Randomized Trial of CPAP vs Surfactant SUPPORT Trial PAS-ATS (2).ppt

Hi Stephanie

I don't like either of these – the colors are not as vibrant. I used the same colors as Wally

I would prefer to use my original

We have used all the Network logos etc

I will see what Rose says

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:** Archer, Stephanie (NIH/NICHD) [E] [mailto:archerst@mail.nih.gov]  
**Sent:** Tuesday, April 06, 2010 8:24 AM  
**To:** Finer, Neil  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Randomized Trial of CPAP vs Surfactant SUPPORT Trial PAS-ATS (2).ppt

Hi Neil,

Rose asked me to work with you to reformat your presentation to conform with the NRN presentation templates. Which of the two attached templates do you want to use?

I have the version of your presentation that you sent to Rose on Monday. I can take the information in it and put it into the template for you. If you have a more updated version, please send it to me.

Thank you,

Stephanie

---

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The Eunice Kennedy Shriver  
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---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Monday, April 05, 2010 3:16 PM  
**To:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** Randomized Trial of CPAP vs Surfactant SUPPORT Trial PAS-ATS (2).ppt

Can you put the NRN logo on the title slide and can you fix the acknowledgement slide to include one slide for 2004-2009 and SUPPORT Trial study sites??

Thanks  
Rose

**From:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**To:** [Archer, Stephanie \(NIH/NICHD\) \[E\]](#)  
**Subject:** Randomized Trial of CPAP vs Surfactant SUPPORT Trial PAS-ATS (2).ppt  
**Date:** Monday, April 05, 2010 3:16:00 PM  
**Attachments:** [Randomized Trial of CPAP vs Surfactant SUPPORT Trial PAS-ATS \(2\).ppt](#)

---

Can you put the NRN logo on the title slide and can you fix the acknowledgement slide to include one slide for 2004-2009 and SUPPORT Trial study sites??

Thanks  
Rose



# Randomized Trial of Early CPAP versus Surfactant in Extremely Preterm Infants The SUPPORT Trial



The SUPPORT Study Group of the  
*Eunice Kennedy Shriver* NICHD  
Neonatal Research Network



NICHD



## **Disclosure Statement**

Dr. Finer has documented that he has no relevant financial relationships to disclose or COIs to resolve

Dr. Finer has documented that his presentation will not involve discussion of unapproved or off-label, experimental or investigational use agents.

## Background

- ✓ Surfactant treatment at less than 2 hours of life significantly decreases rates of death, air leak, and death or bronchopulmonary dysplasia (BPD) in preterm infants.
- ✓ Prophylactic surfactant has not been reported to significantly reduce the risk of BPD alone,
- ✓ Trials comparing early with later rescue use of surfactant have shown a decreased risk of chronic lung disease with early use
- ✓ Several studies have demonstrated that the use of surfactant does not significantly affect the risk of subsequent neurodevelopmental impairment



## Background

- ✓ No surfactant study had a comparison group who received early CPAP
- ✓ Follow-up from a randomized trial found that early ( mean 31 minutes of age) versus later ( mean 202 minutes of age) surfactant treatment was associated with significant increases in the frequency of infants with increased muscle tone and a delay in rolling from supine to prone (Hentschel et al, Acta Paediatr. 2009 Apr; 98:654-9)

## Background



- ✓ Multiple reports from retrospective cohort studies have demonstrated that the early use of CPAP in very preterm infants with respiratory distress, not initially treated with surfactant, may decrease the need for mechanical ventilation without an increase in morbidity
- ✓ Morley et al reported the results of the COIN Trial of 610 infants between 25 0/7 to 28 6/7 weeks gestation at birth, who were able to breathe at 5 minutes of age and had evidence of respiratory distress

## **COIN Trial**

**Morley et al. NEJM2008; 358(7):700-708**

- ✓ Infants randomized to either intubation and ventilation, or CPAP at 8 cm H<sub>2</sub>O; CPAP infants were intubated if they met criteria for CPAP failure.
- ✓ No protocol requirement for surfactant administration
- ✓ As compared to the intubated group, the CPAP group had no significant reduction in the rate of death or need for oxygen at 36 weeks (the primary outcome), and a significantly higher rate of pneumothoraces (9.1% vs. 3.0%), most occurring within the first 2 days, consistent with the findings of an earlier meta analysis.



## Rationale

- ✓ Trials of ELBW infants randomized to early treatment with CPAP compared with early surfactant are needed to determine the optimal approach for such infants
- ✓ The SUPPORT Trial was designed to test such a comparison using early CPAP and a limited ventilator strategy and the administration of surfactant within 1 hour of birth

# Hypothesis

We hypothesized that early CPAP and a limited ventilator strategy compared to early Surfactant would reduce the incidence of death or survival with BPD at 36 weeks



## Method – Patients

- ✓ Inborn infants of 24<sup>0/7</sup> to 27<sup>6/7</sup> weeks gestation for whom a decision had been made to provide full resuscitation were eligible
- ✓ Parental consent was obtained
- ✓ Enrollment from February 2005 to February 2009
- ✓ Randomization was stratified by center and by gestational age (24 and 25 weeks; 26 and 27 weeks)

# Factorial Design

- Infants also randomized to 2 ranges of SpO<sub>2</sub> using purpose built blinded oximeters
- Ranges 85% to 89% vs 91% to 95%
- Below 84% and above 96% oximeters read actual SpO<sub>2</sub> values
- Results of this Trial presented by Dr Carlo at Clinical Epidemiology Session

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- ✓ In the delivery room, a T-piece resuscitator, a neonatal ventilator, or an equivalent CPAP methodology was used for the administration of CPAP. CPAP or ventilation with PEEP (at a recommended 5 cm H<sub>2</sub>O), was utilized if the infant received positive pressure during resuscitation. CPAP was continued until admission to the NICU
- ✓ Intubation was not performed for the sole purpose of surfactant administration in infants randomized to CPAP, but those infants who required intubation for resuscitation based on standard NRP indications were given surfactant within 60 minutes of birth

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In the NICU, infants randomized to CPAP could be intubated if they met any of the following criteria:

- ✓  $\text{FiO}_2$  greater than 0.50 required to maintain an indicated  $\text{SpO}_2$  at or above 88% for one hour,
- ✓ an arterial  $\text{PaCO}_2$  greater than 65 torr documented on a single blood gas within 1 hour prior to intubation
- ✓ hemodynamic instability defined as a low blood pressure for gestational age and/or poor perfusion, requiring volume and/or pressor support
- ✓ If intubated within the first 48 hours of life, infants were to receive surfactant.

## Methods – Intervention - CPAP

Extubation of infants in the CPAP arm was to be attempted within 24 hours of meeting all of the following criteria:

- ✓ a PaCO<sub>2</sub> below 65 torr with a pH greater than 7.20
- ✓ an SpO<sub>2</sub> greater than 88% with an FiO<sub>2</sub> below 50%
- ✓ a mean airway pressure (MAP) below 10 cm H<sub>2</sub>O, ventilator rate below 20 bpm, an amplitude below 2X MAP if on high frequency ventilation (HFV),
- ✓ hemodynamically stable, and without a clinically significant patent ductus arteriosus

## Methods – Intervention - Surfactant

- ✓ Infants were to receive surfactant within 1 hour of life,
- ✓ All infants were to be extubated within 24 hours of meeting all of the following criteria:
  - ✓ PaCO<sub>2</sub> below 50 torr and pH greater than 7.30
  - ✓ FiO<sub>2</sub>.35 or below with a SpO<sub>2</sub> 88% or higher, a MAP 8 cm H<sub>2</sub>O or lower , ventilator rate 20 bpm or less, an amplitude less than 2X MAP if on HFV, and hemodynamically stable without evidence of clinically significant PDA.
- ✓ Once extubated, infants were treated using NICU standard practice.

## **Methods – Duration of Intervention**

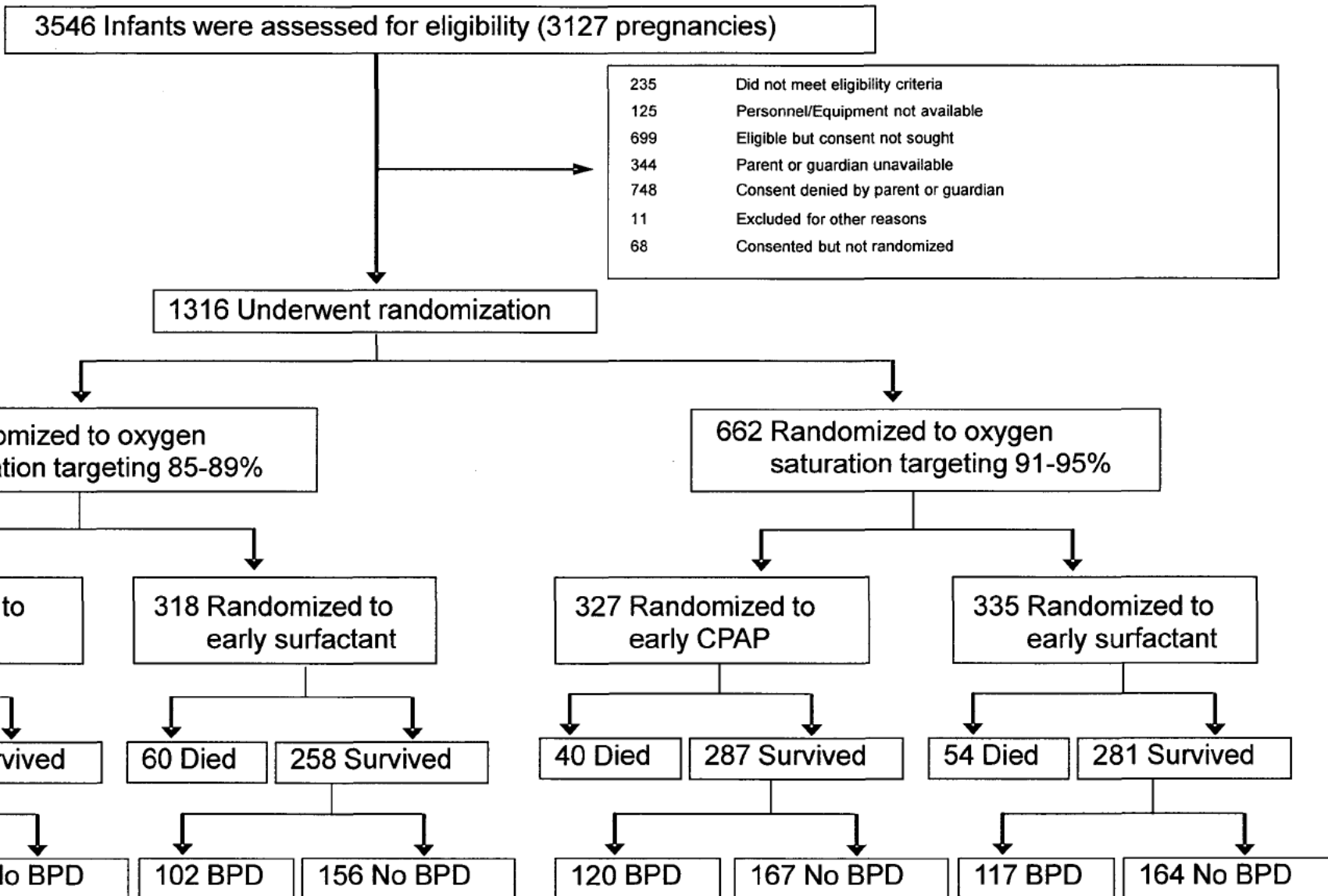
- ✓ The criteria for both arms were in effect for the first 14 days of life, following which the infant was treated as per NICU standard practice. For both arms, intubation could be performed at any time for the occurrence of repetitive apnea requiring bag and mask ventilation, clinical shock, sepsis, and/or the need for surgery.

## **Methods – BPD Definitions**

- ✓ For the primary outcome, BPD was defined using the physiologic definition as the receipt of more than 30% oxygen at 36 weeks or the need for positive pressure support; or any oxygen dependence which was confirmed for infants requiring less than 30% oxygen at 36 weeks by attempted oxygen withdrawal.
- ✓ Pre-specified secondary outcomes included the evaluation of BPD defined by the receipt of oxygen at 36 weeks.



## Consort Diagram



## Results – Patient Population

	Lower Saturation Group (N = 654)	Higher Saturation Group (N = 662)
Birthweight Overall (Mean ± StdDev)	835 ± 188.2	826 ± 198.1
Gestational Age (Mean ± StdDev)	26.2 ± 1.1	26.2 ± 1.1
Gestational Age --- 24 to 25 6/7ths	43% (285/663)	42.9% (280/653)
--- 26 to 27 6/7ths	57% (378/663)	57.1% (373/653)
Race, White/Black/Hispanic (%)	38.3 / 37.7 / 20.3	36 / 41.5/ 18.5
Antenatal corticosteroids	96.8%	95.6%
.....	96.8%	94.3%

## Results – Primary Outcome

	<b>CPAP N=654</b>	<b>Surfactant N=662</b>	<b>Adjusted Relative Risk (95% CI)</b>
<b>Death or BPD (Physiologic)</b>	<b>47.8% (317/663)</b>	<b>51.0% (333/653)</b>	<b>0.95 (0.85, 1.05)</b>
<b>BPD - Physiologic</b>	<b>39.2% (223/569)</b>	<b>40.6% (219/539)</b>	<b>0.99 (0.87, 1.14)</b>
<b>Death</b>	<b>14.2% (94/663)</b>	<b>17.5% (114/653)</b>	<b>0.81 (0.63, 1.03)</b>

## Results – Delivery Room

<b>Variable</b>	<b>CPAP (N=663)</b>	<b>Surfactant (N=653)</b>	<b>Relative Risk for CPAP vs. Surfactant (95% CI)</b>	<b>Adjusted P- value</b>
Apgar at 1 minute <3	23.3% (154/661)	25.6% (167/653)	0.92 (0.76, 1.11)	0.38
Apgar at 5 minutes <3	3.9% (26/663)	4.9% (32/653)	0.82 (0.5, 1.34)	0.43
PPV in the DR	65.7% (435/662)	92.9% (606/652)	0.71 (0.67, 0.75)	<0.0001
Intubated in DR	34.4% (227/660)	93.4% (609/652)	0.37 (0.34, 0.42)	<0.0001
DR intubation for resuscitation	32.6% (215/660)	27.0% (176/652)	1.21 (1.02, 1.43)	0.02
Surfactant in DR or NICU	67.1% (443/660)	98.9% (646/653)	0.67 (0.64, 0.71)	<0.0001
Epinephrine in DR	2.0% (13/660)	4.1% (27/653)	0.48 (0.25, 0.91)	0.02

## Results – Other Pre-specified Outcomes \* = p<0.05

	CPAP N=654	Surfactant N=662	Relative Risk or Difference in Means for CPAP vs. Surfactant
BPD (physiologic), 36 wks	39.2%	40.6%	0.99 (0.87, 1.14)
BPD (O <sub>2</sub> use at 36 wks)	40.2%	44.3%	0.94 (0.82, 1.06)
BPD (O <sub>2</sub> use) or death, 36 wks	48.5%	54.2%	0.91 (0.83, 1.01)
Severe ROP among survivors	13.1%	13.7%	0.94 (0.69, 1.28)
Any air leaks (14 days)	6.8%	7.4%	0.89 (0.6, 1.32)
Days on mechanical vent (HFV & CV)	24.8 ± 1.0	27.7 ± 1.1	-3.0 (-5.6, -0.3)*
Alive and off MV (HFV/CV) at 7 days	55.3% (362/655)	48.8% (318/652)	1.14 (1.03, 1.25)*
Postnatal steroids for BPD	7.2%	13.2%	0.57 (0.41, 0.78)*

## **SUPPORT – Other Results**

- ✓ There were no differences in the incidence of PDA, PDA requiring surgery, Medical or Surgical NEC
- ✓ There were no differences between the groups for Severe IVH/PVL
- For the 24 to 25 weeks strata there was a significant decrease in death for the CPAP infants :  
CPAP 20.0% vs Surfactant 29.3%  
Relative Risk difference 0.68 (0.5, 0.92)

## SUMMARY

- ✓ There was no significant difference for the primary outcome of death or BPD
- ✓ Fewer CPAP infants required intubation in the DR or overall,  $p < 0.001$ , and more were alive and off mechanical ventilation by day 7, ( $p = 0.011$ ) and they required fewer days of ventilation ( $p = 0.03$ ).
- ✓ The rate of use of postnatal steroids for BPD was lower in the CPAP group compared with the surfactant group ( $p < 0.001$ )
- ✓ Infants 24 to 25 6/7 weeks gestation randomized to CPAP had a significantly lower mortality rate while hospitalized

## Conclusions

- ✓ Early CPAP and a limited ventilator strategy is an effective alternative to early Surfactant for the initial stabilization and ongoing management of the extremely low birth weight infant
- ✓ CPAP was not associated with any increase in adverse neonatal outcomes including air leaks
- ✓ All surviving infants will have a full neurodevelopmental evaluation at 18 to 22 months



**Thanks to the many parents, infants,  
and NICU staff**



**Thanks to the members of the  
Neonatal Research Network**

# NICHD Neonatal Research Network Centers (2001-2006)

- Brown University
- Case Western Reserve University
- Duke University
- Emory University
- Indiana University
- Research Triangle Institute
- Stanford University
- University of Alabama – Birmingham
- University of California – San Diego
- University of Cincinnati
- University of Miami
- University of Rochester
- University of Texas, Southwestern – Dallas
- University of Texas – Houston
- Wake Forest University
- Wayne State University
- Yale University



# NICHD Neonatal Research Network Centers (2006-2011)

- Brown University
- Case Western Reserve University
- Duke University
- Emory University
- Indiana University
- Research Triangle Institute
- Stanford University
- Tufts Medical Center
- University of Cincinnati
- University of Alabama – Birmingham
- University of Iowa
- University of New Mexico
- University of Texas, Southwestern – Dallas
- University of Texas – Houston
- University of Utah
- Wayne State University
- Yale University



## 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,	80.8 ± 2.3	80.3 ± 2.4	0.5 (-5.8, 6.9)	0.86
Unadjusted Median (IQR) (N=421)	79.5 (51.5, 108.5)	79 (52, 110)		
Days on mechanical vent (HFV & CV) † Adjusted Mean ± StdErr, Unadjusted Median (IQR) (N=421)	35.8 ± 1.5	38.7 ± 1.6	-3.0 (-7.2, 1.3)	0.17
Unadjusted Median (IQR) (N=421)	29.5 (10, 48)	33 (14, 56)		
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

## 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

# Methods – Sample Size Estimate

- Baseline rate of BPD/Death of 50%
- Absolute risk difference of 10%
- Increased by 1.12 to allow for multiples randomized to same treatment
- Increased by 1.17 to adjust for attrition
- Increased further to minimize Type I error using a conservative 2% level of significance
- Final sample size was 1310 infants

# Methods – Data Analysis

- The primary and categorical outcomes were analyzed using Poisson regression implementation in a Generalized Estimating Equation (GEE) model to obtain adjusted relative risk and 95% CI
- Continuous outcomes were analyzed using mixed effects linear models to produce adjusted means and standard errors
- Adjustment was performed for pre-specified stratification (center and GA) and for familial clustering as multiple births were randomized to the same treatment arms

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Evans, Patricia W"; "Mcdavid, Georgia E"  
**Cc:** "Gantz, Marie"; "Poundstone, Margaret"  
**Subject:** RE: SUPPORT FU OUTCOMES  
**Date:** Monday, April 05, 2010 12:30:00 PM

---

WE have her on the most current list

Thanks  
Rose

-----Original Message-----

From: Evans, Patricia W [mailto:Patricia.W.Evans@uth.tmc.edu]  
Sent: Monday, March 29, 2010 12:02 PM  
To: Higgins, Rosemary (NIH/NICHD) [E]; Mcdavid, Georgia E  
Cc: 'Gantz, Marie'; Poundstone, Margaret  
Subject: RE: SUPPORT FU OUTCOMES

For the e-mails regarding Support FU outcomes, can you please remove Georgia McDavid from the list and replace her with Margaret Poundstone? She is the research coordinator for follow-up and responsible for this information.

Thanks so much,

Patricia Wilder Evans, MD  
Assistant Professor, Department of Pediatrics  
Medical Director, High-Risk Infant Clinic  
6431 Fannin St, MSB 3.218  
713-500-5311 office  
713-500-5794 fax  
Patricia.W.Evans@uth.tmc.edu<mailto:Patricia.W.Evans@uth.tmc.edu>

---

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]  
Sent: Thursday, March 18, 2010 12:58 PM  
To: Kennedy, Kathleen A; Evans, Patricia W; Tyson, Jon E; Mcdavid, Georgia E  
Cc: 'Gantz, Marie'  
Subject: SUPPORT FU OUTCOMES

Hi,

We are missing the following SUPPORT Follow up outcomes. Let us know how you are doing and THANKS for all the hard work!!!

Rose  
CENTER

NETWORK

FU\_message

18

(b)

FU window has closed but NF05 and NF09a have not been completed.

18



(b)

FU window has closed but NF05 and NF09a have not been completed.

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network  
Pregnancy and Perinatology Branch  
Center for Developmental Biology and Perinatal Medicine  
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Bethesda, MD 20892  
For overnight delivery use Rockville, MD 20852  
301-496-5575  
301-496-3790 (FAX)  
higginsr@mail.nih.gov

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "adas@rti.org"; "wcarlo@peds.uab.edu"; "sam@rti.org"  
**Cc:** "rwebb@rti.org"  
**Subject:** Re: New England Journal of Medicine 10-00843  
**Date:** Friday, April 02, 2010 4:24:21 PM

---

This works - we can use our call-in line

Rose

----- Original Message -----

**From:** Das, Abhik <adas@rti.org>  
**To:** Wally Carlo, M.D. <WCarlo@peds.uab.edu>; McDonald, Scott A. <sam@rti.org>  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Mon Mar 29 11:41:41 2010  
**Subject:** RE: New England Journal of Medicine 10-00843

How about Tuesday April 6 at 1 pm EDT? We would need to confirm with Rose after she gets back.

Thanks

Abhik

-----Original Message-----

**From:** Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]  
**Sent:** Monday, March 29, 2010 11:38 AM  
**To:** Das, Abhik; McDonald, Scott A.  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: New England Journal of Medicine 10-00843

Agree

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: 205 266 (b)

-----Original Message-----

**From:** Das, Abhik [mailto:adas@rti.org]  
**Sent:** Monday, March 29, 2010 9:09 AM  
**To:** Wally Carlo, M.D.; McDonald, Scott A.  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: New England Journal of Medicine 10-00843

Sure, perhaps we should talk early next week after Rose gets back?

Thanks

Abhik

-----Original Message-----

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]  
Sent: Sunday, March 28, 2010 10:09 AM  
To: Das, Abhik; McDonald, Scott A.  
Cc: Higgins, Rosemary (NIH/NICHD) [E]  
Subject: FW: New England Journal of Medicine 10-00843

Hi Abhik and Scott:

Rose and I reviewed the comments of the reviewers. We felt that the main issues that may need to be addressed are the statistical ones but you are the experts so it would be great if we could work together to have a recommendation of changes to be made to the paper, if any, in response to the reviews. We are not sending it back to NEJM so it is not necessary to draft a response or even change the paper if we do not think the change will improve the manuscript.

We have a conf call on April 22 and I would like to have any suggested changes settled maybe a few days before so we can circulate them and give them time to review before the call.

Would this work?

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: 205 266 (b)

-----Original Message-----

From: onbehalfof+editorial+nejm.org@manuscriptcentral.com  
[mailto:onbehalfof+editorial+nejm.org@manuscriptcentral.com] On Behalf Of editorial@nejm.org  
Sent: Tuesday, February 16, 2010 7:47 AM  
To: Wally Carlo, M.D.  
Subject: New England Journal of Medicine 10-00843

Dear Dr. Carlo,

Your manuscript, "Cytokines and Neurodevelopmental Outcomes in Extremely Low Birth Weight Infants," was evaluated by external reviewers and was discussed among the editors. Although it is interesting, I am sorry to say it was not accepted for publication. This was an editorial decision and reflects an assessment of the merits of your manuscript as compared with the many others we receive. Unfortunately, many manuscripts must be declined for lack of space.

Thank you very much for the opportunity to review this manuscript.

Sincerely,

Caren G. Solomon, M.D.  
Deputy Editor

New England Journal of Medicine  
10 Shattuck Street  
Boston, MA 02115  
(617) 734-9800  
Fax: (617) 739-9864  
<http://www.nejm.org>

Reviewer: 1

<b>Comments for the Author</b>

(b) (4) [Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

(b) (4)  
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[Redacted text block]

[Redacted text block]



**From:** [Johnson, Karen](#)  
**To:** [Johnson, Karen](#); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Eastman, Diane](#); [Bell, Edward](#); [Acarregui, Michael](#)  
**Cc:** [Gantz, Marie](#); [Auman, Jeanette O.](#)  
**Subject:** RE: SUPPORT FU OUTCOMES  
**Date:** Friday, April 02, 2010 4:15:30 PM

---

Has anyone checked to see if these appear now in the DMS?

## Karen

---

Karen Johnson, RN  
Neonatal Research Network Coordinator  
Pediatrics, Neonatology  
8900 JPP  
University of Iowa Children's Hospital  
Iowa City, Iowa 52242  
(319) 356-2924  
pager (319) 356-(b) ask for pager (b)

---

**From:** Johnson, Karen  
**Sent:** Monday, March 22, 2010 10:23 AM  
**To:** 'Higgins, Rosemary (NIH/NICHD) [E]'; Eastman, Diane; Bell, Edward; Acarregui, Michael  
**Cc:** Gantz, Marie; 'Auman, Jeanette O.'  
**Subject:** RE: SUPPORT FU OUTCOMES

We show that these were entered on 3/6.

## Karen

---

Karen Johnson, RN  
Neonatal Research Network Coordinator  
Pediatrics, Neonatology  
8900 JPP  
University of Iowa Children's Hospital  
Iowa City, Iowa 52242  
(319) 356-2924  
pager (319) 356-(b) ask for pager (b)

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]  
**Sent:** Friday, March 19, 2010 7:44 AM  
**To:** Eastman, Diane; Bell, Edward; Johnson, Karen; Acarregui, Michael  
**Cc:** Gantz, Marie; 'Auman, Jeanette O.'  
**Subject:** RE: SUPPORT FU OUTCOMES

Great  
I have copied Jenny to see if she can locate the forms

Thanks  
Rose

---

**From:** Eastman, Diane [mailto:diane-eastman@uiowa.edu]  
**Sent:** Thursday, March 18, 2010 6:15 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Bell, Edward; Johnson, Karen; Acarregui, Michael  
**Cc:** Gantz, Marie  
**Subject:** RE: SUPPORT FU OUTCOMES

Rose,  
(b) and (b) (6) the forms were done, so will check to see why they were not entered.  
(b) is the family that moved to Maryland and the person who will do the Bayley is currently on maternity leave. I'm to contact her in April regarding arranging the appt. Diane

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Thursday, March 18, 2010 1:01 PM  
**To:** Bell, Edward; Johnson, Karen; Acarregui, Michael; Eastman, Diane  
**Cc:** 'Gantz, Marie'  
**Subject:** SUPPORT FU OUTCOMES

Hi,

We are missing the following SUPPORT Follow up outcomes. Let us know how you are doing and THANKS for all the hard work!!!

Rose

CENTER	NETWORK	FU_message
24	(b)	FU marked as complete (per NF10/SF10) but NF09a has not been completed.
24	(b)	FU marked as complete (per NF10/SF10) but NF09a has not been completed.
24	(b)	FU window has closed but NF05 has not been completed.

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network  
Pregnancy and Perinatology Branch  
Center for Developmental Biology and Perinatal Medicine  
Eunice Kennedy Shriver National Institute of Child Health and Human Development  
National Institutes of Health  
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MSC 7510  
Bethesda, MD 20892  
For overnight delivery use Rockville, MD 20852  
301-496-5575  
301-496-3790 (FAX)  
higginsr@mail.nih.gov



**From:** [Cunningham, Meg](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\)](#) [E]  
**Subject:** Quick Question  
**Date:** Friday, March 26, 2010 3:59:37 PM

---

Hi Rose,

I am helping Kris get out the SUPPORT papers to the DSMC. We were wondering if we should include Gordon Avery. Since he is no longer part of the DSMC, we weren't sure where the guidelines on that stood. What should I do?

Thanks and I promise this is my last email before your vacation!  
Meg

*Meg Cunningham*  
*RTI International*  
*701 13th St. NW, Ste. 750*  
*Washington, DC 20005*  
*tel: 202-974-7837*  
*fax: 202-728-2095*  
[www.rti.org](http://www.rti.org)

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Vivien Phillips"; "wacarlo@uab.edu"; "ambal@uab.edu"; "Myriam Peralta, M.D."; "Monica Collins"; "Shirley Cosby"  
**Cc:** "Gantz, Marie"  
**Subject:** RE: SUPPORT FU OUTCOMES  
**Date:** Friday, March 26, 2010 2:19:00 PM

---

As always, AWESOME

THANKS  
ROSE

---

**From:** Vivien Phillips [mailto:VPhillips@peds.uab.edu]  
**Sent:** Friday, March 26, 2010 2:19 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; wacarlo@uab.edu; ambal@uab.edu; Myriam Peralta, M.D.; Monica Collins; Shirley Cosby  
**Cc:** Gantz, Marie  
**Subject:** RE: SUPPORT FU OUTCOMES

(b) - moved to another state and attempts to see child didn't work out. Lost to follow up form will be entered.

(b) - home visit done last week and forms entered this week.

(b) - currently tracking

(b) - not really sure why these NF09a forms are showing up as "not completed" as they've been previously keyed.

Vivien

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Thursday, March 18, 2010 12:58 PM  
**To:** wacarlo@uab.edu; 'Ambal (ambal@uab.edu)'; Myriam Peralta, M.D.; Monica Collins; Shirley Cosby; Vivien Phillips  
**Cc:** 'Gantz, Marie'  
**Subject:** SUPPORT FU OUTCOMES

Hi,

We are missing the following SUPPORT Follow up outcomes. Let us know how you are doing and THANKS for all the hard work!!! This is terrific given your outstanding recruitment---

Rose

16	(b)	FU window has closed but NF05 and NF09a have not been completed.
16	(b)	FU window has closed but NF05 and NF09a have not been completed.
16	(b)	FU window has closed but NF05 and NF09a have not been completed.
16	(b)	FU window has closed but NF05 and NF09a have not been completed.
16	(b)	FU marked as complete (per NF10/SF10) but NF09a has not been completed.
16	(b)	FU marked as complete (per NF10/SF10) but NF09a has not been completed.

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network  
Pregnancy and Perinatology Branch  
Center for Developmental Biology and Perinatal Medicine  
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Bethesda, MD 20892

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For overnight delivery use Rockville, MD 20852  
301-496-5575  
301-496-3790 (FAX)  
higginsr@mail.nih.gov

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Wally Carlo, M.D."  
**Subject:** RE: Randomized Trial of Oxygen Saturation Targets 3-26-10.ppt  
**Date:** Friday, March 26, 2010 1:08:00 PM

---

NO problem - Remember, my husband (b) (6)

-----Original Message-----

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]  
Sent: Friday, March 26, 2010 1:08 PM  
To: Higgins, Rosemary (NIH/NICHD) [E]  
Subject: RE: Randomized Trial of Oxygen Saturation Targets 3-26-10.ppt

Sorry for the Ma'am. I guess it is a Southern thing.

Sent from my Windows Mobile phone

-----Original Message-----

From: Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov>  
Sent: Friday, March 26, 2010 11:50 AM  
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Subject: Randomized Trial of Oxygen Saturation Targets 3-26-10.ppt

To the SUPPORT SUBCOMMITTEE:

Attached is the oximetry SUPPORT presentation. This will be used for PAS as well as ATS. Please send comments directly to Wally.

Thanks  
Rose

**From:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**To:** "[Finer, Neil](#)"; "[wacarlo@uab.edu](#)"; "[Rich, Wade](#)"; "[Nancy Newman](#)"; "[mcw3@case.edu](#)"; "[Brad Yoder \(Bradley.yoder@hsc.utah.edu\)](#)"; "[Roger Faix](#)"; "[alaptook@WIHRI.org](#)"; "[Kurt Schibler \(kurt.schibler@cchmc.org\)](#)"; "[Gantz, Marie](#)"; "[Abhik Das](#)"  
**Cc:** [Archer, Stephanie \(NIH/NICHD\) \[E\]](#); "[Zaterka-Baxter, Kristin](#)"; "[Cunningham, Meg](#)"  
**Subject:** Randomized Trial of Oxygen Saturation Targets 3-26-10.ppt  
**Date:** Friday, March 26, 2010 12:50:00 PM  
**Attachments:** [Randomized Trial of Oxygen Saturation Targets 3-26-10.ppt](#)

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Thanks  
Rose

NICHD



# Randomized Trial of Oxygen Saturation Targets in Premature Infants - the SUPPORT Trial

The SUPPORT Study Group of the  
Eunice Kennedy Shriver NICHD  
Neonatal Research Network



# **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.**

# Background

- 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 oxygen saturation target range (85 to 89%) compared to a higher oxygen saturation target range (91 to 95%) reduces the incidence of the composite outcome of severe ROP or death among infants of 24<sup>0/7</sup> to 27<sup>6/7</sup> weeks gestational age

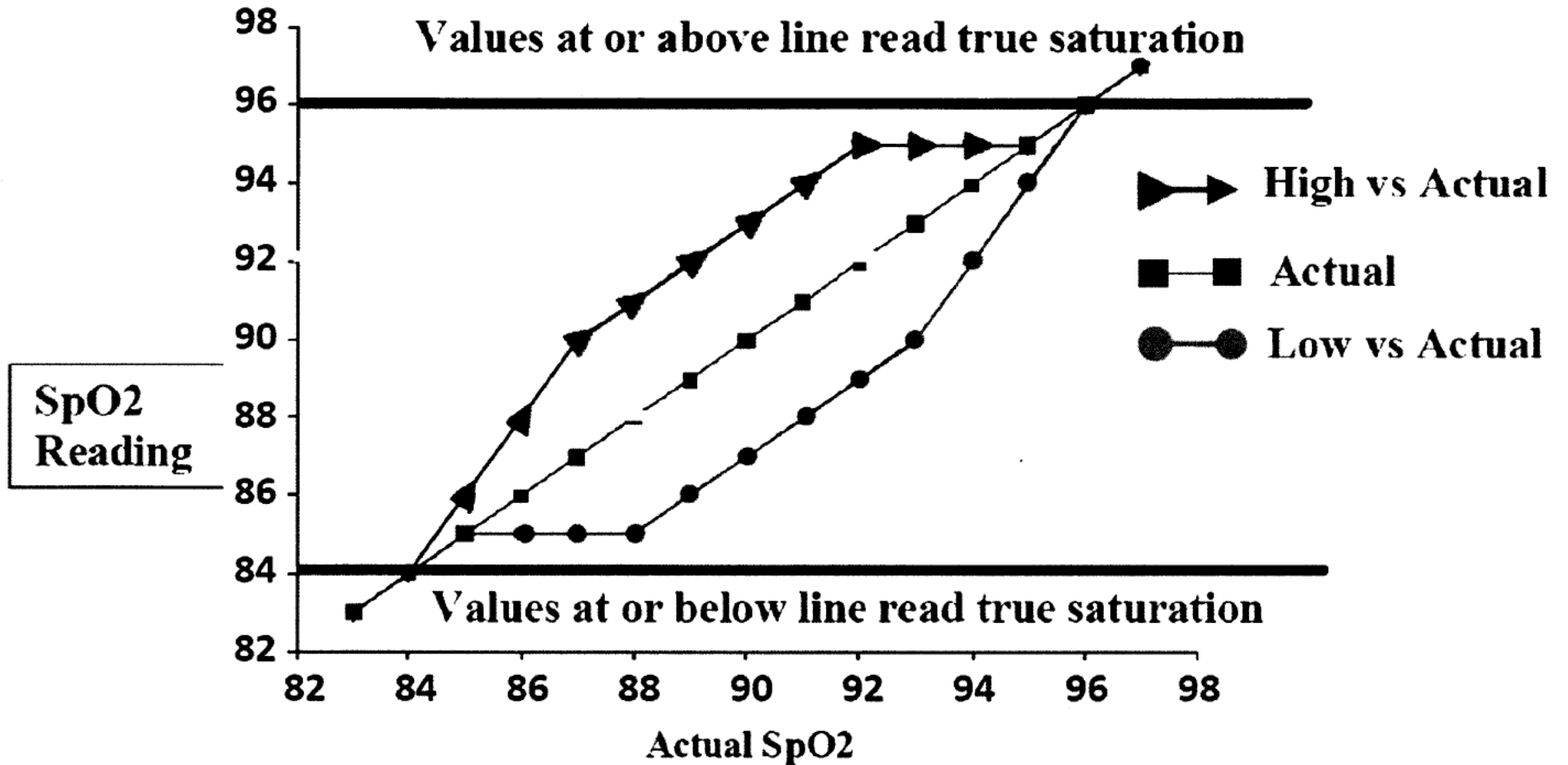
# Method – Patients

- Inborn infants of 24<sup>0/7</sup> to 27<sup>6/7</sup> weeks gestation for whom a decision had been made to provide full resuscitation were eligible
- Parental consent was obtained
- Enrollment 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 Oximeter that displayed saturation levels of 88 to 92% for both saturation target ranges using an offset of 3%, with transitions outside of this range and reversion to actual values when saturations were  $<85\%$  and  $>95\%$

## Actual vs Low and Hi Reading SaO2



SpO2 Group	Displayed Target	Actual Target	Alarm Values
Low SpO2	88-92%	85-89%	<85 and >95%
High SpO2	88-92%	91-95%	<85 and >95%

## Methods – Intervention (2)

- Oxygen saturation targeting was initiated within the first two hours after birth and was continued until 36 weeks post-menstrual age or until the infant remained 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 – ROP Assessments

- Trained ophthalmologists followed the infants until the study endpoint *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
  - In zone II: plus disease with stage 2 or 3 ROP
  - If ophthalmologic surgery and/or bevacizumab ROP treatment was used

# Methods – Data Analysis

- The primary and categorical outcomes were analyzed using Poisson regression implementation in a Generalized Estimating Equation (GEE) model to obtain adjusted relative risk and 95% CI
- Continuous outcomes were analyzed using mixed effects linear models to produce adjusted means and standard errors
- Adjustment was performed for pre-specified stratification (center and GA) and for familial clustering as multiple births were randomized to the same treatment arms

# Methods – Sample Size Estimate

- Baseline rate of severe ROP/Death of 50%
- Absolute risk difference of 10%
- Increased by 1.12 to allow for multiples randomized to same treatment
- Increased by 1.17 to adjust for attrition
- Increased further to minimize Type I error using a conservative 2% level of significance
- Final sample size was 1310 infants



# Methods – Monitoring

- An independent DSMC reviewed primary outcomes, adverse events, and other interim results at 25%, 50%, and 75% of outcome assessment
- The DSMC evaluated compliance with oxygen saturation targeting

# Results – Patient Population\*

	Lower Saturation Group (N = 654)	Higher Saturation Group (N = 662)
Birth weight	836±193g	825±193g
Gestational age	26±1w	26±1w
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

3546 Infants were assessed for eligibility (3127 pregnancies)\*

235 Did not meet eligibility criteria  
125 Personnel/Equipment not available  
699 Eligible but consent not sought  
•Parent unavailable for consent  
•Consent denied by parent or guardian  
11 Excluded for other reasons  
68 Consented but not randomized

1316 Underwent randomization

654 Were assigned to oxygen saturation targeting 85-89%

662 Were assigned to oxygen saturation targeting 91-95%

130 Died before discharge

524 Survived to discharge, transfer one year of life

107 Died before discharge

555 Survived to discharge, transfer or one year of life

41 Severe ROP

434 No severe ROP

49 Final ROP outcome missing

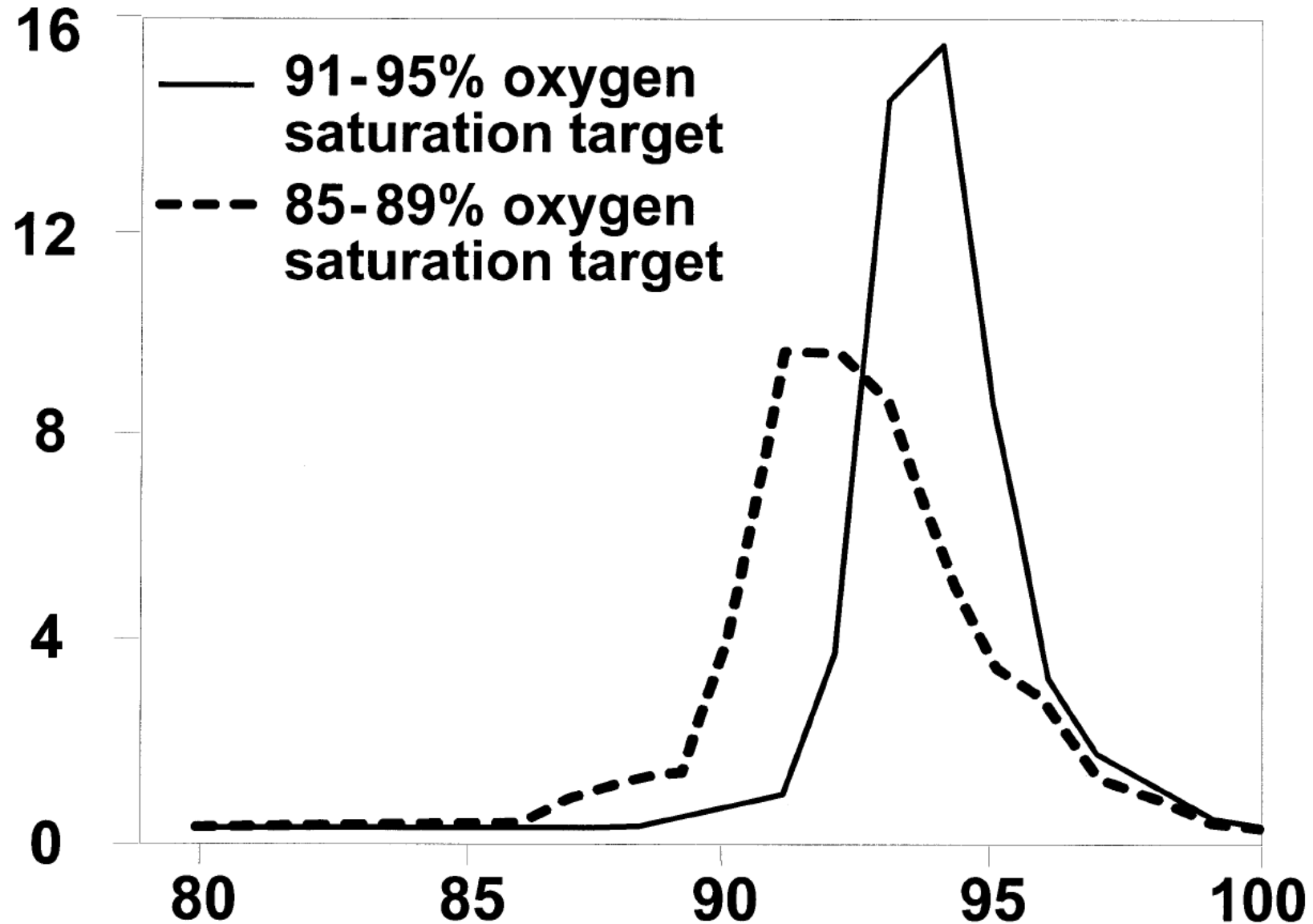
91 Severe ROP

418 No severe ROP

46 Final ROP outcome missing

# Actual Median Oxygen Saturation (%)

## Percent of Infants (%)



# Results – Primary Outcome

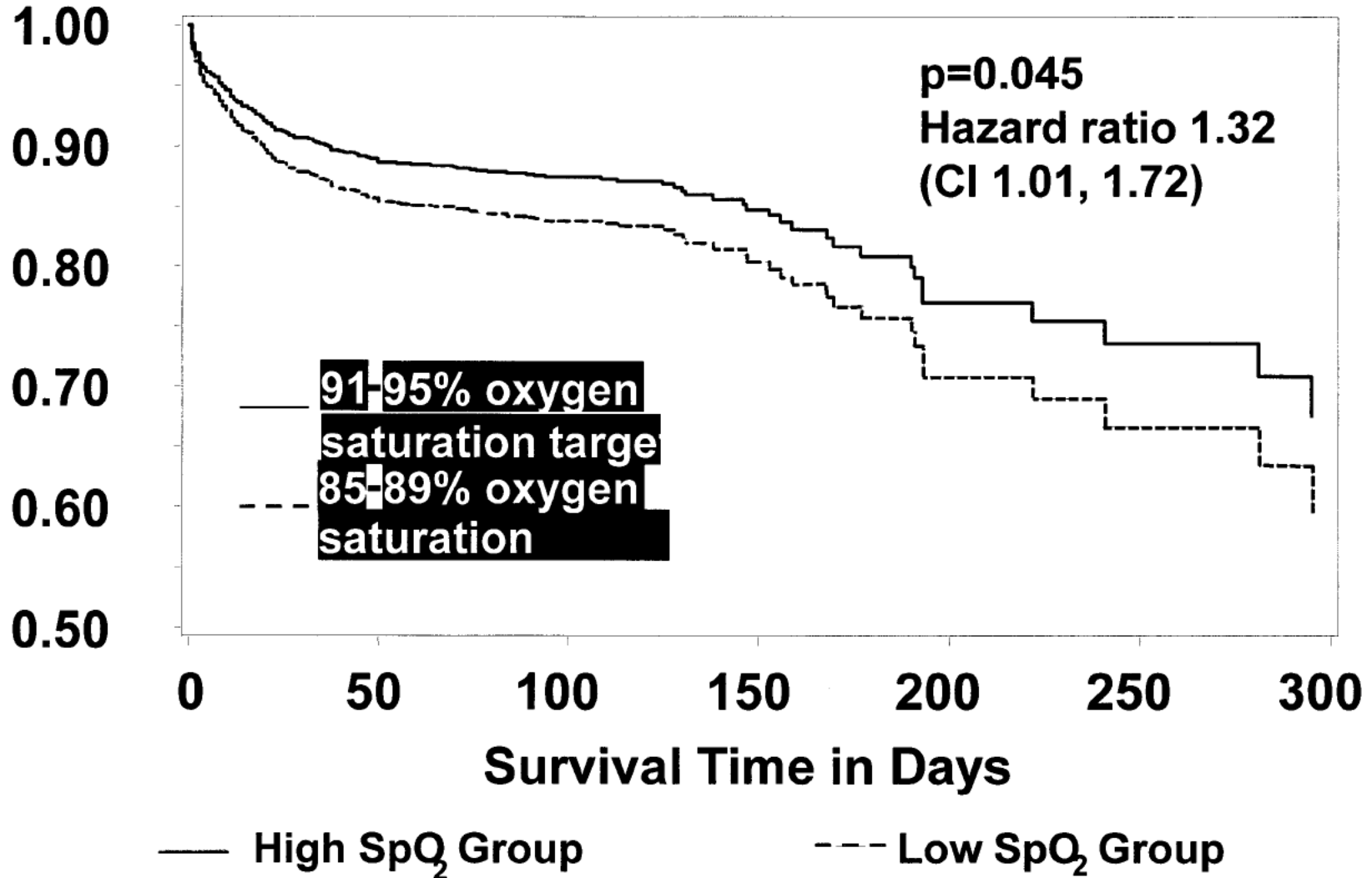
	<b>Lower Saturation Group N=654</b>	<b>Higher Saturation Group N=662</b>	<b>Adjusted Relative Risk (95% CI)</b>	
<b>Severe ROP/death</b>	<b>28.3%</b>	<b>32.1%</b>	<b>0.90 (0.76, 1.06)</b>	
<b>Severe ROP</b>	<b>8.6%</b>	<b>17.9%</b>	<b>0.52 (0.37, 0.73)</b>	<b>NNT= 11</b>
<b>Death</b>	<b>19.9%</b>	<b>16.2%</b>	<b>1.27 (1.01, 1.60)</b>	<b>NNH= 27</b>

# Results – ROP Adjudication Analysis

	<b>Lower Saturation Group (N=654)</b>	<b>Higher Saturation Group (N=662)</b>	<b>Relative Risk for Low SpO<sub>2</sub> vs. High SpO<sub>2</sub> (95% CI)</b>	
<b>Severe ROP</b>	<b>8.6%</b>	<b>17.9%</b>	<b>0.52 (0.37, 0.73)</b>	<b>NNT=11</b>
<b>Severe ROP with adjudication (98.6%)</b>	<b>8.0%</b>	<b>16.6%</b>	<b>0.52 (0.37, 0.73)</b>	<b>NNT=12</b>
<b>Severe ROP with ROP if lost to F/U (100%)</b>	<b>10.1%</b>	<b>17.5%</b>	<b>0.62 (0.45, 0.84)</b>	<b>NNT=14</b>

# Survival Curve for Mortality

## Survivor Function Estimate



## Results – BPD and other pulmonary outcomes

	<b>Lower Saturation n Group N=654</b>	<b>Higher Saturation n Group N=662</b>	<b>Adjusted Relative Risk (95% CI)</b>
<b>BPD (O<sub>2</sub> use at 36 w)</b>	<b>37.6%</b>	<b>46.7%</b>	<b>0.82 (0.72, 0.93)</b>
<b>BPD (O<sub>2</sub> use) or death, 36 w</b>	<b>48.5%</b>	<b>54.2%</b>	<b>0.91 (0.83, 1.01)</b>
<b>BPD (physiologic), 36 w</b>	<b>38.0%</b>	<b>41.7%</b>	<b>0.92 (0.81, 1.05)</b>
<b>BPD (physiologic) or death, 36 w</b>	<b>48.8%</b>	<b>50.0%</b>	<b>0.99 (0.90, 1.10)</b>
<b>Pneumothorax</b>	<b>7.2%</b>	<b>6.5%</b>	<b>1.12 (0.74, 1.68)</b>
<b>Any air leaks (14 days)</b>	<b>7.8%</b>	<b>6.3%</b>	<b>1.23 (0.83, 1.83)</b>
<b>Postnatal steroids for BPD</b>	<b>9.6%</b>	<b>10.7%</b>	<b>0.91 (0.67, 1.24)</b>



# Results – PDA

	<b>Lower Saturation Group N=654</b>	<b>Higher Saturation Group N=662</b>	<b>Adjusted Relative Risk (95% CI)</b>
<b>PDA</b>	<b>47.9%</b>	<b>50.0%</b>	<b>0.96 (0.86, 1.07)</b>
<b>Medical treatment for PDA</b>	<b>34.5%</b>	<b>36.1%</b>	<b>0.95 (0.82, 1.09)</b>
<b>Surgical treatment for PDA</b>	<b>11.4%</b>	<b>10.5%</b>	<b>1.09 (0.80, 1.48)</b>

# Results – Other Major Outcomes

	<b>Lower Saturation Group N=654</b>	<b>Higher Saturation Group N=662</b>	<b>Adjusted Relative Risk (95% CI)</b>
<b>IVH, grade 3 or 4</b>	<b>13.2%</b>	<b>12.7%</b>	<b>1.06 (0.80, 1.40)</b>
<b>PVL</b>	<b>3.8%</b>	<b>4.7%</b>	<b>0.83 (0.49, 1.42)</b>
<b>NEC, stage <math>\geq</math> 2</b>	<b>11.9%</b>	<b>10.8%</b>	<b>1.11 (0.82, 1.51)</b>
<b>Late onset sepsis</b>	<b>36.5%</b>	<b>35.6%</b>	<b>1.03 (0.89, 1.18)</b>

# Summary

- O<sub>2</sub> saturation targeting in the range of 85-89% did not affect severe ROP/death
- O<sub>2</sub> 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
- The potential to reduce the risk of severe ROP must be carefully weighed against the possibility of increased risk of death
- Follow up of these infants and data from the similarly designed ongoing trials will be important

**Thanks to the many parents,  
infants, and NICU staff**

**Thanks to the members of the  
Neonatal Research Network**

# NICHD Neonatal Research Network Centers (1996-2006)

- Brown University
- Case Western Reserve University
- Duke University
- Emory University
- Indiana University
- Research Triangle Institute
- Stanford University
- University of Alabama – Birmingham
- University of California – San Diego
- University of Cincinnati
- University of Miami
- University of New Mexico
- University of Rochester
- University of Tennessee – Memphis
- University of Texas, Southwestern – Dallas
- University of Texas – Houston
- Wake Forest University
- Wayne State University
- Yale University



# NICHD Neonatal Research Network Centers (2006-2011)

- Brown University
- Case Western Reserve University
- Duke University
- Emory University
- Indiana University
- Research Triangle Institute
- Stanford University
- Tufts Medical Center
- University of Cincinnati
- University of Alabama – Birmingham
- University of Iowa
- University of New Mexico
- University of Texas, Southwestern – Dallas
- University of Texas – Houston
- University of Utah
- Wayne State University
- Yale University



# Results – Causes of Death

	Lower Saturation Group (N = 130)	Higher Saturation Group (N = 107)
Respiratory distress syndrome	23.8%	29.0%
Infection	19.2%	19.6%
Necrotizing enterocolitis	17.7%	13.1%
Bronchopulmonary dysplasia	10.8%	9.3%
Central nervous system insult	9.2%	8.4%
Immaturity	5.4%	2.8%
Other	13.8%	17.8%



# Other Outcomes

	Lower Saturation Group	Higher Saturation Group	Adjusted P value
Length of stay (days) m+SE	104 ± 2.0	106 ± 2.0	0.45
Duration of MV (days) m+SE	26 ± 1	27 ± 1	0.30
Duration of O <sub>2</sub> suppl (days) m+SE	60 ± 2	67 ± 2	0.0002
CPAP (days) m+SE	17 ± 1	17 ± 1	0.94
Nasal SIMV (days) m+SE	3 ± 0.3	4 ± 0.3	0.14

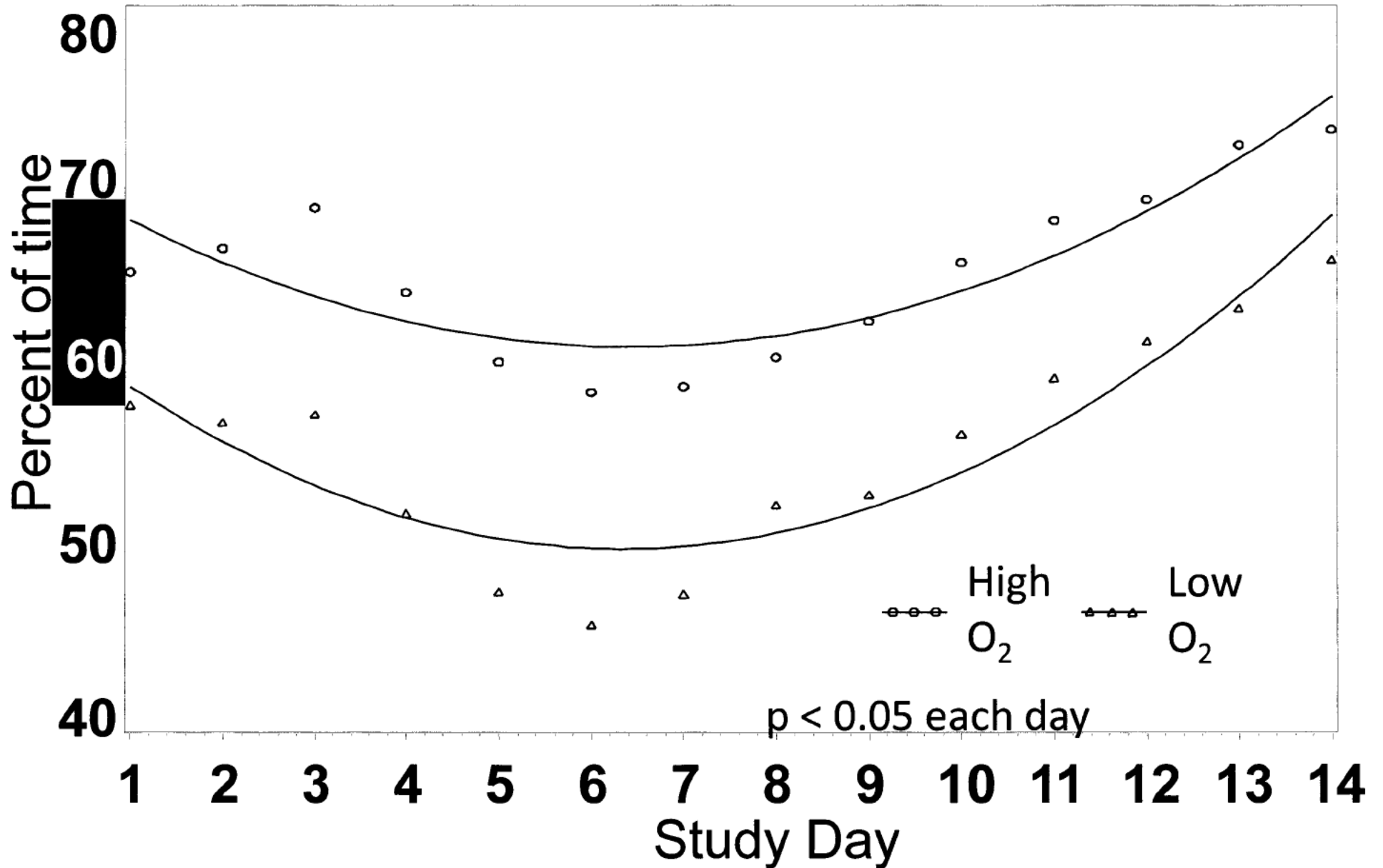
# Mean percent of time spent in SpO<sub>2</sub> ranges while on supplemental oxygen

<b>SpO<sub>2</sub> range</b>	<b>Lower Saturation Group Mean % of time in range (95% CI)</b>	<b>Higher Saturation Group Mean % of time in range (95% CI)</b>	<b>P-value</b>
<b>&gt;96%</b>	<b>20.1 (18.8, 21.3)</b>	<b>23.2 (22.0, 24.5)</b>	<b>0.0001</b>
<b>&lt;80%</b>	<b>7.3 (6.6, 8.1)</b>	<b>5.5 (4.8, 6.3)</b>	<b>0.0002</b>
<b>&lt;75%</b>	<b>4.5 (3.8, 5.2)</b>	<b>3.6 (2.9, 4.3)</b>	<b>0.0486</b>
<b>&lt;70%</b>	<b>2.5 (1.9, 3.1)</b>	<b>2.1 (1.5, 2.7)</b>	<b>0.4090</b>

# Median percent of time spent in SpO<sub>2</sub> ranges while on supplemental oxygen

<b>SpO<sub>2</sub> range</b>	<b>Lower Saturation Group Median % of time in range</b>	<b>Higher Saturation Group Median % of time in range</b>	<b>P-value</b>
<b>&gt;96%</b>	<b>16.0</b>	<b>19.6</b>	<b>&lt;0.0001</b>
<b>&lt;80%</b>	<b>5.9</b>	<b>3.9</b>	<b>&lt;0.0001</b>
<b>&lt;75%</b>	<b>3.3</b>	<b>2.1</b>	<b>&lt;0.0001</b>
<b>&lt;70%</b>	<b>1.5</b>	<b>0.9</b>	<b>&lt;0.0001</b>

# Percent of time on oxygen by day and group



**From:** Higgins, Rosemary (NIH/NICHD) [E]  
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**Cc:** Archer, Stephanie (NIH/NICHD) [E]; "Zaterka-Baxter, Kristin"; "Cunningham, Meg"; "Huitema, Carolyn Petrie"; "Irene, Amanda"; "Webb, Robin E."  
**Subject:** SUPPORT Intermittent Hypoxia (3)  
**Date:** Friday, March 26, 2010 11:23:00 AM  
**Attachments:** SUPPORT Intermittent Hypoxia (3).doc

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Hi,

Here is a study approved by the SUPPORT subcommittee for review by protocol review.

Robin is already setting up call times.

thanks  
Rose

## Intermittent Hypoxia in Preterm Infants enrolled in the SUPPORT trial

### Secondary Study

Juliann Di Fiore, BSEE, Ryan Foglyano, BSBE, Richard Martin, MD,

Chris Wilson PhD, Michele Walsh, MD

[Case Western Reserve University School of Medicine, Cleveland, OH]

#### Abstract

Episodes of oxygen saturation are almost universal in very low birthweight infants. Neither their incidence, nor potential adverse effects on later neurodevelopmental outcome are known. The NICHD Neonatal Research Network, of which we are a participant, has completed a multicenter trial in which preterm infants of 24-28 weeks gestation were randomized to high versus low levels of baseline oxygen saturation. We have previously received approval from the NICHD Neonatal Research Network to perform a secondary study on a subcohort of the SUPPORT trial infants, entitled *INCIDENCE AND CONSEQUENCES OF EPISODIC DESATURATION IN PRETERM INFANTS ENROLLED IN THE NICHD NEONATAL NETWORK OXYGEN SATURATION [SUPPORT] STUDY*, to 1) characterize and compare the incidence and magnitude of episodic desaturation episodes in infants randomized to high versus low baseline oxygen saturation targets in the SUPPORT Trial 2) correlate the incidence and magnitude of such desaturation episodes over the first month of life with neurodevelopmental outcome at 18-22 months and 3) correlate the incidence of early intermittent hypoxia with a history of sleep disordered breathing (SDB) at 18-22 months.

Field Code Changed

To accurately detect the incidence of desaturation episodes, our current secondary study only includes infants from the San Diego and Cleveland sites where pulse oximetry data were acquired at high resolution (2 sec averaging time and 2 second sample). In contrast, the SUPPORT trial oximetry data at all other sites have been acquired at low resolution (16 second averaging time and 10 second sample rate). With the SUPPORT trial findings of increased mortality in the low baseline saturation group, there is interest in expanding the secondary study database to include a second cohort of infants with low resolution data as well. This may be problematic as the prolonged averaging times will smooth the SaO<sub>2</sub> waveform and may decrease the accuracy of detection of desaturation events. The low sample rate of 10 sec may further exacerbate this problem.

#### A. Specific Aim:

The aim of this study is to expand our current database of infants with high resolution pulse oximetry data to include the remaining low resolution pulse oximetry data SUPPORT infants. Using these two separate infant cohorts we aim to:

1. Assess the effect of data resolution (2/2sec, averaging time/sample rate versus 16/10sec, averaging time/sample rate) on the incidence, duration and magnitude of desaturation events between low and high baseline SaO<sub>2</sub> infant groups.
2. Assess the relationship between the incidence of desaturation events and the development of Retinopathy of Prematurity (ROP).
3. Analyze the correlation between the incidence of desaturation events and neurodevelopmental outcome.
4. Analyze the correlation between the incidence of desaturation events and mortality.
5. Analyze the correlation between the incidence of desaturation events and bronchopulmonary dysplasia (BPD).

B. Hypothesis:

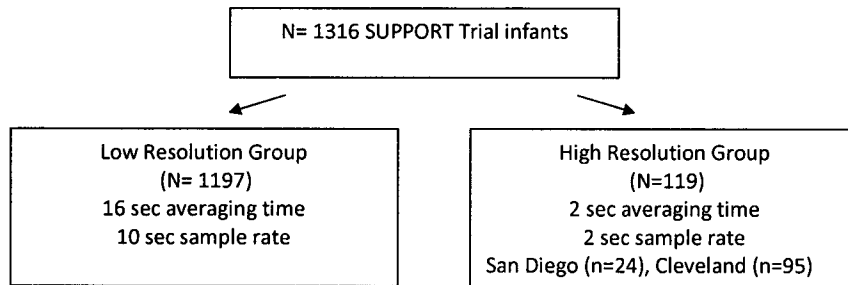
We hypothesize that:

1. Infants with low resolution oximetry data will have fewer desaturation events and of smaller magnitude than infants with high resolution data.
2. Infants with severe ROP requiring laser therapy will have a higher incidence of desaturation events.
3. A higher incidence of episodic desaturation in neonates is associated with greater neurodevelopmental handicap at 18-22 months.
4. A higher incidence of desaturation events is associated with an increase in infant mortality.
5. A higher incidence of desaturation events is associated with BPD.

C. Rationale:

The SUPPORT Trial randomized infants to two ranges of SpO<sub>2</sub> in order to test the hypothesis that use of a lower SpO<sub>2</sub> range will result in an increase in survival of preterm infants without the occurrence of threshold retinopathy of prematurity [ROP] and/or the need for surgical intervention. However, the potential risk of a lower baseline SpO<sub>2</sub> range in increasing the incidence of episodic desaturation is unknown. In addition, prior studies in animal models have suggested that the neural effects of intermittent or episodic hypoxia may differ greatly than those of sustained hypoxia. Our previously approved secondary study represented a unique opportunity to acquire data to characterize the risk factors and consequences of episodic desaturation. Although we currently have 119 Infants in the high resolution cohort there are an additional 1197 infants enrolled in the SUPPORT trial in whom we may be able to extract additional desaturation data with low resolution. Although differences in monitor settings does not allow for combining the two infant cohorts, the

larger sample size in the low resolution infant group may enable us to detect more subtle associations between desaturation events and baseline saturation, ROP, mortality and detriments in neurodevelopmental outcome.



The low resolution group has a much larger sample size which increases the chances of finding a relationship between intermittent hypoxia and both morbidity and mortality. However, the low resolution of saturation data may limit the ability to accurately detect desaturation events in this cohort. Previous data (Ahmed) have suggested that application of a 16 sec averaging time window may result in an underestimation of short events (<30sec) and events of greater severity (<70%) and an overestimation of events of long duration (>300sec) when compared to application of a 2 sec averaging time window. If comparisons between low and high resolution groups reveal statistically significant differences in event detection parameters, interpretation of associations of desaturation events with baseline SaO<sub>2</sub> and morbidity may be limited to the infants in whom data were acquired with high resolution group (n=119). Due to the low incidence of infant mortality in the high resolution cohort we may not have the ability to assess the association between desaturation events and infant mortality.

If event parameters do not differ between low and high resolution groups the increased sample size of 1197 in the low resolution group may increase the ability to detect an association between these events and baseline SaO<sub>2</sub>, mortality, and neurodevelopmental outcome. Lastly, even if desaturation event detection is significantly compromised in the low resolution group, the low resolution may still be adequate to detect differences between the incidence of intermittent hypoxia and mortality/morbidity in this large infant cohort.

#### D. Methodologies:

##### Aim 1: Effect of data acquisition resolution and baseline SpO<sub>2</sub>

The saturation files will be analyzed in two phases. In phase one, the data will be cleaned, the skew will be corrected and the true saturation values restored. We will collaborate with RTI to confirm that both processes are consistent with those used for the main trial. To perform this Ms. DiFiore will require knowledge of the assigned group. In the second phase, Mr. Foglyano will receive the cleaned and corrected raw data identified only by patient study ID. In this way,



he will analyze for desaturation events while masked to the Group assignment. This will prevent any unintentional biases during the data analysis. The desaturation data, identified only by patient ID, will then be sent back to RTI where it will be reassigned to the randomization group for statistical analysis.

None of the personnel involved in the saturation data analysis participate in developmental follow up of the enrolled cohort and thus cannot influence the outcome evaluations at CWRU, and thus are not a threat to the integrity of the main trial neurodevelopmental evaluations. To prevent inadvertent disclosure, all data files will be sequestered in the office of Ms. Juliann Di Fiore and will not be accessible to other members of the CWRU team. Further, data files will remain identified only by study number and not by the infant's name. We will use software that is currently being developed to document the occurrence, duration and magnitude of desaturation events  $\leq 80\%$  in the low resolution group. To comply with Nyquist sampling theorem limitations (2 x sample rate) and to distinguish intermittent hypoxia from prolonged changes in baseline SpO<sub>2</sub>, only events  $\geq 20$ sec and  $\leq 3$  min will be included in the analysis. Data will be analyzed for the first 8 weeks of life or shorter time periods for infants who completed the SUPPORT trial before 8 weeks post natal age. All desaturation events will be included regardless of the need for supplemental oxygen or ventilator support.

We will compare the occurrence, duration and magnitude of desaturation events for

1. Acquisition Resolution
  - a. High (2 sec average, 2 second sample rate) versus low (16 sec average and 10 sec sample rate) resolution in the low baseline SpO<sub>2</sub> infant groups
  - b. High versus low resolution in the high baseline SpO<sub>2</sub> infant groups
2. Baseline SpO<sub>2</sub>
  - a. Low versus High baseline SpO<sub>2</sub> in the low resolution group
  - b. Low versus High baseline SpO<sub>2</sub> in the high resolution group (previous secondary study)

#### Aim 2: Retinopathy of Prematurity

We will compare the incidence of desaturation events detected in Aim 1 between infants with and without severe retinopathy of prematurity (ROP). To minimize disparities in diagnosis of less severe forms of ROP, infants will be classified as 1) those requiring laser treatment for ROP or 2) those with either no ROP or ROP not severe enough to require laser therapy. The definitions used and reported in the SUPPORT main trial will be utilized for classifications of eye outcomes. If ROP data is missing we will use adjudicated results produced in the main trial.. Lastly, the competing outcome of ROP/death will also be included in the analysis.

#### Aim 3: Neurodevelopmental Outcome

To analyze the correlation between the incidence of desaturation events and neurodevelopmental outcome we will include parameters acquired through the SUPPORT trial protocol including:

neurodevelopmental impairment at 18-22 months based on Bayley III using the accepted NRN definition

Death by discharge status

IVH

PVL

Cerebral palsy @ 18-22 months

The neurodevelopmental impairments listed above will be analyzed with and without the competing outcome of death. This aim will be completed only after the primary follow up analysis is accepted for publication.

#### Aim 4: Mortality

We will analyze the correlation between the incidence of desaturation events and mortality with and without the inclusion of baseline saturation randomization as a covariate.

#### Aim 5: BPD

We will analyze the correlation between the incidence of desaturation events and BPD, defined as an oxygen requirement at 36 weeks of age. We do not anticipate this being an overlap of the BPD secondary study as that analysis does not include intermittent hypoxia.

#### Statistical Analyses

Statistical analyses will include a linear mixed model to assess the time course of desaturation events for all infants and to identify the association between the number of events and ROP requiring laser treatment adjusting for baseline SpO<sub>2</sub> randomization group, gestational age, race, gender, and multiple births. Based on previous work [Di Fiore] the square root of the number of desaturation events will be used to better meet normality assumptions of the mixed model. A linear regression model will be used to assess the univariate relationship between continuous variables such as the number of desaturation events and mental and motor scores at 18-22 months. We will collaborate with RTI for the statistical analyses to use to compare the number of desaturation events between the low and high baseline SpO<sub>2</sub> groups, and mortality.

#### E. Discussion of Anticipated Results

We anticipate that a lower number of desaturation events will be detected in the low versus high resolution group. Previous work has suggested that the 16 second average time used in the SUPPORT trial may result in an underestimation of events <30 seconds and events of greater severity (<70%) and an overestimation of events of long duration (>300sec)[Ahmed].

This study will focus on desaturation events of  $\leq 80\%$  for  $\geq 20$  sec and  $\leq 3$  min in duration. Thus, we do anticipate a significant difference between low and high resolutions due to events of greater severity or of long duration as proposed by Ahmed et al. However, the prolonged average time in the low resolution group may inhibit our ability to detect desaturation events between 20 and 30 seconds in duration. We may have a further compromise in event detection due to the low sample rate of 10 seconds versus 2 seconds in the low and high resolution infant groups, respectively. Although a higher incidence of desaturation events has been shown to be associated with severe ROP [Di Fiore], it is currently unknown whether the characteristics of the desaturation event, in terms of duration and severity, are additional risk factors. Therefore, if short desaturation events are not as detrimental to the development of ROP, even with a compromise in detection of all desaturation events in the low resolution group we may still be able to detect differences in the number of events in the low and high baseline SpO<sub>2</sub> groups and in infants with and without severe ROP.

We speculate that if a higher incidence of desaturation events is found in the low baseline SpO<sub>2</sub> group, this will be associated with both infant mortality and lower neurodevelopmental outcome scores at 18-22 months of age.

If there is no difference in event detection in the high versus low resolution group, and no difference in the number of desaturation events between the low and high baseline SpO<sub>2</sub> infant groups we will conclude that keeping the infants in the low saturation target range does not put them at risk for episodic desaturation. If a difference in event detection is found between low and high resolution groups our conclusions between the low and high baseline saturation ranges will be limited by the ability to compare severe events and events of shorter duration.

#### F. Budget

##### Equipment:

We have previously acquired and analyzed desaturation data in 79 preterm infants with high resolution over a time period of comparable duration as the infants enrolled in the SUPPORT trial [Di Fiore]. Based on these infants, we estimate that the raw and processed data files for the 1316 SUPPORT trial infants will take approximately 400 gigabytes of storage space. For data safety/quality assurance concerns, we would like to purchase a password protected server dedicated to storage of this dataset. We estimate that the server with RAID 0 mirroring of the data will cost approximately \$1000. Only investigators working on this project will have access to the server. Additionally, we will maintain a backup of our datasets. Currently, a 1000 gigabyte hard drive costs \$200 through local computer stores. The server will be equipped with a writable DVD drive to maintain additional backups as needed. We currently use automated software to perform data backups once per week. Both the backup hard drive and DVDs will be stored in a locked cabinet in the locked office of Juliann Di Fiore and only she will have access to these backup devices. These files will be de-identified for patient confidentiality.

##### Data Analysis and Project Duration:

Under Dr. Chris Wilson as PI, Juliann Di Fiore and Ryan Foglyano will currently be receiving grant funding to develop software to automate additional analyses of saturation data on the infants enrolled in the currently approved secondary study, INCIDENCE AND CONSEQUENCES OF EPISODIC DESATURATION IN PRETERM INFANTS ENROLLED IN THE NICHD NEONATAL NETWORK OXYGEN SATURATION [SUPPORT] STUDY. This infant cohort includes SUPPORT infants enrolled at the Cleveland and San Diego sites with high resolution, and 79 additional preterm infants at the Cleveland site that were not enrolled in the SUPPORT trial. The purpose of this grant is to develop a suite of linear and non-linear analysis algorithms to quantify patterns of intermittent hypoxia (IH), and to evaluate the relationship between IH patterns and severe ROP requiring laser surgery. The initial phase of this grant will require development of automated software code to identify desaturation events from the infant data files. Once developed, we plan to use this software for analysis of the additional 1197 SUPPORT trial infants.

Based on previous data analysis of desaturation events in 79 preterm infants with high resolution analyzed over a time period of comparable duration as the infants enrolled in the SUPPORT trial, we are currently able to analyze 5-7 infants per day. We anticipate an increase in the number of infants analyzed per day with automation of the software. Based on our previous experience and additional time needed for summary data analysis, we anticipate 10 months of time will be needed to complete this protocol. This will include cleaning of the raw data and data analysis.

**Study Budget:**

Equipment:	\$1200
HARDDRIVE \$200; RAID 0 [PROTECTED SERVER] \$1000	
Engineering: cleaning raw saturation data, analysis:	\$65 per pt *1316 pts= \$85,540
One trip to RTI to work with RTI Staff:	<u>\$1500</u>
<b>TOTAL:</b>	<b>\$88,240</b>

References:

1. Ahmed SJ, Rich W, Finer NN. The effect of averaging time on oximetry values in the premature infant. *Pediatrics* 2010:e115-e121.
2. Di Fiore JM, Bloom JN, Orge F, Schutt A, Schluchter M, Cheruvu VK, Walsh M, Finer N, Martin RJ. A higher incidence of intermittent hypoxemic episodes is associated with severe retinopathy of prematurity. *J of Peds* ( In press).

**From:** [Juliann DiFiore](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\)](#) [E]  
**Cc:** [Michele Walsh](#); [Julie Di Fiore](#)  
**Subject:** SUPPORT Intermittent Hypoxia Protocol  
**Date:** Friday, March 26, 2010 11:18:48 AM  
**Attachments:** [SUPPORT Intermittent Hypoxia.doc](#)

---

Rose,

Attached is the updated version of the SUPPORT trial intermittent hypoxia protocol. I believe we have addressed the concerns discussed on the conference call but if there are any questions please feel free to call/email me.

Regards,

Julie

--

Juliann Di Fiore  
Research Engineer  
Rainbow Babies & Children's Hospital  
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11100 Euclid Ave  
Cleveland, OH 44106  
(216) 844-1478

## Intermittent Hypoxia in Preterm Infants enrolled in the SUPPORT trial

### Secondary Study

Juliann Di Fiore, BSEE, Ryan Foglyano, BSBE, Richard Martin, MD,

Chris Wilson PhD, Michele Walsh, MD

[Case Western Reserve University School of Medicine, Cleveland, OH]

#### Abstract

Episodes of oxygen saturation are almost universal in very low birthweight infants. Neither their incidence, nor potential adverse effects on later neurodevelopmental outcome are known. The NICHD Neonatal Research Network, of which we are a participant, has completed a multicenter trial in which preterm infants of 24-28 weeks gestation were randomized to high versus low levels of baseline oxygen saturation. We have previously received approval from the NICHD Neonatal Research Network to perform a secondary study on a subcohort of the SUPPORT trial infants, entitled *INCIDENCE AND CONSEQUENCES OF EPISODIC DESATURATION IN PRETERM INFANTS ENROLLED IN THE NICHD NEONATAL NETWORK OXYGEN SATURATION [SUPPORT] STUDY*, to 1) characterize and compare the incidence and magnitude of episodic desaturation episodes in infants randomized to high versus low baseline oxygen saturation targets in the SUPPORT Trial 2) correlate the incidence and magnitude of such desaturation episodes over the first month of life with neurodevelopmental outcome at 18-22 months and 3) correlate the incidence of early intermittent hypoxia with a history of sleep disordered breathing (SDB) at 18-22 months.

Field Code Changed

To accurately detect the incidence of desaturation episodes, our current secondary study only includes infants from the San Diego and Cleveland sites where pulse oximetry data were acquired at high resolution (2 sec averaging time and 2 second sample). In contrast, the SUPPORT trial oximetry data at all other sites have been acquired at low resolution (16 second averaging time and 10 second sample rate). With the SUPPORT trial findings of increased mortality in the low baseline saturation group, there is interest in expanding the secondary study database to include a second cohort of infants with low resolution data as well. This may be problematic as the prolonged averaging times will smooth the SaO<sub>2</sub> waveform and may decrease the accuracy of detection of desaturation events. The low sample rate of 10 sec may further exacerbate this problem.

#### A. Specific Aim:

The aim of this study is to expand our current database of infants with high resolution pulse oximetry data to include the remaining low resolution pulse oximetry data SUPPORT infants. Using these two separate infant cohorts we aim to:



1. Assess the effect of data resolution (2/2sec, averaging time/sample rate versus 16/10sec, averaging time/sample rate) on the incidence, duration and magnitude of desaturation events between low and high baseline SaO<sub>2</sub> infant groups.
2. Assess the relationship between the incidence of desaturation events and the development of Retinopathy of Prematurity (ROP).
3. Analyze the correlation between the incidence of desaturation events and neurodevelopmental outcome.
4. Analyze the correlation between the incidence of desaturation events and mortality.
5. Analyze the correlation between the incidence of desaturation events and bronchopulmonary dysplasia (BPD).

B. Hypothesis:

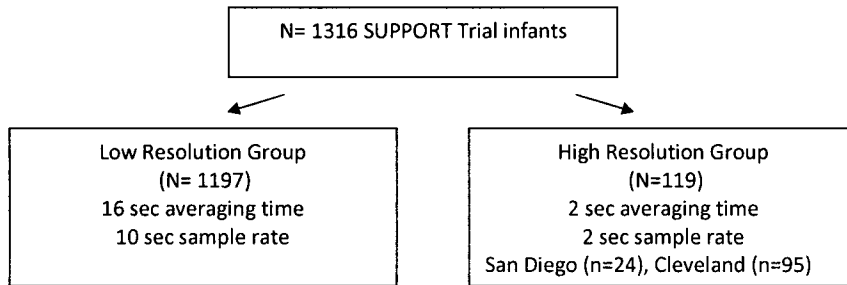
We hypothesize that:

1. Infants with low resolution oximetry data will have fewer desaturation events and of smaller magnitude than infants with high resolution data.
2. Infants with severe ROP requiring laser therapy will have a higher incidence of desaturation events.
3. A higher incidence of episodic desaturation in neonates is associated with greater neurodevelopmental handicap at 18-22 months.
4. A higher incidence of desaturation events is associated with an increase in infant mortality.
5. A higher incidence of desaturation events is associated with BPD.

C. Rationale:

The SUPPORT Trial randomized infants to two ranges of SpO<sub>2</sub> in order to test the hypothesis that use of a lower SpO<sub>2</sub> range will result in an increase in survival of preterm infants without the occurrence of threshold retinopathy of prematurity [ROP] and/or the need for surgical intervention. However, the potential risk of a lower baseline SpO<sub>2</sub> range in increasing the incidence of episodic desaturation is unknown. In addition, prior studies in animal models have suggested that the neural effects of intermittent or episodic hypoxia may differ greatly than those of sustained hypoxia. Our previously approved secondary study represented a unique opportunity to acquire data to characterize the risk factors and consequences of episodic desaturation. Although we currently have 119 Infants in the high resolution cohort there are an additional 1197 infants enrolled in the SUPPORT trial in whom we may be able to extract additional desaturation data with low resolution. Although differences in monitor settings does not allow for combining the two infant cohorts, the

larger sample size in the low resolution infant group may enable us to detect more subtle associations between desaturation events and baseline saturation, ROP, mortality and detriments in neurodevelopmental outcome.



The low resolution group has a much larger sample size which increases the chances of finding a relationship between intermittent hypoxia and both morbidity and mortality. However, the low resolution of saturation data may limit the ability to accurately detect desaturation events in this cohort. Previous data (Ahmed) have suggested that application of a 16 sec averaging time window may result in an underestimation of short events (<30sec) and events of greater severity (<70%) and an overestimation of events of long duration (>300sec) when compared to application of a 2 sec averaging time window. If comparisons between low and high resolution groups reveal statistically significant differences in event detection parameters, interpretation of associations of desaturation events with baseline SaO<sub>2</sub> and morbidity may be limited to the infants in whom data were acquired with high resolution group (n=119). Due to the low incidence of infant mortality in the high resolution cohort we may not have the ability to assess the association between desaturation events and infant mortality.

If event parameters do not differ between low and high resolution groups the increased sample size of 1197 in the low resolution group may increase the ability to detect an association between these events and baseline SaO<sub>2</sub>, mortality, and neurodevelopmental outcome. Lastly, even if desaturation event detection is significantly compromised in the low resolution group, the low resolution may still be adequate to detect differences between the incidence of intermittent hypoxia and mortality/morbidity in this large infant cohort.

#### D. Methodologies:

##### Aim 1: Effect of data acquisition resolution and baseline SpO<sub>2</sub>

The saturation files will be analyzed in two phases. In phase one, the data will be cleaned, the skew will be corrected and the true saturation values restored. We will collaborate with RTI to confirm that both processes are consistent with those used for the main trial. To perform this Ms. DiFiore will require knowledge of the assigned group. In the second phase, Mr. Foglyano will receive the cleaned and corrected raw data identified only by patient study ID. In this way,

he will analyze for desaturation events while masked to the Group assignment. This will prevent any unintentional biases during the data analysis. The desaturation data, identified only by patient ID, will then be sent back to RTI where it will be reassigned to the randomization group for statistical analysis.

None of the personnel involved in the saturation data analysis participate in developmental follow up of the enrolled cohort and thus cannot influence the outcome evaluations at CWRU, and thus are not a threat to the integrity of the main trial neurodevelopmental evaluations. To prevent inadvertent disclosure, all data files will be sequestered in the office of Ms. Juliann Di Fiore and will not be accessible to other members of the CWRU team. Further, data files will remain identified only by study number and not by the infant's name. We will use software that is currently being developed to document the occurrence, duration and magnitude of desaturation events  $\leq 80\%$  in the low resolution group. To comply with Nyquist sampling theorem limitations (2 x sample rate) and to distinguish intermittent hypoxia from prolonged changes in baseline SpO<sub>2</sub>, only events  $\geq 20$ sec and  $\leq 3$  min will be included in the analysis. Data will be analyzed for the first 8 weeks of life or shorter time periods for infants who completed the SUPPORT trial before 8 weeks post natal age. All desaturation events will be included regardless of the need for supplemental oxygen or ventilator support.

We will compare the occurrence, duration and magnitude of desaturation events for

1. Acquisition Resolution
  - a. High (2 sec average, 2 second sample rate) versus low (16 sec average and 10 sec sample rate) resolution in the low baseline SpO<sub>2</sub> infant groups
  - b. High versus low resolution in the high baseline SpO<sub>2</sub> infant groups
2. Baseline SpO<sub>2</sub>
  - a. Low versus High baseline SpO<sub>2</sub> in the low resolution group
  - b. Low versus High baseline SpO<sub>2</sub> in the high resolution group (previous secondary study)

#### Aim 2: Retinopathy of Prematurity

We will compare the incidence of desaturation events detected in Aim 1 between infants with and without severe retinopathy of prematurity (ROP). To minimize disparities in diagnosis of less severe forms of ROP, infants will be classified as 1) those requiring laser treatment for ROP or 2) those with either no ROP or ROP not severe enough to require laser therapy. The definitions used and reported in the SUPPORT main trial will be utilized for classifications of eye outcomes. If ROP data is missing we will use adjudicated results produced in the main trial.. Lastly, the competing outcome of ROP/death will also be included in the analysis.

#### Aim 3: Neurodevelopmental Outcome

To analyze the correlation between the incidence of desaturation events and neurodevelopmental outcome we will include parameters acquired through the SUPPORT trial protocol including:

neurodevelopmental impairment at 18-22 months based on Bayley III using the accepted NRN definition

Death by discharge status

IVH

PVL

Cerebral palsy @ 18-22 months

The neurodevelopmental impairments listed above will be analyzed with and without the competing outcome of death. This aim will be completed only after the primary follow up analysis is accepted for publication.

#### Aim 4: Mortality

We will analyze the correlation between the incidence of desaturation events and mortality with and without the inclusion of baseline saturation randomization as a covariate.

#### Aim 5: BPD

We will analyze the correlation between the incidence of desaturation events and BPD, defined as an oxygen requirement at 36 weeks of age. We do not anticipate this being an overlap of the BPD secondary study as that analysis does not include intermittent hypoxia.

#### Statistical Analyses

Statistical analyses will include a linear mixed model to assess the time course of desaturation events for all infants and to identify the association between the number of events and ROP requiring laser treatment adjusting for baseline SpO<sub>2</sub> randomization group, gestational age, race, gender, and multiple births. Based on previous work [Di Fiore] the square root of the number of desaturation events will be used to better meet normality assumptions of the mixed model. A linear regression model will be used to assess the univariate relationship between continuous variables such as the number of desaturation events and mental and motor scores at 18-22 months. We will collaborate with RTI for the statistical analyses to use to compare the number of desaturation events between the low and high baseline SpO<sub>2</sub> groups, and mortality.

#### E. Discussion of Anticipated Results

We anticipate that a lower number of desaturation events will be detected in the low versus high resolution group. Previous work has suggested that the 16 second average time used in the SUPPORT trial may result in an underestimation of events <30 seconds and events of greater severity (<70%) and an overestimation of events of long duration (>300sec)[Ahmed].

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#### F. Budget

##### Equipment:

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**Study Budget:**

Equipment:	\$1200
HARDDRIVE \$200; RAID 0 [PROTECTED SERVER] \$1000	
Engineering: cleaning raw saturation data, analysis:	\$65 per pt *1316 pts= \$85,540
One trip to RTI to work with RTI Staff:	<u>\$1500</u>
<b>TOTAL:</b>	<b>\$88,240</b>

References:

1. Ahmed SJ, Rich W, Finer NN. The effect of averaging time on oximetry values in the premature infant. *Pediatrics* 2010:e115-e121.
2. Di Fiore JM, Bloom JN, Orge F, Schutt A, Schluchter M, Cheruvu VK, Walsh M, Finer N, Martin RJ. A higher incidence of intermittent hypoxemic episodes is associated with severe retinopathy of prematurity. *J of Peds* ( In press).



**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Wally Carlo, M.D."  
**Subject:** RE: New England Journal of Medicine 09-11781.R2  
**Date:** Friday, March 26, 2010 9:20:00 AM

---

I am not sure that we should tell them what to do,; we could mention that the study has been accepted for presentation at both meetings.

Rose

-----Original Message-----

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]  
Sent: Thursday, March 25, 2010 7:10 PM  
To: Higgins, Rosemary (NIH/NICHD) [E]  
Subject: RE: New England Journal of Medicine 09-11781.R2

I was hoping that it would be just before PAS. Maybe we can tell Brendan in case they are flexible. What do you think?

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: 205 266 (b)

-----Original Message-----

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
Sent: Thursday, March 25, 2010 5:38 PM  
To: Wally Carlo, M.D.  
Subject: Re: New England Journal of Medicine 09-11781.R2

Ok

(b) (6)

I am definitely reachable via email and cell phone if needed. Perhaps this will be late April or early May for the publication.

Thanks  
Rose

----- Original Message -----

From: Wally Carlo, M.D. <WCarlo@peds.uab.edu>  
To: Higgins, Rosemary (NIH/NICHD) [E]  
Sent: Thu Mar 25 18:26:07 2010  
Subject: RE: New England Journal of Medicine 09-11781.R2

Not yet.

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: 205 266 (b)

-----Original Message-----

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
Sent: Thursday, March 25, 2010 10:18 AM  
To: Wally Carlo, M.D.  
Subject: RE: New England Journal of Medicine 09-11781.R2

Any word on a date????

-----Original Message-----

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]  
Sent: Thursday, March 25, 2010 11:09 AM  
To: Abel, Brendan; 'Wally Carlo, M.D.'  
Cc: Higgins, Rosemary (NIH/NICHD) [E]  
Subject: RE: New England Journal of Medicine 09-11781.R2

Brendan.

Thanks so much.

wally

Sent from my Windows Mobile phone

-----Original Message-----

From: Abel, Brendan <babel@nejm.org>  
Sent: Thursday, March 25, 2010 9:30 AM  
To: 'Wally Carlo, M.D.' <WCarlo@peds.uab.edu>  
Cc: Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov>  
Subject: RE: New England Journal of Medicine 09-11781.R2

Hi Wally,

That is great. We'll plan on retaining the first paragraph as the support statement, which will appear right before the disclosure statement. The Disclosure statement will be "Dr. Van Meurs reports receiving reimbursement for travel expenses from Ikaria Holdings, Inc. No other potential conflict of interest relevant to this article was reported. Disclosure forms provided by the authors are available with the full text of this article at NEJM.org"

The second paragraph (re: Masimo) will likely be briefly incorporated into the methods section of the manuscript. I've sent a note to the manuscript editors, who will be sure this occurs at galleys.

Let me know if you have any questions.

Thanks!

Brendan

-----Original Message-----

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]  
Sent: Wednesday, March 24, 2010 9:06 PM  
To: onbehalfof+babel+nejm.org@manuscriptcentral.com; Abel, Brendan  
Cc: Higgins, Rosemary (NIH/NICHD) [E]  
Subject: New England Journal of Medicine 09-11781.R2  
Importance: High

Brendan:

Is this ok?

Supported by grants from the National Institutes of Health and from the Eunice Kennedy Shriver National Institute of Child Health and Human Development, which provided overall oversight for study conduct. All data analyses and interpretation were done independently of the funding agency.

Participating centers purchased pulse oximeters from Masimo Radical Pulse Oximeter, Irvine, CA. Masimo customized the oximeters to mask the oxygenation ranges from clinical and study personnel during the intervention. Masimo played no role in the study design, data collection, data analysis, or manuscript preparation or revision.

Dr. Van Meurs reports receiving reimbursement for travel expenses from Ikaria Holdings, Inc. No other potential conflict of interest relevant to this article was reported.

We thank our medical and nursing colleagues and the infants and their parents.

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: 205 266 (b)

-----Original Message-----

From: onbehalfof+babel+nejm.org@manuscriptcentral.com  
[mailto:onbehalfof+babel+nejm.org@manuscriptcentral.com] On Behalf Of

babel@nejm.org

Sent: Tuesday, March 23, 2010 3:08 PM

To: Wally Carlo, M.D.

Subject: New England Journal of Medicine 09-11781.R2

Re: 09-11781.R2 - A Randomized Trial of Oxygen Saturation Targets in Extremely Preterm Infants

Dear Dr. Carlo:

Your Journal article has been selected to have an accompanying CME activity. Consequently, the Accreditation Council for Continuing Medical Education (AACME) requires that a financial disclosure (statement of any author's relevant financial relationships or attestation of no relevant financial relationships) appear with the article.

As the corresponding author, we ask that you draft a disclosure statement for your manuscript based on the information in the submitted disclosure forms (attached). The statement should specify the type of relationships (e.g., consulting, paid speaking, grant support, equity, patents) each author has with each company. The information should be consistent with the authors' signed financial disclosure forms.

Section 2 pertains to the funding for the paper itself, which I believe is mentioned elsewhere in the paper, so you should pay particular attention to the information listed in Section 3 of the forms.

Let me know if you have any further questions. Please email the completed statement to me via email.

Sincerely,

Brendan Abel  
Editorial Assistant  
New England Journal of Medicine  
(617) 487-6584

New England Journal of Medicine  
10 Shattuck Street  
Boston, MA 02115  
(617) 734-9800  
Fax: (617) 739-9864  
<http://www.nejm.org>

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**From:** Pablo Sanchez  
**To:** Archer, Stephanie (NIH/NICHD) [E]  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: \*\*\*\*\*REVIEW NEJM SUPPORT papers | author list and boilerplates\*\*\*\*\*  
**Date:** Thursday, March 25, 2010 3:06:54 PM  
**Attachments:** Boilerplate, Finer, SUPPORT Ventilation, 2010-03-24 2-FINAL.doc  
Boilerplate, Carlo, SUPPORT Oximetry, 2010-03-24 1-FINAL.doc

---

Hi Stephanie--the only thing is Diana's title--a dash rather than a comma--i have no idea of it makes any difference....but ...i don't know how you keep up withthis, it drives me crazy and it's just one site!  
Diana M Vasil, RNC-NIC

--thanks, all of the other contributors whom i previously excluded by mistake have been added---i appreciate it!--  
pablo

>>> "Archer, Stephanie (NIH/NICHD) [E]" <archerst@mail.nih.gov> 3/24/10 12:34 PM >>>

As many of you have pointed out, I had some duplications between the authors and having their names in the boilerplate. I have corrected that in the attached files. Please let Rose and I know by tomorrow of any additional changes you need make.

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:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Wednesday, March 24, 2010 9:51 AM  
**To:** Finer, Neil; 'Rich, Wade'; Gantz, Marie; Poole, W. Kenneth; 'Nancy Newman'; (susie.buchter@oz.ped.emory.edu); Laroia, Nirupama; 'Phelps, Dale'; 'Duara, Shahnaz'; Vivek Narendran; 'Sood, Beena'; 'Michael O'Shea'; 'vineet.bhandari@yale.edu'; Anthony Piazza (Anthony.Piazza@oz.ped.emory.edu); Brenda Morris; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Matthew Bizzarro; Michelle Walsh; Mickey Caplan; Oh William (E-mail); Pablo Sanchez; Roger Faix; Ronald Goldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa  
**Cc:** 'Zaterka-Baxter, Kristin'; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** \*\*\*\*\*REVIEW NEJM SUPPORT papers | author list and boilerplates\*\*\*\*\*  
**Importance:** High

Hi ALL-

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Also, Dr. Carlo has been contacted by NEJM and his paper has been selected to have an accompanying CME activity.

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Thanks for all your help

Rose

**From:** Ronald N Goldberg  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** Re: \*\*\*\*\*REVIEW NEJM SUPPORT papers | author list and boilerplates\*\*\*\*\*  
**Date:** Wednesday, March 24, 2010 5:22:18 PM

---

hi Rose,  
Kim's last name is Fisher.  
ron

Ronald N. Goldberg, M.D.  
Shaad-McBryde Professor of Pediatrics  
Chief, Neonatal-Perinatal Medicine  
Box 2739  
Duke University Medical Center  
Durham, NC 27710  
Phone: 919-681-6037  
Fax: 919-681-6065  
email: goldb008@mc.duke.edu

"Higgins, Rosemary (NIH/NICHD) [E]"  
<higginsr@mail.nih.gov>

03/24/2010 09:52 AM

To "Finer, Neil" <nfiner@ucsd.edu>, "Rich, Wade" <wrich@ucsd.edu>, "Gantz, Marie" <mgantz@rti.org>, "Poole, W. Kenneth" <poo@rti.org>, "Nancy Newman" <nxs5@case.edu>, "susie.buchter@oz.ped.emory.edu" <susie.buchter@oz.ped.emory.edu>, "Laroia, Nirupama" <Nirupama\_Laroia@URMC.Rochester.edu>, "Phelps, Dale" <Dale\_Phelps@URMC.Rochester.edu>, "Duara, Shahnaz" <SDuara@med.miami.edu>, Vivek Narendran <Vivek.Narendran@cchmc.org>, "Sood, Beena" <bsood@med.wayne.edu>, "Michael O'Shea" <moshea@wfubmc.edu>, "vineet.bhandari@yale.edu" <vineet.bhandari@yale.edu>, "Anthony Piazza (Anthony.Piazza@oz.ped.emory.edu)" <Anthony.Piazza@oz.ped.emory.edu>, Brenda Morris <(b) (6) (Luc.Brion@UTSouthwestern.edu)> <Luc.Brion@UTSouthwestern.edu>, " (rohls@unm.edu)" <rohls@unm.edu>, "aaf2@po.cwru.edu" <aaf2@po.cwru.edu>, Abhik Das <adas@rti.org>, "alaptook@WHRI.org" <alaptook@WHRI.org>, "Ambal (ambal@uab.edu)" <ambal@uab.edu>, "Brad Yoder (Bradley.yoder@hsc.utah.edu)" <Bradley.yoder@hsc.utah.edu>, Brenda Poindexter <bpoindex@iupui.edu>, "Carlo Waldemar (E-mail)" <wcarlo@peds.uab.edu>, "cotte010@mc.duke.edu" <cotte010@mc.duke.edu>, Dennis Wallace <dwallace@rti.org>, Ed Bell <Edward-bell@uiowa.edu>, Ed Donovan <edward.donovan@cchmc.org>, "Ehrenkranz Richard (E-mail)" <richard.ehrenkranz@yale.edu>, "Ivan Frantz (ifrantz@tuftsmedicalcenter.org)" <ifrantz@tuftsmedicalcenter.org>, "Kennedy, Kathleen A" <Kathleen.A.Kennedy@uth.tmc.edu>, Kristi Watterberg <kwatterberg@salud.unm.edu>, "Kurt Schibler [kurt.schibler@cchmc.org]" <kurt.schibler@cchmc.org>, Matthew Bizzarro <matthew.bizzarro@yale.edu>, Michelle Walsh <mcw3@po.cwru.edu>, Mickey Caplan <mcaplan@northshore.org>, "Oh William (E-mail)" <william\_oh@brown.edu>, Pablo Sanchez <Pablo.Sanchez@UTSouthwestern.edu>, Roger Faix <Roger.Faix@hsc.utah.edu>, Ronald Goldberg <goldb008@mc.duke.edu>, Seetha Shankaran <sshankar@med.wayne.edu>, "Stevenson David (E-mail)" <dstevenson@stanford.edu>, "Stoll Barbara (E-mail)" <barbara\_stoll@oz.ped.emory.edu>, "Tyson Jon (E-mail)" <Jon.E.Tyson@uth.tmc.edu>, "VanMeurs, Krisa" <vanmeurs@leland.stanford.edu>

cc "Zaterka-Baxter, Kristin" <kzaterka@rti.org>, "Archer, Stephanie (NIH/NICHD) [E]" <archerst@mail.nih.gov>

Subject \*\*\*\*\*REVIEW NEJM SUPPORT papers | author list and boilerplates\*\*\*\*\*

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Thanks for all your help

Rose

[attachment "Boilerplate, Carlo, SUPPORT Oximetry, 2010-03-24.doc" deleted by Ronald N Goldberg/Pediatrics/mc/Duke] [attachment "Boilerplate, Finer, SUPPORT Ventilation, 2010-03-24.doc" deleted by Ronald N Goldberg/Pediatrics/mc/Duke]



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**From:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**To:** ["Irene, Amanda"](#)  
**Subject:** SUPPORT03232010 2  
**Date:** Wednesday, March 24, 2010 3:32:00 PM  
**Attachments:** [SUPPORT03232010 2.doc](#)

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## **SUPPORT – Intermittent Hypoxia Secondary March 22, 2010**

**Participants:** Rose Higgins, Wade Rich, Wally Carlo, Neil Finer, Abbot Laptook, Marie Gantz, Kurt Schibler, Michelle Walsh, Abhik Das, Juliann Di Fiore, Meg Cunningham, Kris Zaterka-Baxter, Amanda Irene

- Juliann Di Fiore presented an overview of her secondary study, *Intermittent Hypoxia in Preterm Infants enrolled in the SUPPORT trial*
  - The aim of the study is to expand the current database of infants with high resolution pulse oximetry data to include the remaining low resolution pulse oximetry data SUPPORT infants.
  - **Hypothesis:** infants with low resolution oximetry data will have fewer desaturation events and of smaller magnitude than infants with high resolution data; Infants with severe ROP requiring laser therapy will have a higher incidence of desaturation events.
  - There are currently 119 Infants in the high resolution cohort, and there are an additional 1316 infants enrolled in the SUPPORT trial whom we may be able to extract additional desaturation data with low resolution.
  - The low resolution group has a much larger sample size which increases the chances of finding a relationship between intermittent hypoxia and both morbidity and mortality.
  - Due to the low incidence of infant mortality in the high resolution cohort we may not have the ability to assess the association between desaturation events and infant mortality.
  - If there is no difference in event detection in the high versus low resolution group, and no difference in the number of desaturation events between the low and high baseline SpO<sub>2</sub> infant groups, we will conclude that keeping the infants in the low saturation target range does not put them at risk for episodic desaturation
    - If a difference in event detection is found between low and high resolution groups the conclusions between the low and high baseline saturation ranges will be limited by the ability to compare severe events and events of shorter duration.
- The SUPPORT subcommittee discussed how the data on the low and high resolution groups would be acquired and analyzed.
  - The data acquired from Juliann's study are from data points at a 2 second sample rate; data acquired from the SUPPORT trial are from a 16 second sample rate.
  - With the collection of data from a 2 second point as opposed to the 16 second SUPPORT collection, the goal is to be able to see a lot more short intermittent events.
  - For data analysis, RTI will send Juliann the raw data
  - There are some funding issues with this study; the materials that need to be bought to store the data are relatively cheap.
    - The amount of money needed is around \$109,000 in total.
- The adjudicated data will be used for the 7% of infants with missing ROP data.
- Dr. Higgins suggested looking at BPD in this model; BPD may also be affected by desaturation.
- Juliann will speak with the PIs to discuss sharing the software programs with RTI.
- As opposed to be unblinded, the study will be masked by group A and B; this is better from the protocol review standpoint.
- Dr. Higgins will find out what the budgetary restrictions are for network funds.  
Addendum: The NRN can budget funds for this type of secondary analysis
- All in agreement to advance the secondary to the protocol review subcommittee.
  - A call will be set up with the protocol review subcommittee to discuss.

**From:** Archer, Stephanie (NIH/NICHD) [E]  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; "Rich, Wade"; Gantz, Marie; Poole, W. Kenneth; "Nancy Newman"; (susie.buchter@oz.ped.emory.edu); Laroia, Nirupama; "Phelps, Dale"; "Duara, Shahnaz"; Vivek Narendran; "Sood, Beena"; "Michael O`Shea"; "vineet.bhandari@yale.edu"; Anthony Piazza (Anthony.Piazza@oz.ped.emory.edu); Brenda Morris; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Matthew Bizzarro; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Roger Faix; Ronald GOLDBERG; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa  
**Cc:** "Zaterka-Baxter, Kristin"  
**Subject:** RE: \*\*\*\*\*REVIEW NEJM SUPPORT papers | author list and boilerplates\*\*\*\*\*  
**Date:** Wednesday, March 24, 2010 1:34:18 PM  
**Attachments:** Boilerplate, Finer, SUPPORT Ventilation, 2010-03-24.doc  
Boilerplate, Carlo, SUPPORT Oximetry, 2010-03-24.doc

---

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Stephanie

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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:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Wednesday, March 24, 2010 9:51 AM  
**To:** Finer, Neil; 'Rich, Wade'; Gantz, Marie; Poole, W. Kenneth; 'Nancy Newman'; (susie.buchter@oz.ped.emory.edu); Laroia, Nirupama; 'Phelps, Dale'; 'Duara, Shahnaz'; Vivek Narendran; 'Sood, Beena'; 'Michael O`Shea'; 'vineet.bhandari@yale.edu'; Anthony Piazza (Anthony.Piazza@oz.ped.emory.edu); Brenda Morris; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Matthew Bizzarro; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Roger Faix; Ronald GOLDBERG; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa  
**Cc:** 'Zaterka-Baxter, Kristin'; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** \*\*\*\*\*REVIEW NEJM SUPPORT papers | author list and boilerplates\*\*\*\*\*  
**Importance:** High

Hi ALL-

Attached are the two SUPPORT paper mastheads for authorship and the boilerplates.

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We do not as yet have a target publication date.

Thanks for all your help

Rose

**From:** Shankaran, Seetha  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** FW: \*\*\*\*\*REVIEW NEJM SUPPORT papers | author list and boilerplates\*\*\*\*\*  
**Date:** Wednesday, March 24, 2010 1:25:55 PM  
**Attachments:** [Boilerplate, Carlo, SUPPORT Oximetry, 2010-03-24.doc](#)  
[Boilerplate, Finer, SUPPORT Ventilation, 2010-03-24.doc](#)  
**Importance:** High

---

Rose

Since Beena is listed as author, I think she should not be in boiler plate right  
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:** Wednesday, March 24, 2010 9:51 AM  
**To:** Finer, Neil; 'Rich, Wade'; Gantz, Marie; Poole, W. Kenneth; 'Nancy Newman'; (susie.buchter@oz.ped.emory.edu); Laroia, Nirupama; 'Phelps, Dale'; 'Duara, Shahnaz'; Vivek Narendran; Sood, Beena; 'Michael O`Shea'; 'vineet.bhandari@yale.edu'; Anthony Piazza (Anthony.Piazza@oz.ped.emory.edu); Brenda Morris; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Matthew Bizzarro; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Roger Faix; Ronald Goldberg; Shankaran, Seetha; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa  
**Cc:** 'Zaterka-Baxter, Kristin'; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** \*\*\*\*\*REVIEW NEJM SUPPORT papers | author list and boilerplates\*\*\*\*\*  
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**From:** Phelps, Dale  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Zaterka-Baxter, Kristin; Archer, Stephanie (NIH/NICHD) [E]; Reubens, Linda  
**Subject:** RE: \*\*\*\*\*REVIEW NEJM SUPPORT papers | author list and boilerplates\*\*\*\*\*  
**Date:** Wednesday, March 24, 2010 12:31:48 PM  
**Attachments:** Boilerplate Finer SUPPORT Ventilation 2010-03-24 (2).doc  
Boilerplate Carlo SUPPORT Oximetry 2010-03-24.doc

---

Hi Rose,

*Query:*

Authors in the Masthead are listed again in the Boilerplate on both papers.  
I thought we had decided that authors in the Masthead are NOT to be listed again in the Masthead. I have lighted and done 'strike out' for these for Rochester.

**>>> I checked on some of the other centers, and the listings are NOT consistent throughout the boilerplate.**

**Some repeat the masthead authors in the Boilerplate, and others do not.**

**If you want me to proof throughout for this, please let me know.**

Changes:

1. I inadvertently left out our Department on both papers, and have put it in now on each masthead. Highlighted in green for you to find easily.
2. Finer: SUPPORT CPAP --- Gary Markowitz belongs only on the Carlo oximetry paper, not on the Ventilation Paper.

Dale Phelps  
for the University of Rochester

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Wednesday, March 24, 2010 6:51 AM  
**To:** Finer, Neil; 'Rich, Wade'; Gantz, Marie; Poole, W. Kenneth; 'Nancy Newman'; (susie.buchter@oz.ped.emory.edu); Laroia, Nirupama; Phelps, Dale; 'Duara, Shahnaz'; Vivek Narendran; 'Sood, Beena'; 'Michael O` Shea'; vineet.bhandari@yale.edu; Anthony Piazza (Anthony.Piazza@oz.ped.emory.edu); Brenda Morris; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptok@WIIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Matthew Bizzarro; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Roger Faix; Ronald GOLDBERG; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa  
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**From:** Archer, Stephanie (NIH/NICHD) [E]  
**To:** "Ed Donovan"  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: \*\*\*\*\*REVIEW NEJM SUPPORT papers | author list and boilerplates\*\*\*\*\*  
**Date:** Wednesday, March 24, 2010 11:02:37 AM  
**Attachments:** Boilerplate, Finer, SUPPORT Ventilation, 2010-03-24.doc

---

Corrected.

---

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

-----Original Message-----

From: Higgins, Rosemary (NIH/NICHD) [E]  
Sent: Wednesday, March 24, 2010 11:01 AM  
To: Archer, Stephanie (NIH/NICHD) [E]  
Subject: FW: \*\*\*\*\*REVIEW NEJM SUPPORT papers | author list and boilerplates\*\*\*\*\*

IS this right??

-----Original Message-----

From: Edward Donovan [mailto:Edward.Donovan@cchmc.org]  
Sent: Wednesday, March 24, 2010 11:00 AM  
To: Higgins, Rosemary (NIH/NICHD) [E]  
Subject: Re: \*\*\*\*\*REVIEW NEJM SUPPORT papers | author list and boilerplates\*\*\*\*\*

masthead has me working in Boston which I don't

Edward F. Donovan, M.D.  
Ohio Perinatal Quality Collaborative  
www.OPQC.net

Child Policy Research Center  
Children's Hospital Medical Center  
3333 Burnet Avenue, ML 7014  
Cincinnati, OH 45229-3039  
Phone 513-636-0169  
Fax 513-636-0171  
www.cincinnatichildrens.org/cprc

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**To:** "Finer, Neil"; "Rich, Wade"; "Gantz, Marie"; "Poole, W. Kenneth"; "Nancy Newman"; "(susie.buchter@oz.ped.emory.edu)"; "Laroia, Nirupama"; "Phelps, Dale"; "Duara, Shahnaz"; "Vivek Narendran"; "Sood, Beena"; "Michael O`Shea"; "vineet.bhandari@yale.edu"; "Anthony Piazza (Anthony.Piazza@oz.ped.emory.edu)"; "Brenda Morris"; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; "Abhik Das"; alaptook@WIHLI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); "Brenda Poindexter"; "Carlo Waldemar (E-mail)"; cotte010@mc.duke.edu; "Dennis Wallace"; "Ed Bell"; "Ed Donovan"; "Ehrenkranz Richard (E-mail)"; Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; "Kristi Watterberg"; Kurt Schibler (kurt.schibler@cchmc.org); "Matthew Bizzarro"; "Michelle Walsh"; "Mickey Caplan"; "Oh William (E-mail)"; "Pablo Sanchez"; "Roger Faix"; "Ronald Goldberg"; "Seetha Shankaran"; "Stevenson David (E-mail)"; "Stoll Barbara (E-mail)"; "Tyson Jon (E-mail)"; VanMeurs, Krisa  
**Cc:** "Zaterka-Baxter, Kristin"; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** \*\*\*\*\*REVIEW NEJM SUPPORT papers | author list and boilerplates\*\*\*\*\*  
**Date:** Wednesday, March 24, 2010 9:51:00 AM  
**Attachments:** Boilerplate, Carlo, SUPPORT Oximetry, 2010-03-24.doc  
Boilerplate, Finer, SUPPORT Ventilation, 2010-03-24.doc  
**Importance:** High

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**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Subject:** \*\*\*\*\*REVIEW NEJM SUPPORT papers | author list and boilerplates\*\*\*\*\*  
**Date:** Wednesday, March 24, 2010 9:34:37 AM  
**Attachments:** [Boilerplate, Carlo, SUPPORT Oximetry, 2010-03-24.doc](#)  
[Boilerplate, Finer, SUPPORT Ventilation, 2010-03-24.doc](#)

---

Here are the updated author lists and boilerplates for Wally's and Neil's papers.

**From:** [Irene, Amanda](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Subject:** SUPPORT secondary  
**Date:** Wednesday, March 24, 2010 9:21:00 AM  
**Attachments:** [SUPPORT03232010.2.doc](#)

---

Hi Rose,

Ive attached the SUPPORT secondary minutes from yesterdays call.

Let me know of any changes.

Thanks!  
Amanda

## **SUPPORT – Intermittent Hypoxia Secondary** **March 22, 2010**

**Participants:** Rose Higgins, Wade Rich, Wally Carlo, Neil Finer, Abbot Laptook, Marie Gantz, Kurt Schibler, Michelle Walsh, Abhik Das, Juliann Di Fiore, Meg Cunningham, Kris Zaterka-Baxter, Amanda Irene

- Juliann Di Fiore presented an overview of her secondary study, *Intermittent Hypoxia in Preterm Infants enrolled in the SUPPORT trial*
  - The aim of the study is to expand the current database of infants with high resolution pulse oximetry data to include the remaining low resolution pulse oximetry data SUPPORT infants.
  - **Hypothesis:** infants with low resolution oximetry data will have fewer desaturation events and of smaller magnitude than infants with high resolution data; Infants with severe ROP requiring laser therapy will have a higher incidence of desaturation events.
  - There are currently 119 Infants in the high resolution cohort, and there are an additional 1316 infants enrolled in the SUPPORT trial whom we may be able to extract additional desaturation data with low resolution.
  - The low resolution group has a much larger sample size which increases the chances of finding a relationship between intermittent hypoxia and both morbidity and mortality.
  - Due to the low incidence of infant mortality in the high resolution cohort we may not have the ability to assess the association between desaturation events and infant mortality.
  - If there is no difference in event detection in the high versus low resolution group, and no difference in the number of desaturation events between the low and high baseline SpO<sub>2</sub> infant groups, we will conclude that keeping the infants in the low saturation target range does not put them at risk for episodic desaturation
    - If a difference in event detection is found between low and high resolution groups the conclusions between the low and high baseline saturation ranges will be limited by the ability to compare severe events and events of shorter duration.
- The SUPPORT subcommittee discussed how the data on the low and high resolution groups would be acquired and analyzed.
  - The data acquired from Juliann's study are from data points at a 2 second sample rate; data acquired from the SUPPORT trial are from a 16 second sample rate.
  - With the collection of data from a 2 second point as opposed to the 16 second SUPPORT collection, the goal is to be able to see a lot more short intermittent events.
  - For data analysis, RTI will send Juliann the raw data
  - There are some funding issues with this study; the materials that need to be bought to store the data are relatively cheap.
    - The amount of money needed is around \$109,000 in total.
- The adjudicated data will be used for the 7% of infants with missing ROP data.
- Dr. Higgins suggested looking at BPD in this model; BPD may also be affected by desaturation.
- Juliann will speak with the PIs to discuss sharing the software programs with RTI.
- As opposed to be unblinded, the study will be masked by group A and B; this is better from the protocol review standpoint.
- Dr. Higgins will find out what the budgetary restrictions are for network funds.  
Addendum: The NRN can budget funds for this type of secondary analysis
- All in agreement to advance the secondary to the protocol review subcommittee.
  - A call will be set up with the protocol review subcommittee to discuss.

**From:** [Das, Abhik](#)  
**To:** [nfiner@ucsd.edu](mailto:nfiner@ucsd.edu); [Higgins, Rosemary \(NIH/NICHD\)](#) [E]  
**Cc:** [Gantz, Marie](#)  
**Subject:** FW: SUPPORT call  
**Date:** Monday, March 22, 2010 2:59:49 PM

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RTI comments on the SUPPORT intermittent hypoxia secondary study:

- 1) Even though we have an algorithm for calculating "actual" SpO2 values from the "display" values, in our analyses we have found it necessary to smooth the data in those "actual" categories when creating graphs, and we would anticipate needing to smooth the data similarly when doing any analysis with the data. This might be less of an issue when looking at desaturations, because it will likely involve looking at the lower ranges of SpO2 values (<80%) where the "actual" and "display" values are the same. However, it would be wise for the investigators to collaborate with RTI to make sure we all take a similar approach (so our analyses will be consistent with one another).
- 2) Assuming that the investigators are going to be processing the raw data supplied by RTI (subject to signed data sharing agreements) to detect desaturations, we would urge them to share that information back with the Network (and RTI) so that we don't have to reprocess the data again if we need that information. At a minimum we would like the methods and algorithms for detecting desaturations to be shared with us.
- 3) The analysis section does not talk about adjusting for design variables such as GA stata and site. Also, we don't understand the reference to repeated measures analysis. While the analysis plan calls for looking at the association between the number of desaturations and various outcomes such as ROP, NDI and death, we don't see how repeated measures come into play.

Thanks

Abhik

**Abhik Das, Ph.D.**  
**Senior Research Statistician**  
**RTI International**  
6110 Executive Blvd., Suite 902  
Rockville, MD 20852-3903  
e-mail: [adas@rti.org](mailto:adas@rti.org)  
Phone: 301-770-8214  
Fax: 301-230-4646

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Wally Carlo, M.D."; "Cunningham, Meg"; "Finer, Neil"; "mcw3@case.edu"; "Bradley Yoder"; "Roger Faix"; "alaptook@WIHRI.org"; "kurt.schibler@cchmc.org"; "Das, Abhik"; "Wallace, Dennis"; "nancy newman"; "Rich, Wade"; "Gantz, Marie"  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; "Zaterka-Baxter, Kristin"; "Huitema, Carolyn Petrie"; "Irene, Amanda"; "Starlett Williams"; "fmartinez@ucsd.edu"; "Carolyn.Grier@UHhospitals.org"; "bvecchio@careNE.org"  
**Subject:** RE: SUPPORT Intermittent Hypoxia  
**Date:** Monday, March 22, 2010 2:00:00 PM  
**Attachments:** [Comments on the intermittent hypoxia secondary study.doc](#)

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My comments  
Rose

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network

---

**From:** Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]  
**Sent:** Monday, March 22, 2010 1:39 PM  
**To:** Cunningham, Meg; Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; mcw3@case.edu; Bradley Yoder; Roger Faix; alaptook@WIHRI.org; kurt.schibler@cchmc.org; Das, Abhik; Wallace, Dennis; nancy newman; Rich, Wade; Gantz, Marie  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Huitema, Carolyn Petrie; Irene, Amanda; Starlett Williams; fmartinez@ucsd.edu; Carolyn.Grier@UHhospitals.org; bvecchio@careNE.org  
**Subject:** RE: SUPPORT Intermittent Hypoxia

Here is my review.

Wally

---

**From:** Cunningham, Meg [mailto:mcunningham@rti.org]  
**Sent:** Monday, March 22, 2010 7:38 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; Wally Carlo, M.D.; mcw3@case.edu; Bradley Yoder; Roger Faix; alaptook@WIHRI.org; kurt.schibler@cchmc.org; Das, Abhik; Wallace, Dennis; nancy newman; Rich, Wade; Gantz, Marie  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Huitema, Carolyn Petrie; Irene, Amanda; Starlett Williams; fmartinez@ucsd.edu; Carolyn.Grier@UHhospitals.org; bvecchio@careNE.org  
**Subject:** RE: SUPPORT Intermittent Hypoxia

Reminder for today's call.

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**From:** Webb, Robin E.  
**Sent:** Thursday, February 25, 2010 11:38 AM  
**To:** Webb, Robin E.; 'Higgins, Rosemary (NIH/NICHD) [E]'; 'Finer, Neil'; 'Wally Carlo, M.D.'; 'mcw3@case.edu'; 'Bradley Yoder'; 'Roger Faix'; 'alaptook@WIHRI.org'; 'Kurt Schibler [kurt.schibler@cchmc.org]'; Das, Abhik; Wallace, Dennis; 'nancy newman'; 'Rich, Wade'; Gantz, Marie  
**Cc:** 'Archer, Stephanie (NIH/NICHD) [E]'; Zaterka-Baxter, Kristin; Cunningham, Meg; Huitema, Carolyn Petrie; Irene, Amanda; StWilliams@peds.uab.edu; fmartinez@ucsd.edu; Carolyn.Grier@UHhospitals.org; 'bvecchio@careNE.org'  
**Subject:** SUPPORT Intermittent Hypoxia

The call to review the secondary study has been scheduled for:

**Monday, 3/22**  
**2:00pm ET**



Dial:

**Within the USA**

866-675-(b) [REDACTED]

or

**Outside the USA**

1-203-310-(b) (6)

Then, enter Participant Passcode:

(b) (6)

Comments on the intermittent hypoxia secondary study.

How will missing ROP data be handled? Do the authors intend to use the adjudication results from the ophthalmologists for these missing variables?

Should BPD be analyzed in a similar fashion or will this overlap with the BPD secondary study already described as a secondary outcome?

ROP primary outcome – should this be threshold ROP?

The third aim should only be done after the primary follow up analysis is accepted for publication.

For the software issues, RTI should address.

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Walsh, Michele"  
**Subject:** RE: SUPPORT Intermittent Hypoxia  
**Date:** Monday, March 22, 2010 10:53:00 AM

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The SUPPORT subcommittee is reviewing the secondary proposal. You can certainly answer questions, but I don't think anyone thought there would be slides.

Rose

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**From:** Walsh, Michele [mailto:Michele.Walsh@UHhospitals.org]  
**Sent:** Monday, March 22, 2010 10:49 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** FW: SUPPORT Intermittent Hypoxia

Hi Rose: I missed this earlier message- are we expected to lead this presentation With slides?

Michele Walsh  
beeper (b) (6)  
Ph 216 844 3759

---

**From:** Cunningham, Meg [mailto:mcunningham@rti.org]  
**Sent:** Monday, March 22, 2010 8:38 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; Wally Carlo, M.D.; mcw3@case.edu; Bradley Yoder; Roger Faix; alaptook@WIHRI.org; kurt.schibler@cchmc.org; Das, Abhik; Wallace, Dennis; nancy newman; Rich, Wade; Gantz, Marie  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Huitema, Carolyn Petrie; Irene, Amanda; StWilliams@peds.uab.edu; fmartinez@ucsd.edu; Grier, Carolyn; bvecchio@careNE.org  
**Subject:** RE: SUPPORT Intermittent Hypoxia

Reminder for today's call.

---

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**Sent:** Thursday, February 25, 2010 11:38 AM  
**To:** Webb, Robin E.; 'Higgins, Rosemary (NIH/NICHD) [E]'; 'Finer, Neil'; 'Wally Carlo, M.D.'; 'mcw3@case.edu'; 'Bradley Yoder'; 'Roger Faix'; 'alaptook@WIHRI.org'; 'Kurt Schibler [kurt.schibler@cchmc.org]'; Das, Abhik; Wallace, Dennis; 'nancy newman'; 'Rich, Wade'; Gantz, Marie  
**Cc:** 'Archer, Stephanie (NIH/NICHD) [E]'; Zaterka-Baxter, Kristin; Cunningham, Meg; Huitema, Carolyn Petrie; Irene, Amanda; StWilliams@peds.uab.edu; fmartinez@ucsd.edu; Carolyn.Grier@UHhospitals.org; 'bvecchio@careNE.org'  
**Subject:** SUPPORT Intermittent Hypoxia

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**Monday, 3/22**  
**2:00pm ET**

Dial:  
**Within the USA**  
866-675-(b) (6)

or

**Outside the USA**

1-203-310 (b) (6)

Then, enter Participant Passcode:

(b) (6)

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**From:** Walsh, Michele  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** FW: SUPPORT Intermittent Hypoxia  
**Date:** Monday, March 22, 2010 10:51:11 AM  
**Attachments:** SUPPORT Intermittent Hypoxia.doc

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Hi Rose: I missed this earlier message- are we expected to lead this presentation  
With slides?

Michele Walsh  
beeper (b) (6)  
Ph 216 844 3759

---

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**Sent:** Monday, March 22, 2010 8:38 AM  
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**Cc:** Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Huitema, Carolyn Petrie; Irene, Amanda; StWilliams@peds.uab.edu; fmartinez@ucsd.edu; Grier, Carolyn; bvecchio@careNE.org  
**Subject:** RE: SUPPORT Intermittent Hypoxia

Reminder for today's call.

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**Cc:** 'Archer, Stephanie (NIH/NICHD) [E]'; Zaterka-Baxter, Kristin; Cunningham, Meg; Huitema, Carolyn Petrie; Irene, Amanda; StWilliams@peds.uab.edu; fmartinez@ucsd.edu; Carolyn.Grier@UHhospitals.org; 'bvecchio@careNE.org'  
**Subject:** SUPPORT Intermittent Hypoxia

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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.

## Intermittent Hypoxia in Preterm Infants enrolled in the SUPPORT trial

### Secondary Study

Juliann Di Fiore, BSEE, Ryan Foglyano, BSBE, Richard Martin, MD,

Chris Wilson PhD, Michele Walsh, MD

[Case Western Reserve University School of Medicine, Cleveland, OH]

#### Abstract

Episodes of oxygen saturation are almost universal in very low birthweight infants. Neither their incidence, nor potential adverse effects on later neurodevelopmental outcome are known. The NICHD Neonatal Research Network, of which we are a participant, has completed a multicenter trial in which preterm infants of 24-28 weeks gestation were randomized to high versus low levels of baseline oxygen saturation. We have previously received approval from the NICHD Neonatal Research Network to perform a secondary study on a subcohort of the SUPPORT trial infants, entitled *INCIDENCE AND CONSEQUENCES OF EPISODIC DESATURATION IN PRETERM INFANTS ENROLLED IN THE NICHD NEONATAL NETWORK OXYGEN SATURATION [SUPPORT] STUDY*, to 1) characterize and compare the incidence and magnitude of episodic desaturation episodes in infants randomized to high versus low baseline oxygen saturation targets in the SUPPORT Trial 2) correlate the incidence and magnitude of such desaturation episodes over the first month of life with neurodevelopmental outcome at 18-22 months and 3) correlate the incidence of early intermittent hypoxia with a history of sleep disordered breathing (SDB) at 18-22 months.

Field Code Changed

To accurately detect the incidence of desaturation episodes, our current secondary study only includes infants from the San Diego and Cleveland sites where pulse oximetry data were acquired at high resolution (2 sec averaging time and 2 second sample). In contrast, the SUPPORT trial oximetry data at all other sites have been acquired at low resolution (16 second averaging time and 10 second sample rate). With the SUPPORT trial findings of increased mortality in the low baseline saturation group, there is interest in expanding the secondary study database to include a second cohort of infants with low resolution data as well. This may be problematic as the prolonged averaging times will smooth the SaO<sub>2</sub> waveform and may decrease the accuracy of detection of desaturation events. The low sample rate of 10 sec may further exacerbate this problem.

#### A. Specific Aim:

The aim of this study is to expand our current database of infants with high resolution pulse oximetry data to include the remaining low resolution pulse oximetry data SUPPORT infants. Using these two separate infant cohorts we aim to:

1. Assess the effect of data resolution (2/2sec, averaging time/sample rate versus 16/10sec, averaging time/sample rate) on the incidence, duration and magnitude of desaturation events between low and high baseline SaO<sub>2</sub> infant groups.
2. Assess the relationship between the incidence of desaturation events and the development of Retinopathy of Prematurity (ROP).
3. Analyze the correlation between the incidence of desaturation events and neurodevelopmental outcome.
4. Analyze the correlation between the incidence of desaturation events and mortality.

B. Hypothesis:

We hypothesize that:

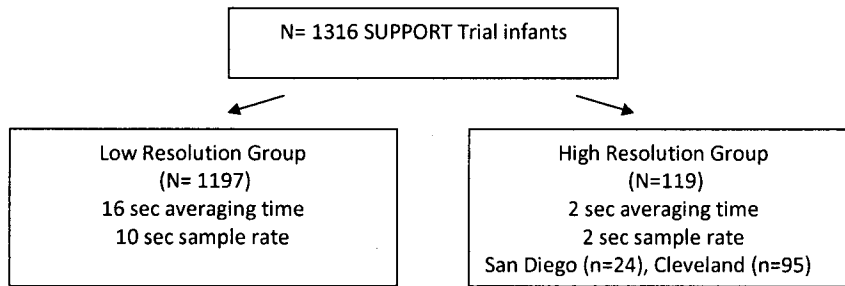
1. Infants with low resolution oximetry data will have fewer desaturation events and of smaller magnitude than infants with high resolution data.
2. Infants with severe ROP requiring laser therapy will have a higher incidence of desaturation events.
3. A higher incidence of episodic desaturation in neonates is associated with greater neurodevelopmental handicap at 18-22 months.
4. A higher incidence of desaturation events is associated with an increase in infant mortality.

C. Rationale:

The SUPPORT Trial randomized infants to two ranges of SpO<sub>2</sub> in order to test the hypothesis that use of a lower SpO<sub>2</sub> range will result in an increase in survival of preterm infants without the occurrence of threshold retinopathy of prematurity [ROP] and/or the need for surgical intervention. However, the potential risk of a lower baseline SpO<sub>2</sub> range in increasing the incidence of episodic desaturation is unknown. In addition, prior studies in animal models have suggested that the neural effects of intermittent or episodic hypoxia may differ greatly than those of sustained hypoxia. Our previously approved secondary study represented a unique opportunity to acquire data to characterize the risk factors and consequences of episodic desaturation. Although we currently have 119 Infants in the high resolution cohort there are an additional 1316 infants enrolled in the SUPPORT trial in whom we may be able to extract additional desaturation data with low resolution. Although differences in monitor settings does not allow for combining the two infant cohorts, the larger sample size in the low resolution infant group may enable us to detect more subtle



associations between desaturation events and baseline saturation, ROP, mortality and detriments in neurodevelopmental outcome.



The low resolution group has a much larger sample size which increases the chances of finding a relationship between intermittent hypoxia and both morbidity and mortality. However, the low resolution of saturation data may limit the ability to accurately detect desaturation events in this cohort. Previous data (Ahmed) have suggested that application of a 16 sec averaging time window may result in an underestimation of short events (<30sec) and events of greater severity (<70%) and an overestimation of events of long duration (>300sec) when compared to application of a 2 sec averaging time window. If comparisons between low and high resolution groups reveal statistically significant differences in event detection parameters, interpretation of associations of desaturation events with baseline SaO<sub>2</sub> and morbidity may be limited to the infants in whom data were acquired with high resolution group (n=119). Due to the low incidence of infant mortality in the high resolution cohort we may not have the ability to assess the association between desaturation events and infant mortality.

If event parameters do not differ between low and high resolution groups the increased sample size of 1316 in the low resolution group may increase the ability to detect an association between these events and baseline SaO<sub>2</sub>, mortality, and neurodevelopmental outcome. Lastly, even if desaturation event detection is significantly compromised in the low resolution group, the low resolution may still be adequate to detect differences between the incidence of intermittent hypoxia and mortality/morbidity in this large infant cohort.

#### D. Methodologies:

##### Aim 1: Effect of data acquisition resolution and baseline SpO<sub>2</sub>

We request to be unblinded to the infant cohorts and have access to the saturation data corrected for the SUPPORT trial SpO<sub>2</sub> baseline randomization. None of the personnel involved in the saturation data analysis participate in developmental followup of the enrolled cohort and

thus cannot influence the outcome evaluations at CWRU, and thus are not a threat to the integrity of the main trial neurodevelopmental evaluations. To prevent inadvertent disclosure, all data files will be sequestered in the office of Ms. Juliann Di Fiore and will not be accessible to other members of the CWRU team. Further, data files will remain identified only by study number and not by the infant's name.

We will use currently developed software to document the occurrence, duration and magnitude of desaturation events  $\leq 80\%$  in the low resolution group. To comply with Nyquist sampling theorem limitations (2 x sample rate) and to distinguish intermittent hypoxia from prolonged changes in baseline SpO<sub>2</sub>, only events  $\geq 20$ sec and  $\leq 3$  min will be included in the analysis. Data will be analyzed for the first 8 weeks of life or shorter time periods for infants who completed the SUPPORT trial before 8 weeks post natal age. All desaturation events will be included regardless of the need for supplemental oxygen or ventilator support.

We will compare the occurrence, duration and magnitude of desaturation events for

1. Acquisition Resolution
  - a. High (2 sec average, 2 second sample rate) versus low (16 sec average and 10 sec sample rate) resolution in the low baseline SpO<sub>2</sub> infant groups
  - b. High versus low resolution in the high baseline SpO<sub>2</sub> infant groups
2. Baseline SpO<sub>2</sub>
  - a. Low versus High baseline SpO<sub>2</sub> in the low resolution group
  - b. Low versus High baseline SpO<sub>2</sub> in the high resolution group (previous secondary study)

#### Aim 2: Retinopathy of Prematurity

We will compare the incidence of desaturation events detected in Aim 1 between infants with and without severe retinopathy of prematurity (ROP). To minimize disparities in diagnosis of less severe forms of ROP, infants will be classified as 1) those requiring laser treatment for ROP or 2) those with either no ROP or ROP not severe enough to require laser therapy. The definitions used and reported in the SUPPORT main trial will be utilized for classifications of eye outcomes.

#### Aim 3: Neurodevelopmental Outcome

To analyze the correlation between the incidence of desaturation events and neurodevelopmental outcome we will include parameters acquired through the SUPPORT trial protocol including:

neurodevelopmental impairment at 18-22 months based on Bayley III using the accepted NRN definition

Death by discharge status

BPD @36wks

IVH

PVL

Cerebral palsy @ 18-22 months

#### Aim 4: Mortality

We will analyze the correlation between the incidence of desaturation events and mortality with and without the inclusion of baseline saturation randomization as a covariate.

#### Statistical Analyses

Statistical analyses will include a linear mixed model for repeated measures analysis to assess the time course of desaturation events for all infants and to identify the association between the number of events and ROP requiring laser treatment adjusting for baseline SpO<sub>2</sub> randomization group, gestational age, race, gender, and multiple births. Based on previous work [Di Fiore] the square root of the number of desaturation events will be used to better meet normality assumptions of the mixed model. A linear regression model will be used to assess the univariate relationship between continuous variables such as the number of desaturation events and mental and motor scores at 18-22 months. To compare the number of desaturation events between the low and high baseline SpO<sub>2</sub> groups, and mortality, we will use a two way ANOVA with repeated measures.

#### E. Discussion of Anticipated Results

We anticipate that a lower number of desaturation events will be detected in the low versus high resolution group. Previous work has suggested that the 16 second average time used in the SUPPORT trial may result in an underestimation of events <30 seconds and events of greater severity (<70%) and an overestimation of events of long duration (>300sec)[Ahmed]. This study will focus on desaturation events of ≤80% for ≥20 sec and ≤3min in duration. Thus, we do anticipate a significant difference between low and high resolutions due to events of greater severity or of long duration as proposed by Ahmed et al. However, the prolonged average time in the low resolution group may inhibit our ability to detect desaturation events between 20 and 30seconds in duration. We may have a further compromise in event detection due to the low sample rate of 10 seconds versus 2 seconds in the low and high resolution infant groups, respectively. Although a higher incidence of desaturation events has been shown to be associated with severe ROP [Di Fiore], it is currently unknown whether the characteristics of the desaturation event, in terms of duration and severity, are additional risk factors. Therefore, if short desaturation events are not as detrimental to the development of ROP, even with a compromise in detection of all desaturation events in the low resolution group we may still be able to detect differences in the number of events in the low and high baseline SpO<sub>2</sub> groups and in infants with and without severe ROP.

We speculate that if a higher incidence of desaturation events is found in the low baseline SpO<sub>2</sub> group, this will be associated with both infant mortality and lower neurodevelopmental outcome scores at 18-22 months of age.

If there is no difference in event detection in the high versus low resolution group, and no difference in the number of desaturation events between the low and high baseline SpO<sub>2</sub> infant groups we will conclude that keeping the infants in the low saturation target range does not put them at risk for episodic desaturation. If a difference in event detection is found between low and high resolution groups our conclusions between the low and high baseline saturation ranges will be limited by the ability to compare severe events and events of shorter duration.

#### F. Budget

##### Equipment:

We have previously acquired and analyzed desaturation data in 79 preterm infants with high resolution over a time period of comparable duration as the infants enrolled in the SUPPORT trial [Di Fiore]. Based on these infants, we estimate that the raw and processed data files for the 1316 SUPPORT trial infants will take approximately 400 gigabytes of storage space. For data safety/quality assurance concerns, we would like to purchase a password protected server dedicated to storage of this dataset. We estimate that the server with RAID 0 mirroring of the data will cost approximately \$1000. Only investigators working on this project will have access to the server. Additionally, we will maintain a backup of our datasets. Currently, a 1000 gigabyte hard drive costs \$200 through local computer stores. The server will be equipped with a writable DVD drive to maintain additional backups as needed. We currently use automated software to perform data backups once per week. Both the backup hard drive and DVDs will be stored in a locked cabinet in the locked office of Juliann Di Fiore and only she will have access to these backup devices. These files will be de-identified for patient confidentiality.

##### Salary Support and Project Duration:

Under Dr. Chris Wilson as PI, Juliann Di Fiore and Ryan Foglyano will currently be receiving grant funding to develop software to automate additional analyses of saturation data on the infants enrolled in the currently approved secondary study, INCIDENCE AND CONSEQUENCES OF EPISODIC DESATURATION IN PRETERM INFANTS ENROLLED IN THE NICHD NEONATAL NETWORK OXYGEN SATURATION [SUPPORT] STUDY. This infant cohort includes SUPPORT infants enrolled at the Cleveland and San Diego sites with high resolution, and 79 additional preterm infants at the Cleveland site that were not enrolled in the SUPPORT trial. The purpose of this grant is to develop a suite of linear and non-linear analysis algorithms to quantify patterns of intermittent hypoxia (IH), and to evaluate the relationship between IH patterns and severe ROP requiring laser surgery. The initial phase of this grant will require development of automated software code to identify desaturation events from the infant data files. Once developed, we plan to use this software for analysis of the additional 1197 SUPPORT trial infants.

Based on previous data analysis of desaturation events in 79 preterm infants with high resolution analyzed over a time period of comparable duration as the infants enrolled in the SUPPORT trial, we are currently able to analyze 5-7 infants per day. We anticipate an increase in the number of infants analyzed per day with automation of the software. Based on our previous experience and additional time needed for summary data analysis, we anticipate 10 months of time will be needed to complete this protocol.

Salary support will include 50% for Juliann Di Fiore 33% for Ryan Foglyano and, as it is difficult to estimate, support for a biostatistician to be determined. (Table).

Travel:

We anticipate travel to RTI for statistical analysis (\$1500.00) and the steering committee meeting (\$1500.00) to present the results. (Table)

References:

1. Ahmed SJ, Rich W, Finer NN. The effect of averaging time on oximetry values in the premature infant. *Pediatrics* 2010:e115-e121.
2. Di Fiore JM, Bloom JN, Orge F, Schutt A, Schluchter M, Cheruvu VK, Walsh M, Finer N, Martin RJ. A higher incidence of intermittent hypoxemic episodes is associated with severe retinopathy of prematurity. *J of Peds* ( In press).

Program Director/Principal Investigator (Last, First, Middle):

<b>DETAILED BUDGET FOR INITIAL BUDGET PERIOD DIRECT COSTS ONLY</b>	FROM	THROUGH
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List PERSONNEL (Applicant organization only)  
Use Cal, Acad, or Summer to Enter Months Devoted to Project  
Enter Dollar Amounts Requested (omit cents) for Salary Requested and Fringe Benefits

NAME	ROLE ON PROJECT	Cal. Mths	Acad. Mths	Summer Mths	INST.BASE SALARY	SALARY REQUESTED	FRINGE BENEFITS	TOTAL
Michele Walsh	PD/PI							
Juliann Di Fiore		1			(b)	38,425	8,838	47,263
Ryan Foglyano		(b)			(b)	15,557	3,578	19,135
<b>SUBTOTALS</b> →						<b>53,982</b>	<b>12,416</b>	<b>66,398</b>

<b>CONSULTANT COSTS</b>		
Statistical Analysis- Biostatistician from RTI cost TBD		
<b>EQUIPMENT (Itemize)</b>		
Hard drive \$200		
RAID 0 [protected server] \$1000		1,200
<b>SUPPLIES (Itemize by category)</b>		
<b>TRAVEL</b>		
Travel to RTI (\$1500) and steering committee meeting (\$1500)		3,000
<b>INPATIENT CARE COSTS</b>		
<b>OUTPATIENT CARE COSTS</b>		
<b>ALTERATIONS AND RENOVATIONS (Itemize by category)</b>		
<b>OTHER EXPENSES (Itemize by category)</b>		

CONSORTIUM/CONTRACTUAL COSTS	DIRECT COSTS	
<b>SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD (Item 7a, Face Page)</b>		<b>\$ 70,598</b>
CONSORTIUM/CONTRACTUAL COSTS	FACILITIES AND ADMINISTRATIVE COSTS	38,531
<b>TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD</b>		<b>\$ 109,129</b>

**From:** [Roger Faix](#)  
**To:** [mcunningham@rti.org](mailto:mcunningham@rti.org); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Bradley Yoder](#); [nfiner@ucsd.edu](mailto:nfiner@ucsd.edu)  
**Subject:** SUPPORT secondary teleconference  
**Date:** Sunday, March 21, 2010 8:35:20 PM

---

Hi all!

Just to let you know, I am scheduled to give a talk tomorrow in Salat Lake from 1115-1215 Mountain time (immediately after a presentation by Brad), so I will join the teleconference a bit late. I suspect Brad will be able to join the conference on time and suspect he will share opinions on the secondary proposal perfectly well.

I'll talk to you (albiet belatedly) tomorrow.

Roger



**From:** [Gantz, Marie](#)  
**To:** [Wally Carlo, M.D.](#); [Das, Abhik](#); [ambal@uab.edu](mailto:ambal@uab.edu)  
**Cc:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Subject:** RE: ROP protocol draft 1.0  
**Date:** Friday, March 19, 2010 2:26:23 PM

---

Thanks for the clarification. I will get back to you with my suggestions for the analysis section next week. With respect to completing the analysis by PAS, we will certainly do our best to complete some initial analyses to address questions that are likely to come up at PAS. But, it might be overly ambitious to try to finish all of the analyses by that time, especially if we find that we need to reprocess the oximeter data to address our questions. Reprocessing alone could take two weeks. I hope that sounds like a reasonable approach.

Marie

Marie Gantz, Ph.D.  
Research Statistician  
RTI International  
[mgantz@rti.org](mailto:mgantz@rti.org)  
828-254-6255

-----Original Message-----

From: Wally Carlo, M.D. [<mailto:WCarlo@peds.uab.edu>]  
Sent: Friday, March 19, 2010 12:19 PM  
To: Gantz, Marie; Das, Abhik; [ambal@uab.edu](mailto:ambal@uab.edu)  
Cc: higgins  
Subject: RE: ROP protocol draft 1.0

Marie:

Sorry. Ideally, I would prefer the analysis to be completed by PAS as it is likely we will get important questions.

Wally

-----Original Message-----

From: Gantz, Marie [<mailto:mgantz@rti.org>]  
Sent: Friday, March 19, 2010 11:07 AM  
To: Wally Carlo, M.D.; Das, Abhik; [ambal@uab.edu](mailto:ambal@uab.edu)  
Cc: higgins  
Subject: RE: ROP protocol draft 1.0

Hi Wally,

For clarification, are you wanting to have the protocol written by May 1 or have the analysis completed by May 1?

Marie

Marie Gantz, Ph.D.  
Research Statistician  
RTI International  
[mgantz@rti.org](mailto:mgantz@rti.org)

828-254-6255

-----Original Message-----

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]  
Sent: Friday, March 19, 2010 12:05 PM  
To: Gantz, Marie; Das, Abhik; ambal@uab.edu  
Cc: higgins  
Subject: RE: ROP protocol draft 1.0

Hi Marie:

It is not a rush. Take your time. I would like to have it analyzed by PAS (May 1) so we can be prepared for questions.

Wally

-----Original Message-----

From: Gantz, Marie [mailto:mgantz@rti.org]  
Sent: Friday, March 19, 2010 10:23 AM  
To: Wally Carlo, M.D.; Das, Abhik; ambal@uab.edu  
Cc: higgins  
Subject: RE: ROP protocol draft 1.0

Hi Wally,

It sounds like we're on the same page. I will work with you on the statistical analysis plan. What is your time line for finalizing the protocol?

Marie

Marie Gantz, Ph.D.  
Research Statistician  
RTI International  
mgantz@rti.org  
828-254-6255

-----Original Message-----

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]  
Sent: Thursday, March 18, 2010 4:47 PM  
To: Das, Abhik; Wally Carlo; ambal@uab.edu  
Cc: Gantz, Marie; higgins  
Subject: RE: ROP protocol draft 1.0

Hi Marie and Abhik.

I agree with you on everything!

1) I focused on ROP for the primary hypothesis but as stated in the analysis part, the competing outcome of death analysis is essential. I also think we should study death only as stated in the protocol.

2) yes. Range may be more imp. Also, hyperoxia may be what is most strongly associated with ROP; desats with death. I will expand it so I broaden the focus beyond the primary hypotheses.

3) and 4) you are the experts on this and I would follow your advice.

Could you help me with the statistical and analysis plan?

I will work on 1) and 2).

Thanks a lot.

wally

Sent from my Windows Mobile phone

-----Original Message-----

From: Das, Abhik <adas@rti.org>

Sent: Thursday, March 18, 2010 3:20 PM

To: Wally Carlo <wcarlo@peds.uab.edu>; ambal@uab.edu <ambal@uab.edu>

Cc: Gantz, Marie <mgantz@rti.org>; higgins <higginsr@mail.nih.gov>

Subject: FW: ROP protocol draft 1.0

Wally and Ambal:

I had Marie take a look at this, given all the work she has done with ROP in SUPPORT. Here are her comments.

Thanks

Abhik

From: Gantz, Marie

Sent: Thursday, March 18, 2010 4:15 PM

To: Das, Abhik

Subject: RE: ROP protocol draft 1.0

These are my thoughts:

1) I realize that the primary objective of the protocol is to look at associations between oxygen saturations and ROP, but should it also look at associations with death since there were more deaths in the low SpO2 group? Unless another protocol is going to look at that question, it seems like an important one to look into, and would potentially use the same type of analysis. I see that death/ROP combined is mentioned in the Statistical Considerations section, but nothing is mentioned about looking at death alone.

2) Median SpO2 is mentioned as the measure that would be used from the saturation data, but in reality, I would expect the analysis to end up being somewhat exploratory in nature. For example, we could look at

periods of time spent in different ranges rather than just looking at the median for each infant (which, I assume, is what Wally is talking about doing). Also, as we work on the problem, other approaches for using the saturation data might occur to us. He doesn't mention looking at desaturations or anything like that, but that information is also available. Is it necessary for all possible approaches to be covered in the protocol?

3) The Statistical Considerations section talks about using ANOVA, but I expect that we would need to control for design factors as we did in the primary papers. Also, it seems backwards to use ANOVA because I assume we would be using oxygen saturation to predict ROP, rather than the other way around. It also says "The effect of oxygen exposure will be analyzed as a continuous measure considering both the inspired oxygen concentration and the duration of exposure." I suppose this could be as simple as predicting ROP based on the median saturation and the duration of time on oxygen, but we might want to do something more complicated that takes into account how long infants were exposed to various ranges. We could consider using a multivariate approach, like discriminant analysis, to find out whether ROP is associated with spending more time in particular ranges of oxygen. That would be one way of trying to look at the distribution of saturations overall rather than focusing on the median value. However, I don't know of software that allows one to do that while also incorporating random effects (although such software might exist).

4) The Statistical Considerations section says "Data will be analyzed by center using a logistic regression analysis to determine the contribution of center and oxygen saturation targets on ROP" but I don't think that's what was meant. We would have center as a covariate in the model rather than doing analysis "by center."

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: Tuesday, March 16, 2010 7:35 AM  
To: Das, Abhik  
Cc: Higgins, Rosemary (NIH/NICHD) [E]; Namasivayam Ambalavanan  
Subject: FW: ROP protocol draft 1.0

Hi Abhik:

Ambal and I are drafting a protocol for ROP/death and we were wondering if you could give us some feedback and ideas to improve the analysis plan. One issue we are struggling with is that the best predictor of ROP may be a range of saturations rather than a median saturation. Right now, it is written as median but we think we should add range as well in those analyses.

Thanks for taking a look at this.

Rose:

We have drafted this secondary protocol. It is not ready for circulation to other but we wanted to let you know we are doing it as I said on the call and to get any early input from you.

Wally

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Johnson, Karen"; "Eastman, Diane"; "Bell, Edward"; "Acarregui, Michael"  
**Cc:** "Gantz, Marie"; "Auman, Jeanette O."  
**Subject:** RE: SUPPORT FU OUTCOMES  
**Date:** Friday, March 19, 2010 9:25:00 AM

---

OK  
That would be fine  
I know they were recently seen.  
Thanks

---

**From:** Johnson, Karen [mailto:karen-johnson@uiowa.edu]  
**Sent:** Friday, March 19, 2010 9:15 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Eastman, Diane; Bell, Edward; Acarregui, Michael  
**Cc:** Gantz, Marie; Auman, Jeanette O.  
**Subject:** RE: SUPPORT FU OUTCOMES

Rose and all,  
I will check on them from the data entry standpoint. Maybe Jenny can wait until I have checked. I'll get back to you on Monday. I'm out of the office today.  
Thanks,  
Karen

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Friday, March 19, 2010 7:44 AM  
**To:** Eastman, Diane; Bell, Edward; Johnson, Karen; Acarregui, Michael  
**Cc:** Gantz, Marie; 'Auman, Jeanette O.'  
**Subject:** RE: SUPPORT FU OUTCOMES

Great  
I have copied Jenny to see if she can locate the forms

Thanks  
Rose

---

**From:** Eastman, Diane [mailto:diane-eastman@uiowa.edu]  
**Sent:** Thursday, March 18, 2010 6:15 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Bell, Edward; Johnson, Karen; Acarregui, Michael  
**Cc:** Gantz, Marie  
**Subject:** RE: SUPPORT FU OUTCOMES

Rose,  
(b) and (b) the forms were done, so will check to see why they were not entered.  
(b) is the family that moved to Maryland and the person who will do the Bayley is currently on maternity leave. I'm to contact her in April regarding arranging the appt. Diane

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Thursday, March 18, 2010 1:01 PM  
**To:** Bell, Edward; Johnson, Karen; Acarregui, Michael; Eastman, Diane  
**Cc:** 'Gantz, Marie'  
**Subject:** SUPPORT FU OUTCOMES

Hi,

We are missing the following SUPPORT Follow up outcomes. Let us know how you are doing and THANKS for all the hard work!!!

Rose

CENTER	NETWORK	FU_message
24	(b)	FU marked as complete (per NF10/SF10) but NF09a has not been completed.
24	(6)	FU marked as complete (per NF10/SF10) but NF09a has not been completed.
24	(b)	FU window has closed but NF05 has not been completed.

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network  
Pregnancy and Perinatology Branch  
Center for Developmental Biology and Perinatal Medicine  
Eunice Kennedy Shriver National Institute of Child Health and Human Development  
National Institutes of Health  
6100 Executive Blvd., Room 4B03  
MSC 7510  
Bethesda, MD 20892  
For overnight delivery use Rockville, MD 20852  
301-496-5575  
301-496-3790 (FAX)  
higginsr@mail.nih.gov

**From:** Bethany Ball  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Krisa Van Meurs; "susan.hintz@stanford.edu"; Bethany Ball; "Gantz, Marie"  
**Subject:** Re: SUPPORT FU OUTCOME  
**Date:** Thursday, March 18, 2010 4:00:56 PM

---

We are continuing to look for this child.  
MBB

On Mar 18, 2010, at 10:55 AM, Higgins, Rosemary (NIH/NICHD) [E] wrote:

Hi,

We are missing the following SUPPORT Follow up outcomes. Let us know how you are doing and THANKS for all the hard work!!!

Rose

CENTER	NETWORK	FU_message
15	(b)	FU window has closed but NF05 and NF09a have not been completed.

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network  
Pregnancy and Perinatology Branch  
Center for Developmental Biology and Perinatal Medicine  
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For overnight delivery use Rockville, MD 20852  
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 FU OUTCOMES  
**Date:** Thursday, March 18, 2010 2:14:00 PM

---

You guys always do so well –  
Marie continues to send me the list and the FU IS VERY IMPORTANT!!!  
Rose

---

**From:** Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]  
**Sent:** Thursday, March 18, 2010 2:08 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: SUPPORT FU OUTCOMES

Thank you. This is very helpful

wally

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Thursday, March 18, 2010 12:58 PM  
**To:** wacarlo@uab.edu; 'Ambal (ambal@uab.edu)'; Myriam Peralta, M.D.; Monica Collins; Shirley Cosby; Vivien Phillips  
**Cc:** 'Gantz, Marie'  
**Subject:** SUPPORT FU OUTCOMES

Hi,

We are missing the following SUPPORT Follow up outcomes. Let us know how you are doing and THANKS for all the hard work!!! This is terrific given your outstanding recruitment---

Rose

16	(b)	FU window has closed but NF05 and NF09a have not been completed.
16	(b)	FU window has closed but NF05 and NF09a have not been completed.
16	(b)	FU window has closed but NF05 and NF09a have not been completed.
16	(b)	FU window has closed but NF05 and NF09a have not been completed.
16	(b)	FU marked as complete (per NF10/SF10) but NF09a has not been completed.
16	(b)	FU marked as complete (per NF10/SF10) but NF09a has not been completed.

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network  
Pregnancy and Perinatology Branch  
Center for Developmental Biology and Perinatal Medicine  
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For overnight delivery use Rockville, MD 20852  
301-496-5575  
301-496-3790 (FAX)  
higginsr@mail.nih.gov

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Kristi Watterberg"; "Conra Backstrom"; "JaFuller@salud.unm.edu"; "Rebecca Montman"  
**Cc:** "Gantz, Marie"  
**Subject:** SUPPORT FU OUTCOMES  
**Date:** Thursday, March 18, 2010 2:02:00 PM

---

Hi,

We are missing the following SUPPORT Follow up outcomes. Let us know how you are doing and THANKS for all the hard work!!!

Rose

CENTER	NETWORK	FU_message
26	(b)	FU window has closed but NF05 and NF09a have not been completed.

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

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Bell, Edward"; "Johnson, Karen"; "Acarregui, Michael"; "Eastman, Diane"  
**Cc:** "Gantz, Marie"  
**Subject:** SUPPORT FU OUTCOMES  
**Date:** Thursday, March 18, 2010 2:00:00 PM

---

Hi,

We are missing the following SUPPORT Follow up outcomes. Let us know how you are doing and THANKS for all the hard work!!!

Rose

CENTER	NETWORK	FU_message
24	(b)	FU marked as complete (per NF10/SF10) but NF09a has not been completed.
24	(b)	FU marked as complete (per NF10/SF10) but NF09a has not been completed.
24	(b)	FU window has closed but NF05 has not been completed.

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network  
Pregnancy and Perinatology Branch  
Center for Developmental Biology and Perinatal Medicine  
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For overnight delivery use Rockville, MD 20852  
301-496-5575  
301-496-3790 (FAX)  
higginsr@mail.nih.gov

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Kennedy, Kathleen A"; "Evans, Patricia W"; "Tyson, Jon E"; "Georgia.E.McDavid@uth.tmc.edu"  
**Cc:** "Gantz, Marie"  
**Subject:** SUPPORT FU OUTCOMES  
**Date:** Thursday, March 18, 2010 1:58:00 PM

---

Hi,

We are missing the following SUPPORT Follow up outcomes. Let us know how you are doing and THANKS for all the hard work!!!

Rose

CENTER	NETWORK	FU_message
18	(b)	FU window has closed but NF05 and NF09a have not been completed.
18	(b)	FU window has closed but NF05 and NF09a have not been completed.

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network  
Pregnancy and Perinatology Branch  
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Bethesda, MD 20892  
For overnight delivery use Rockville, MD 20852  
301-496-5575  
301-496-3790 (FAX)  
higginsr@mail.nih.gov

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "wacarlo@uab.edu"; "Ambal (ambal@uab.edu)"; "Myriam Peralta, M.D."; "Monica Collins"; "scosby@peds.uab.edu"; "Vivien Phillips"  
**Cc:** "Gantz, Marie"  
**Subject:** SUPPORT FU OUTCOMES  
**Date:** Thursday, March 18, 2010 1:57:00 PM

---

Hi,

We are missing the following SUPPORT Follow up outcomes. Let us know how you are doing and THANKS for all the hard work!!! This is terrific given your outstanding recruitment---

Rose

16	(b)	FU window has closed but NF05 and NF09a have not been completed.
16	(b)	FU window has closed but NF05 and NF09a have not been completed.
16	(6)	FU window has closed but NF05 and NF09a have not been completed.
16	(b)	FU window has closed but NF05 and NF09a have not been completed.
16	(b)	FU marked as complete (per NF10/SF10) but NF09a has not been completed.
16	(b)	FU marked as complete (per NF10/SF10) but NF09a has not been completed.

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network  
Pregnancy and Perinatology Branch  
Center for Developmental Biology and Perinatal Medicine  
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For overnight delivery use Rockville, MD 20852  
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301-496-3790 (FAX)  
higginsr@mail.nih.gov

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Krisa Van Meurs"; "susan.hintz@stanford.edu"; "Bethany Ball"  
**Cc:** "Gantz, Marie"  
**Subject:** SUPPORT FU OUTCOME  
**Date:** Thursday, March 18, 2010 1:55:00 PM

---

Hi,

We are missing the following SUPPORT Follow up outcomes. Let us know how you are doing and THANKS for all the hard work!!!

Rose

CENTER	NETWORK	FU_message
15	(b)	FU window has closed but NF05 and NF09a have not been completed.

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For overnight delivery use Rockville, MD 20852  
301-496-5575  
301-496-3790 (FAX)  
higginsr@mail.nih.gov

**From:** Bonnie Siner  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; mcw3@case.edu; "Nancy Newman"; drfjcmd@aol.com  
**Cc:** "Gantz, Marie"  
**Subject:** RE: SUPPORT FU OUTCOMES  
**Date:** Thursday, March 18, 2010 1:53:17 PM

---

It's marked off as keyed. I'll have Angelia re-enter. In any case, it's done.

Bonnie

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Thursday, March 18, 2010 1:46 PM  
**To:** mcw3@case.edu; 'Nancy Newman'; 'Bonnie Siner'; (b) (6)  
**Cc:** 'Gantz, Marie'  
**Subject:** SUPPORT FU OUTCOMES

Hi,

We are missing the following SUPPORT Follow up outcomes. Let us know how you are doing and THANKS for all the hard work!!!

This is terrific given your outstanding recruitment into this trial!!!!

Rose

CENTER	NETWORK	FU_message
3	(b) (6)	FU marked as complete (per NF10/SF10) but NF09a has not been completed.

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network  
Pregnancy and Perinatology Branch  
Center for Developmental Biology and Perinatal Medicine  
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For overnight delivery use Rockville, MD 20852  
301-496-5575  
301-496-3790 (FAX)  
higginsr@mail.nih.gov

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Laptook, Abbot"; "Betty Vohr"; "Angelita Hensman"; "sventura@wihri.org"  
**Cc:** "Gantz, Marie"  
**Subject:** SUPPORT FU OUTCOMES  
**Date:** Thursday, March 18, 2010 1:53:00 PM

---

Hi,

We are missing the following SUPPORT Follow up outcomes. Let us know how you are doing and THANKS for all the hard work!!! This is amazing given your outstanding recruitment!!!

Rose

CENTER	NETWORK	FU_message
14	(b)	FU window has closed but NF05 and NF09a have not been completed.
14	(6)	FU window has closed but NF05 and NF09a have not been completed.
14		FU marked as complete (per NF10/SF10) but NF09a has not been completed.

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network  
Pregnancy and Perinatology Branch  
Center for Developmental Biology and Perinatal Medicine  
Eunice Kennedy Shriver National Institute of Child Health and Human Development  
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Bethesda, MD 20892  
For overnight delivery use Rockville, MD 20852  
301-496-5575  
301-496-3790 (FAX)  
higginsr@mail.nih.gov



**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Bonnie Siner"; "mcw3@case.edu"; "Nancy Newman"; (b) (6)  
**Cc:** "Gantz, Marie"  
**Subject:** RE: SUPPORT FU OUTCOMES  
**Date:** Thursday, March 18, 2010 1:53:00 PM

---

Awesome!!  
THANKS  
ROSE

---

**From:** Bonnie Siner [mailto:bss5@case.edu]  
**Sent:** Thursday, March 18, 2010 1:53 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; mcw3@case.edu; 'Nancy Newman'; (b) (6)  
**Cc:** 'Gantz, Marie'  
**Subject:** RE: SUPPORT FU OUTCOMES

It's marked off as keyed. I'll have Angelia re-enter. In any case, it's done.

Bonnie

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Thursday, March 18, 2010 1:46 PM  
**To:** mcw3@case.edu; 'Nancy Newman'; 'Bonnie Siner'; (b) (6)  
**Cc:** 'Gantz, Marie'  
**Subject:** SUPPORT FU OUTCOMES

Hi,

We are missing the following SUPPORT Follow up outcomes. Let us know how you are doing and THANKS for all the hard work!!!  
This is terrific given your outstanding recruitment into this trial!!!!

Rose

CENTER	NETWORK	FU_message
3	(b) (6)	FU marked as complete (per NF10/SF10) but NF09a has not been completed.

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network  
Pregnancy and Perinatology Branch  
Center for Developmental Biology and Perinatal Medicine  
Eunice Kennedy Shriver National Institute of Child Health and Human Development  
National Institutes of Health  
6100 Executive Blvd., Room 4B03  
MSC 7510  
Bethesda, MD 20892  
For overnight delivery use Rockville, MD 20852  
301-496-5575  
301-496-3790 (FAX)  
higginsr@mail.nih.gov

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Brenda Poindexter"; "Dusick, Anna M."; "fahamer@iupui.edu"; "Leslie Wilson"  
**Cc:** "Gantz, Marie"  
**Subject:** SUPPORT FU OUTCOMES  
**Date:** Thursday, March 18, 2010 1:50:00 PM

---

Hi,

We are missing the following SUPPORT Follow up outcomes. Let us know how you are doing and THANKS for all the hard work!!!

Rose

CENTER	NETWORK	FU_message
12	(b)	FU window has closed but NF05 and NF09a have not been completed.
12	(6)	FU marked as complete (per NF10/SF10) but NF09a has not been completed.
12		FU window has closed but NF05 and NF09a have not been completed.
12		FU marked as complete (per NF10/SF10) but NF09a has not been completed.

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network  
Pregnancy and Perinatology Branch  
Center for Developmental Biology and Perinatal Medicine  
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Bethesda, MD 20892  
For overnight delivery use Rockville, MD 20852  
301-496-5575  
301-496-3790 (FAX)  
higginsr@mail.nih.gov

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Kurt Schibler [kurt.schibler@cchmc.org]"; "Kimberly Yolton@cchmc.org"; "Grisby, Cathy (grisbyca)"; "Teresa.Gratton@uc.edu"  
**Cc:** "Gantz, Marie"  
**Subject:** SUPPORT FU OUTCOMES  
**Date:** Thursday, March 18, 2010 1:49:00 PM

---

Hi,

We are missing the following SUPPORT Follow up outcomes. Let us know how you are doing and THANKS for all the hard work!!!

Rose

CENTER	NETWORK	FU_message
11	(b)	FU window has closed but NF05 and NF09a have not been completed.
11	(b)	FU marked as complete (per NF10/SF10) but NF09a has not been completed.

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network  
Pregnancy and Perinatology Branch  
Center for Developmental Biology and Perinatal Medicine  
Eunice Kennedy Shriver National Institute of Child Health and Human Development  
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Bethesda, MD 20892  
For overnight delivery use Rockville, MD 20852  
301-496-5575  
301-496-3790 (FAX)  
higginsr@mail.nih.gov

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Shankaran, Seetha"; "Sood, Beena"; "Bara, Rebecca"; "Pappas, Athina"  
**Cc:** "Gantz, Marie"  
**Subject:** SUPPORT FU OUTCOMES  
**Date:** Thursday, March 18, 2010 1:46:00 PM

---

Hi,

We are missing the following SUPPORT Follow up outcomes. Let us know how you are doing and THANKS for all the hard work!!!

Rose

CENTER	NETWORK	FU_message
5	(b)	FU window has closed but NF05 and NF09a have not been completed.
5	(6)	FU window has closed but NF09a has not been completed.
5		FU window has closed but NF05 and NF09a have not been completed.
5		FU window has closed but NF05 and NF09a have not been completed.
5		FU window has closed but NF05 and NF09a have not been completed.

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network  
Pregnancy and Perinatology Branch  
Center for Developmental Biology and Perinatal Medicine  
Eunice Kennedy Shriver National Institute of Child Health and Human Development  
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Bethesda, MD 20892  
For overnight delivery use Rockville, MD 20852  
301-496-5575  
301-496-3790 (FAX)  
higginsr@mail.nih.gov

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Stoll Barbara (E-mail)"; "Ellen Hale"; "Ira Adams-Chapman"  
**Cc:** "Gantz, Marie"  
**Subject:** SUPPORT FU OUTCOMES  
**Date:** Thursday, March 18, 2010 1:46:00 PM

---

Hi,

We are missing the following SUPPORT Follow up outcomes. Let us know how you are doing and THANKS for all the hard work!!!

Rose

CENTER	NETWORK	FU_message
9	(b)	FU window has closed but NF05 and NF09a have not been completed.
9	(6)	FU marked as complete (per NF10/SF10) but NF09a has not been completed.

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network  
Pregnancy and Perinatology Branch  
Center for Developmental Biology and Perinatal Medicine  
Eunice Kennedy Shriver National Institute of Child Health and Human Development  
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6100 Executive Blvd., Room 4B03  
MSC 7510  
Bethesda, MD 20892  
For overnight delivery use Rockville, MD 20852  
301-496-5575  
301-496-3790 (FAX)  
higginsr@mail.nih.gov

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "mcw3@case.edu"; "Nancy Newman"; "Bonnie Siner"; "drficmd@aol.com"  
**Cc:** "Gantz, Marie"  
**Subject:** SUPPORT FU OUTCOMES  
**Date:** Thursday, March 18, 2010 1:45:00 PM

---

Hi,

We are missing the following SUPPORT Follow up outcomes. Let us know how you are doing and THANKS for all the hard work!!!

This is terrific given your outstanding recruitment into this trial!!!!

Rose

CENTER	NETWORK	FU_message
3	(b)	FU marked as complete (per NF10/SF10) but NF09a has not been completed.

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network  
Pregnancy and Perinatology Branch  
Center for Developmental Biology and Perinatal Medicine  
Eunice Kennedy Shriver National Institute of Child Health and Human Development  
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6100 Executive Blvd., Room 4B03  
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Bethesda, MD 20892  
For overnight delivery use Rockville, MD 20852  
301-496-5575  
301-496-3790 (FAX)  
higginsr@mail.nih.gov

**From:** [Gantz, Marie](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\)](#) [E]  
**Cc:** [Das, Abhik](#)  
**Subject:** SUPPORT missing FU data  
**Date:** Thursday, March 18, 2010 11:41:06 AM  
**Attachments:** [Infants with missing FU outcomes 18MAR10.xls](#)

---

Rose,

Attached is the list of SUPPORT infants who are missing FU data this month.

Marie

Marie Gantz, Ph.D.  
Research Statistician  
RTI International  
[mgantz@rti.org](mailto:mgantz@rti.org)  
828-254-6255

CENTER	NETWORK	FU_message
3	(b) (6)	FU marked as complete (per NF10/SF10) but NF09a has not been completed.
5		FU window has closed but NF05 and NF09a have not been completed.
5		FU window has closed but NF09a has not been completed.
5		FU window has closed but NF05 and NF09a have not been completed.
5		FU window has closed but NF05 and NF09a have not been completed.
5		FU window has closed but NF05 and NF09a have not been completed.
9		FU window has closed but NF05 and NF09a have not been completed.
9		FU marked as complete (per NF10/SF10) but NF09a has not been completed.
11		FU window has closed but NF05 and NF09a have not been completed.
11		FU marked as complete (per NF10/SF10) but NF09a has not been completed.
12		FU window has closed but NF05 and NF09a have not been completed.
12		FU marked as complete (per NF10/SF10) but NF09a has not been completed.
12		FU window has closed but NF05 and NF09a have not been completed.
12		FU marked as complete (per NF10/SF10) but NF09a has not been completed.
14		FU window has closed but NF05 and NF09a have not been completed.
14		FU window has closed but NF05 and NF09a have not been completed.
14		FU marked as complete (per NF10/SF10) but NF09a has not been completed.
15		FU window has closed but NF05 and NF09a have not been completed.
16		FU window has closed but NF05 and NF09a have not been completed.
16		FU window has closed but NF05 and NF09a have not been completed.
16		FU window has closed but NF05 and NF09a have not been completed.
16		FU window has closed but NF05 and NF09a have not been completed.
16		FU marked as complete (per NF10/SF10) but NF09a has not been completed.
16		FU marked as complete (per NF10/SF10) but NF09a has not been completed.
18		FU window has closed but NF05 and NF09a have not been completed.
18		FU window has closed but NF05 and NF09a have not been completed.
24		FU marked as complete (per NF10/SF10) but NF09a has not been completed.
24		FU marked as complete (per NF10/SF10) but NF09a has not been completed.
24		FU window has closed but NF05 has not been completed.
26		FU window has closed but NF05 and NF09a have not been completed.



**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "fmartinez@ucsd.edu"; "nfiner@ucsd.edu"; "wacarlo@uab.edu"  
**Cc:** "lguterman@palladianpartners.com"; Bock, Robert (NIH/NICHD) [E]; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** Re: Dr. Finer's Availability - SUPPORT PAPERS!!!  
**Date:** Monday, March 15, 2010 3:39:08 PM

---

Reminder for today's call

-----Original Message-----

To: Martinez, Fernando

To: Neil Finer

To: wacarlo@uab.edu

Cc: 'Lila Guterman'

Cc: Robert Bock

Sent: Mar 11, 2010 7:55 PM

Subject: Re: Dr. Finer's Availability - SUPPORT PAPERS!!!

We will do the call on

Monday March 15 from 4-5 pm ET (1 pm ET, 3 pm CT)- call in number;

866-675-(b) with pass code

(b) (6) followed by the pound sign.

Rose

-----Original Message-----

From: Martinez, Fernando

To: Rosemary (NIH/NICHD) [E] Higgins

To: Neil Finer

To: wacarlo@uab.edu

Cc: 'Lila Guterman'

Cc: Robert Bock

Sent: Mar 11, 2010 5:45 PM

Subject: Dr. Finer's Availability - SUPPORT PAPERS!!!

Dear Dr. Higgins,

Please see below for Dr. Finer's availability:

March 12 – anytime before 1 PM ET: Not available, giving lecture in Mexico

March 15 – 4-5 pm et (1-2 pm pt): OK

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

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From: Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]  
Sent: Thursday, March 11, 2010 11:04 AM  
To: Finer, Neil; wacarlo@uab.edu; Martinez, Fernando  
Cc: 'Lila Guterman'; Bock, Robert (NIH/NICHD) [E]  
Subject: SUPPORT PAPERS!!!  
Importance: High

Neil and Wally,

Our public affairs office is

-----Original Message Truncated-----

**From:** Bock, Robert (NIH/NICHD) [E]  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Dr. Finer's Availability - SUPPORT PAPERS!!!  
**Date:** Monday, March 15, 2010 3:40:00 PM

---

Thanks, Rose. You're more dependable than my Microsoft Outlook scheduler.

-----Original Message-----

From: Higgins, Rosemary (NIH/NICHD) [E]  
Sent: Monday, March 15, 2010 3:39 PM  
To: 'fmartinez@ucsd.edu'; 'nfiner@ucsd.edu'; 'wacarlo@uab.edu'  
Cc: 'lguterman@palladianpartners.com'; Bock, Robert (NIH/NICHD) [E]; Archer, Stephanie (NIH/NICHD) [E]  
Subject: Re: Dr. Finer's Availability - SUPPORT PAPERS!!!

Reminder for today's call

-----Original Message-----

To: Martinez, Fernando  
To: Neil Finer  
To: wacarlo@uab.edu  
Cc: 'Lila Guterman'  
Cc: Robert Bock  
Sent: Mar 11, 2010 7:55 PM  
Subject: Re: Dr. Finer's Availability - SUPPORT PAPERS!!!

We will do the call on

Monday March 15 from 4-5 pm ET (1 pm ET, 3 pm CT)- call in number;  
866-675-(b) with pass code  
(b) (6) followed by the pound sign.

Rose

-----Original Message-----

From: Martinez, Fernando  
To: Rosemary (NIH/NICHD) [E] Higgins  
To: Neil Finer  
To: wacarlo@uab.edu  
Cc: 'Lila Guterman'  
Cc: Robert Bock  
Sent: Mar 11, 2010 5:45 PM  
Subject: Dr. Finer's Availability - SUPPORT PAPERS!!!

Dear Dr. Higgins,

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March 12 – anytime before 1 PM ET: Not available, giving lecture in Mexico

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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

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From: Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]

Sent: Thursday, March 11, 2010 11:04 AM

To: Finer, Neil; wacarlo@uab.edu; Martinez, Fernando

Cc: 'Lila Guterman'; Bock, Robert (NIH/NICHD) [E]

Subject: SUPPORT PAPERS!!!

Importance: High

Neil and Wally,

Our public affairs office is

-----Original Message Truncated-----

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**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** Re: Publications | Buchter  
**Date:** Monday, March 15, 2010 2:05:48 PM

---

They may have been from the subcommittee

---

**From:** Archer, Stephanie (NIH/NICHD) [E]  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Mon Mar 15 13:57:40 2010  
**Subject:** FW: Publications | Buchter

Didn't you say you thought you had seen some reviews of Susie's paper?

---

**From:** Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]  
**Sent:** Saturday, March 13, 2010 4:57 PM  
**To:** Archer, Stephanie (NIH/NICHD) [E]  
**Cc:** Cassandra Hudson  
**Subject:** RE: Publications | Buchter

Stephanie:

I believe this is the first time I see this paper. I will send it out for review.

wally

---

**From:** Archer, Stephanie (NIH/NICHD) [E] [mailto:archerst@mail.nih.gov]  
**Sent:** Thursday, March 11, 2010 10:30 AM  
**To:** Wally Carlo, M.D.  
**Cc:** Cassandra Hudson  
**Subject:** FW: Publications | Buchter

Hi Wally,

Just checking back about this, any update?

---

**From:** Archer, Stephanie (NIH/NICHD) [E]  
**Sent:** Wednesday, March 03, 2010 11:44 AM  
**To:** Wally Carlo (wcarlo@peds.uab.edu)  
**Subject:** FW: Publications | Buchter

Hi Wally,

I'm going back through the Pubs Tracker to make sure all of the Drafted/Reviewed/Submitted/Accepted papers have gotten boilerplates, NICHD clearance, and been sent to the Steering Committee.

For Susie's paper, I don't have any records that this was sent to the Steering Committee. I also haven't seen any reviews sent back to her. Do you have these? I know this was exactly when you started a full court press to finish the SUPPORT paper, so it may have fallen through the cracks.

Just checking.

Stephanie

---

**From:** Archer, Stephanie (NIH/NICHD) [E]  
**Sent:** Friday, October 30, 2009 12:29 PM  
**To:** Buchter, Susie; Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** 'Barbara Stoll'; wcarlo@uab.edu  
**Subject:** RE: Publications | Buchter

That may have been because it was saved as a Word 2007 (.docx) file. Attached is a Word 2003 (.doc) version.

FYI, if you are still using Word 2003 (like we are at NICHD), Microsoft has a free patch on their website that will enable you to convert files from Office 2007 to Office 2003 versions.

---

**From:** Buchter, Susie [dbuchte@emory.edu]  
**Sent:** Thursday, October 29, 2009 4:44 PM  
**To:** Buchter, Susie; Archer, Stephanie (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** 'Barbara Stoll'  
**Subject:** RE: Publications | Buchter

Some had trouble opening the attachment yesterday.

I am resending.  
SB

---

**From:** Buchter, Susie  
**Sent:** Wednesday, October 28, 2009 3:47 PM  
**To:** Archer, Stephanie (NIH/NICHD) [E]; Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** 'Barbara Stoll'  
**Subject:** RE: Publications | Buchter

Dear All:  
Attached is my paper for clearance through NRN Publications Subcommittee and NICHD.  
I am sending to Lisa Wrage and Abhik Das at rti for the p values on BW and Gestational Age on Table 1. I am also sending out to co-authors to let them know how I incorporated their revisions.  
Thanks for your patience.  
Susie

---

**From:** Archer, Stephanie (NIH/NICHD) [E] [archerst@mail.nih.gov]  
**Sent:** Tuesday, October 13, 2009 11:37 AM  
**To:** Buchter, Susie  
**Cc:** 'Barbara Stoll'; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: Publications | Buchter

Thanks, Susie.

Just a reminder that all drafts need to go through the NRN Publications Subcommittee and NICHD clearance before submission.

Thanks,

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:** Buchter, Susie [mailto:dbuchte@emory.edu]  
**Sent:** Monday, October 12, 2009 3:56 PM  
**To:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: Publications | Buchter

I have all the revisions from the co-authors. I am trying to decide where to submit. Will update you again before your steering committee.  
SB

---

**From:** Archer, Stephanie (NIH/NICHD) [E] [archerst@mail.nih.gov]  
**Sent:** Friday, October 09, 2009 3:15 PM  
**To:** Buchter, Susie; Susie Buchter  
**Cc:** Barbara Stoll; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: Publications | Buchter

Just a reminder to please send me an update on your paper for the upcoming Steering Committee meeting.

This paper was from a PAS abstract from 2006.

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:** Archer, Stephanie (NIH/NICHD) [E]  
**Sent:** Friday, September 25, 2009 1:56 PM  
**To:** Susie Buchter ([Susie.Buchter@oz.ped.emory.edu](mailto:Susie.Buchter@oz.ped.emory.edu))  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; 'Barbara Stoll'  
**Subject:** Publications | Buchter

Hi Susie,

I'm updating the NRN publications tracker for the upcoming Steering Committee meeting. I'm asking for updates for any items that I have not heard about in 6 months or longer.

Can you please send me an update on your paper?

Status	Center	Author	Working Title	Comments	Last Update
Pending	Emory	Buchter S; Wrage L; Stoll BJ; Laptok A; Kazzi N; Engle W; Rasmussen M; Heldt G; Rhine W; Yao Q; Higgins RD; Walsh MC; for the NICHD Neonatal Research Network for the NICHD Neonatal Research	(b) (6) (b) (6). (b) (4) (b) (6)	4/25/08 Completed 1st draft; Dr. Stoll is working with her on it. Will forward co-authors after our review. 10/14/08 Forwarded to coauthors 1/7/09 Completing revisions	1/7/2009

Network

of the paper; plan on  
completing by end of  
February

Thanks!

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)

---

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**From:** [Newman, Jamie](#)  
**To:** [Susan Hintz](#)  
**Cc:** [Vohr, Betty](#); [Hammond, Jane](#); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Cheng, Helen](#)  
**Subject:** RE: SUPPORT Spanish speaking at sites at 18m  
**Date:** Sunday, March 14, 2010 7:04:59 AM

---

Susan,

I'm glad this is helpful. I think it would be most straight forward if Helen re-ran this every 6 months rather than adding it to the monthly report table. I will put this on my calendar as a reminder.

Thanks, Jamie

-----Original Message-----

From: Susan Hintz [<mailto:srhintz@stanford.edu>]  
Sent: Saturday, March 13, 2010 10:32 AM  
To: Newman, Jamie  
Cc: Vohr, Betty; Hammond, Jane; Rosemary Higgins; Cheng, Helen  
Subject: Re: SUPPORT Spanish speaking at sites at 18m

Thanks Jamie. Obviously this is just the follow-up so far - can we have another installment every 6 months until the end of the 18-22 month follow up for SUPPORT? Or perhaps we should add a column to the tracking report for the SUPPORT extended follow-up in the monthly report?

Thanks again- this is great!

Susan

On Mar 12, 2010, at 7:49 AM, Newman, Jamie wrote:

> Attached is the listing of primary language at 18 mo by Center for  
> those  
> eligible for School Age Follow-up. Please keep in mind that the table  
> continues onto page 2. Dallas has the most Spanish-speakers at 18 mo  
> (17), followed by Stanford (9), and Tufts (8).  
>  
> Please let us know if you have additional questions. Thanks, Helen,  
> for  
> running this table.  
>  
> Following are the Ctr #'s and names:  
> 3:Case Western Univ.  
> 4:Univ. of Texas (D)  
> 5:Wayne State Univ.  
> 9:Emory University  
> 12:Indiana Univ.  
> 14:Brown University  
> 15:Stanford University  
> 16:Univ. of Alabama  
> 18:Univ. of Texas (H)  
> 19:Duke University  
> 21:Children's (NY)  
> 22:UCSD

- > 23:Tufts University
- > 24:U.Iowa
- > 25:U. Utah
- > 26:U.New Mexico

>

> -----Original Message-----

> From: Susan Hintz [mailto:[srhintz@stanford.edu](mailto:srhintz@stanford.edu)]  
> Sent: Wednesday, March 10, 2010 11:40 PM  
> To: Vohr, Betty  
> Cc: Newman, Jamie; Hammond, Jane; Rosemary Higgins  
> Subject: Re: SUPPORT Spanish speaking at sites at 18m

>

> I agree - that does seem high. I look forward to seeing the break  
> down by NRN site. That might help us to give the sites a bit of  
> direction about what they might expect for the extended follow-up -  
> although Spanish as the primary language will likely decrease at least  
> somewhat between 18-22 months and school age. Maybe.

>

> Thanks again for the hard work on this!

>

> Susan

>

> On Mar 10, 2010, at 6:36 PM, Vohr, Betty wrote:

>

>> thanks jamie. Higher than I had expected.

>>

>> -----  
>> From: Newman, Jamie [mailto:[newman@rti.org](mailto:newman@rti.org)]  
>> Sent: Wednesday, March 10, 2010 5:38 PM  
>> To: Vohr, Betty; Susan Hintz  
>> Cc: Hammond, Jane; Rosemary Higgins  
>> Subject: RE: SUPPORT Spanish speaking at sites at 18m

>>

>> Our preliminary look at this reveals that the percentage of pts who  
>> used  
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>> break-down by site.

>> Thanks, Jamie

>>

>>

>> -----Original Message-----

>> From: Vohr, Betty [mailto:[BVohr@WIHRI.org](mailto:BVohr@WIHRI.org)]  
>> Sent: Friday, February 26, 2010 8:03 AM  
>> To: Susan Hintz; Newman, Jamie  
>> Cc: Hammond, Jane; Rosemary Higgins  
>> Subject: RE: SUPPORT Spanish speaking at sites at 18m

>>

>> 10.6 % of the population. Will be interested to see how they are  
>> clustered at sites.

>>

>> -----Original Message-----

>> From: Susan Hintz [mailto:[srhintz@stanford.edu](mailto:srhintz@stanford.edu)]  
>> Sent: Thursday, February 25, 2010 8:26 PM

>> To: Newman, Jamie  
>> Cc: Vohr, Betty; Hammond, Jane; Rosemary Higgins  
>> Subject: Re: SUPPORT Spanish speaking at sites at 18m  
>>  
>> Hi Jamie  
>>  
>> Yes, that would be great.  
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>> S  
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>> Sent from my iPhone  
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>> On Feb 25, 2010, at 12:47 PM, "Newman, Jamie" <newman@rti.org> wrote:  
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>>> In Sept 2008 Marie Gantz looked into how many SUPPORT pts at 18  
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>>> Out of 237 SUPPORT kids who have had the Bayley III exam, 26 exams  
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>>> I can ask her to re-run this with the most recent data but first  
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>>> From: Vohr, Betty [mailto:BVohr@WIHRI.org]  
>>> Sent: Thursday, February 25, 2010 3:19 PM  
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>>> Subject: RE: Gold Standards for SUPPORT MRI School Age  
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>>> BV  
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>>> From: Susan Hintz [mailto:srhintz@stanford.edu]  
>>> Sent: Thursday, February 25, 2010 1:41 PM  
>>> To: Newman, Jamie  
>>> Cc: Jane Hammond; Rosemary Higgins; Vohr, Betty  
>>> Subject: Re: Gold Standards for SUPPORT MRI School Age  
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>  
> <18mo\_SpanSpeakers\_4School AgeFU\_10MAR2010.rtf>

**From:** [Newman, Jamie](#)  
**To:** [Susan Hintz](#); [Vohr, Betty](#)  
**Cc:** [Hammond, Jane](#); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Cheng, Helen](#)  
**Subject:** RE: SUPPORT Spanish speaking at sites at 18m  
**Date:** Friday, March 12, 2010 10:50:14 AM  
**Attachments:** [18mo\\_SpanSpeakers\\_4SchoolAgeFU\\_10MAR2010.rtf](#)

---

Attached is the listing of primary language at 18 mo by Center for those eligible for School Age Follow-up. Please keep in mind that the table continues onto page 2. Dallas has the most Spanish-speakers at 18 mo (17), followed by Stanford (9), and Tufts (8).

Please let us know if you have additional questions. Thanks, Helen, for running this table.

Following are the Ctr #'s and names:

3:Case Western Univ.  
4:Univ. of Texas (D)  
5:Wayne State Univ.  
9:Emory University  
12:Indiana Univ.  
14:Brown University  
15:Stanford University  
16:Univ. of Alabama  
18:Univ. of Texas (H)  
19:Duke University  
21:Children's (NY)  
22:UCSD  
23:Tufts University  
24:U.Iowa  
25:U. Utah  
26:U.New Mexico

-----Original Message-----

From: Susan Hintz [<mailto:srhintz@stanford.edu>]  
Sent: Wednesday, March 10, 2010 11:40 PM  
To: Vohr, Betty  
Cc: Newman, Jamie; Hammond, Jane; Rosemary Higgins  
Subject: Re: SUPPORT Spanish speaking at sites at 18m

I agree - that does seem high. I look forward to seeing the break down by NRN site. That might help us to give the sites a bit of direction about what they might expect for the extended follow-up - although Spanish as the primary language will likely decrease at least somewhat between 18-22 months and school age. Maybe.

Thanks again for the hard work on this!

Susan

On Mar 10, 2010, at 6:36 PM, Vohr, Betty wrote:

> thanks jamie. Higher than I had expected.

>

> From: Newman, Jamie [[newman@rti.org](mailto:newman@rti.org)]

> Sent: Wednesday, March 10, 2010 5:38 PM  
> To: Vohr, Betty; Susan Hintz  
> Cc: Hammond, Jane; Rosemary Higgins  
> Subject: RE: SUPPORT Spanish speaking at sites at 18m  
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> Our preliminary look at this reveals that the percentage of pts who  
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**Neonatal SUPPORT Secondary (10MAR2010)**

**Includes ppts in Jenny A's FOLUP6\_7 dataset (ppts eligible for school age FU)  
language per NF03/SF03 forms**

**The FREQ Procedure**

Primary Language Spoken to Child				
CFLANG	Frequency	Percent	Cumulative Frequency	Cumulative Percent
English	269	78.20	269	78.20
Spanish	57	16.57	326	94.77
Other	18	5.23	344	100.00

**Frequency Missing = 214**

Table of CFLANG by CENTER											
CFLANG(Primary Language Spoken to Child)	CENTER(Center ID number)										
	3	4	5	9	12	14	15	16	18	19	21
Frequency Percent Row Pct Col Pct											
<b>English</b>	42 12.21 15.61 93.33	14 4.07 5.20 42.42	5 1.45 1.86 100.00	2 0.58 0.74 100.00	7 2.03 2.60 100.00	38 11.05 14.13 84.44	14 4.07 5.20 56.00	69 20.06 25.65 98.57	24 6.98 8.92 82.76	4 1.16 1.49 50.00	1 0.29 0.37 100.00
<b>Spanish</b>	2 0.58 3.51 4.44	17 4.94 29.82 51.52	0 0.00 0.00 0.00	0 0.00 0.00 0.00	0 0.00 0.00 0.00	5 1.45 8.77 11.11	9 2.62 15.79 36.00	1 0.29 1.75 1.43	5 1.45 8.77 17.24	0 0.00 0.00 0.00	0 0.00 0.00 0.00
<b>Other</b>	1 0.29 5.56 2.22	2 0.58 11.11 6.06	0 0.00 0.00 0.00	0 0.00 0.00 0.00	0 0.00 0.00 0.00	2 0.58 11.11 4.44	2 0.58 11.11 8.00	0 0.00 0.00 0.00	0 0.00 0.00 0.00	4 1.16 22.22 50.00	0 0.00 0.00 0.00
<b>Total</b>	45 13.08	33 9.59	5 1.45	2 0.58	7 2.03	45 13.08	25 7.27	70 20.35	29 8.43	8 2.33	1 0.29
<b>Frequency Missing = 214</b>											

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Table of CFLANG by CENTER						
CFLANG(Primary Language Spoken to Child)	CENTER(Center ID number)					
Frequency Percent Row Pct Col Pct	22	23	24	25	26	Total
<b>English</b>	8 2.33 2.97 57.14	13 3.78 4.83 46.43	9 2.62 3.35 100.00	18 5.23 6.69 85.71	1 0.29 0.37 50.00	269 78.20
<b>Spanish</b>	6 1.74 10.53 42.86	8 2.33 14.04 28.57	0 0.00 0.00 0.00	3 0.87 5.26 14.29	1 0.29 1.75 50.00	57 16.57
<b>Other</b>	0 0.00 0.00 0.00	7 2.03 38.89 25.00	0 0.00 0.00 0.00	0 0.00 0.00 0.00	0 0.00 0.00 0.00	18 5.23
<b>Total</b>	14 4.07	28 8.14	9 2.62	21 6.10	2 0.58	344 100.00
<b>Frequency Missing = 214</b>						

**From:** [Lila Guterman](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Cc:** [Bock, Robert \(NIH/NICHD\) \[E\]](#)  
**Subject:** RE: Dr. Finer's Availability - SUPPORT PAPERS!!!  
**Date:** Friday, March 12, 2010 6:06:49 AM

---

Thank you for arranging this call! Have a good weekend,

Lila

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)]  
**Sent:** Thursday, March 11, 2010 7:57 PM  
**To:** 'fmartinez@ucsd.edu'; 'nfiner@ucsd.edu'; 'wacarlo@uab.edu'  
**Cc:** 'lguterman@palladianpartners.com'; Bock, Robert (NIH/NICHD) [E]  
**Subject:** Re: Dr. Finer's Availability - SUPPORT PAPERS!!!

We will do the call on

Monday March 15 from 4-5 pm ET (1 pm ET, 3 pm CT)- call in number;  
866-675-(b) with pass code  
(b) (6) followed by the pound sign.

Rose

---

**From:** Martinez, Fernando <[fmartinez@ucsd.edu](mailto:fmartinez@ucsd.edu)>  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil <[nfiner@ucsd.edu](mailto:nfiner@ucsd.edu)>; wacarlo@uab.edu  
<[wacarlo@uab.edu](mailto:wacarlo@uab.edu)>  
**Cc:** 'Lila Guterman' <[lguterman@palladianpartners.com](mailto:lguterman@palladianpartners.com)>; Bock, Robert (NIH/NICHD) [E]  
**Sent:** Thu Mar 11 17:45:07 2010  
**Subject:** Dr. Finer's Availability - SUPPORT PAPERS!!!

Dear Dr. Higgins,

Please see below for Dr. Finer's availability:

**March 12 – anytime before 1 PM ET: Not available, giving lecture in Mexico**  
**March 15 – 4-5 pm et (1-2 pm pt): OK**

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



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---

**From:** Higgins, Rosemary (NIH/NICHHD) [E] [mailto:higginsr@mail.nih.gov]

**Sent:** Thursday, March 11, 2010 11:04 AM

**To:** Finer, Neil; wacarlo@uab.edu; Martinez, Fernando

**Cc:** 'Lila Guterman'; Bock, Robert (NIH/NICHHD) [E]

**Subject:** SUPPORT PAPERS!!!

**Importance:** High

Neil and Wally,

Our public affairs office is interested in discussing the two SUPPORT papers with you.

Are you available to speak with them (and me) by phone either:

March 12 – anytime before 1 PM ET

March 15 – 4-5 pm et

Let me know so I can set this up.

Thanks for all your help

Rose

Rosemary D. Higgins, MD

Program Scientist for the Neonatal Research Network

Pregnancy and Perinatology Branch

Center for Developmental Biology and Perinatal Medicine

Eunice Kennedy Shriver National Institute of Child Health and Human Development

National Institutes of Health

6100 Executive Blvd., Room 4B03

MSC 7510

Bethesda, MD 20892

For overnight delivery use Rockville, MD 20852

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: Dr. Finer's Availability - SUPPORT PAPERS!!!  
**Date:** Thursday, March 11, 2010 8:39:42 PM

---

We will do this monday 4-5 pm

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** 'fmartinez@ucsd.edu' <fmartinez@ucsd.edu>; 'nfiner@ucsd.edu' <nfiner@ucsd.edu>; 'wacarlo@uab.edu' <wacarlo@uab.edu>  
**Cc:** 'lguterman@palladianpartners.com' <lguterman@palladianpartners.com>; Bock, Robert (NIH/NICHD) [E]  
**Sent:** Thu Mar 11 19:57:17 2010  
**Subject:** Re: Dr. Finer's Availability - SUPPORT PAPERS!!!

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Program Scientist for the Neonatal Research Network

Pregnancy and Perinatology Branch

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Eunice Kennedy Shriver National Institute of Child Health and Human Development

National Institutes of Health

6100 Executive Blvd., Room 4B03

MSC 7510

Bethesda, MD 20892

For overnight delivery use Rockville, MD 20852

301-496-5575

301-496-3790 (FAX)

higginsr@mail.nih.gov

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "rwebb@rti.org"  
**Subject:** Fw: Dr. Finer's Availability - SUPPORT PAPERS!!!  
**Date:** Thursday, March 11, 2010 7:58:16 PM

---

Robin-  
I am using the call in line on monday

Rose

---

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**To:** 'fmartinez@ucsd.edu' <fmartinez@ucsd.edu>; 'nfiner@ucsd.edu' <nfiner@ucsd.edu>; 'wacarlo@uab.edu' <wacarlo@uab.edu>  
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Please see below for Dr. Finer's availability:

**March 12 – anytime before 1 PM ET: Not available, giving lecture in Mexico**  
**March 15 – 4-5 pm et (1-2 pm pt): OK**

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



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**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Thursday, March 11, 2010 11:04 AM  
**To:** Finer, Neil; wacarlo@uab.edu; Martinez, Fernando  
**Cc:** 'Lila Guterman'; Bock, Robert (NIH/NICHD) [E]  
**Subject:** SUPPORT PAPERS!!!  
**Importance:** High

Neil and Wally,  
Our public affairs office is interested in discussing the two SUPPORT papers with you.

Are you available to speak with them (and me) by phone either:

March 12 – anytime before 1 PM ET  
March 15 – 4-5 pm et

Let me know so I can set this up.

Thanks for all your help

Rose

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network  
Pregnancy and Perinatology Branch  
Center for Developmental Biology and Perinatal Medicine  
Eunice Kennedy Shriver National Institute of Child Health and Human Development  
National Institutes of Health  
6100 Executive Blvd., Room 4B03  
MSC 7510  
Bethesda, MD 20892  
For overnight delivery use Rockville, MD 20852  
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: \*\*\*\*Important NEJM acknowledgements\*\*\*\*\*  
**Date:** Thursday, March 11, 2010 11:15:00 AM

---

Here is Utah's

---

**From:** Roger Faix [mailto:Roger.Faix@hsc.utah.edu]  
**Sent:** Friday, March 05, 2010 3:32 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: \*\*\*\*Important NEJM acknowledgements\*\*\*\*\*

Hi Rose!

The proposed text is correct.

Roger

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]  
**Sent:** Friday, March 05, 2010 12:59 PM  
**To:** Roger Faix  
**Cc:** Karen Osborne RN  
**Subject:** RE: \*\*\*\*Important NEJM acknowledgements\*\*\*\*\*

Roger – Just so we get it right-

*Current text:*

*University of Utah* University Hospital, Intermountain Medical Center, LDS Hospital, and Primary Children's Medical Center (U10 HD53124, GCRC M01 RR64) – Jill Burnett, RN; Jennifer J. Jensen, RN BSN; Karen A. Osborne, RN BSN CCRC; Cynthia Spencer, RNC; Kimberlee Weaver–Lewis, RN BSN.

*Proposed text:*

*University of Utah* University of Utah Medical Center , Intermountain Medical Center, LDS Hospital, and Primary Children's Medical Center (U10 HD53124, GCRC M01 RR64) – Jill Burnett, RN; Jennifer J. Jensen, RN BSN; Karen A. Osborne, RN BSN CCRC; Cynthia Spencer, RNC; Kimberlee Weaver–Lewis, RN BSN.

Is the proposed text correct??

Thanks

Rose

---

**From:** Roger Faix [mailto:Roger.Faix@hsc.utah.edu]  
**Sent:** Friday, March 05, 2010 2:51 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Karen Osborne RN  
**Subject:** RE: \*\*\*\*Important NEJM acknowledgements\*\*\*\*\*

Hi Rose!

We have no names to add or delete to the boilerplate acknowledgements, BUT would suggest the following changes to the hospital names in the Utah section of the acknowledgements:

For CarloSUPPORT Final version:  
Change University Hospital to University of Utah Medical Center

For FinerSUPPORT Final version:  
Change University Hospital to University of Utah Medical Center

Roger

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]  
**Sent:** Friday, March 05, 2010 7:17 AM  
**To:** 'Finer, Neil'; 'Duara, Shahnaz'; Phelps, Dale; 'Michael O` Shea'; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Bradley Yoder; Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Matthew Bizzarro; Michelle Walsh; Mickey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald Goldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa  
**Cc:** 'Zaterka-Baxter, Kristin'  
**Subject:** \*\*\*\*Important NEJM acknowledgements\*\*\*\*\*

Hi,

It was brought to our attention that at least one site has a staff member missing on the acknowledgements section of the SUPPORT papers. I spoke with Brendan Abel, editorial assistant at NEJM this morning and we will be permitted to insert additional names into the acknowledgements section. He pointed out that no changes can be made to the manuscript without the approval of the editor so the attached papers are final.

**Therefore, I am requesting that each Steering Committee PI (from both cycles of the NRN involved in the study) review the two acknowledgement sections and send me any additional person(s) that deserve to be listed by *Monday March 8*. If someone is an author on the paper, they should not appear in the boilerplate. Further, please check to insure that all of the hospitals that your site recruited from are listed and that all of your staff/hospitals are correctly spelled in the**

## **documents.**

The acknowledgements begin on page 20 for the CPAP/surf paper and on page 21 for the oxygen saturation paper.

Thanks for all your help and remember to keep the manuscripts confidential as NEJM has a very strict embargo policy.

### **Rose**

Rosemary D. Higgins, MD

Program Scientist for the Neonatal Research Network

Pregnancy and Perinatology Branch

Center for Developmental Biology and Perinatal Medicine

Eunice Kennedy Shriver National Institute of Child Health and Human Development

National Institutes of Health

6100 Executive Blvd., Room 4B03

MSC 7510

Bethesda, MD 20892

For overnight delivery use Rockville, MD 20852

301-496-5575

301-496-3790 (FAX)

[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

**From:** [Das, Abhik](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\)](#) [E]  
**Subject:** SUPPORT papers  
**Date:** Thursday, March 11, 2010 10:07:54 AM

---

Rose:

Do you have any notion of when these will come out? RTI would like to do a press release (which we will coordinate with NICHD, respecting the embargo and all that); so I wanted to plan ahead a bit and give people here some idea of a timeline.

Thanks

Abhik

**Abhik Das, Ph.D.**  
**Senior Research Statistician**  
**RTI International**  
6110 Executive Blvd., Suite 902  
Rockville, MD 20852-3903  
e-mail: [adas@rti.org](mailto:adas@rti.org)  
Phone: 301-770-8214  
Fax: 301-230-4646

**From:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](mailto:Higgins.Rosemary@NIH/NICHD)  
**To:** [Archer, Stephanie \(NIH/NICHD\) \[E\]](mailto:Archer.Stephanie@NIH/NICHD)  
**Subject:** RE: Boilerplate | SUPPORT  
**Date:** Wednesday, March 10, 2010 10:59:00 AM

---

Great!!

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network

-----Original Message-----

From: Archer, Stephanie (NIH/NICHD) [E]  
Sent: Wednesday, March 10, 2010 10:59 AM  
To: Higgins, Rosemary (NIH/NICHD) [E]  
Subject: FW: Boilerplate | SUPPORT

I have this from Pablo.

-----Original Message-----

From: Pablo Sanchez [<mailto:Pablo.Sanchez@UTSouthwestern.edu>]  
Sent: Monday, March 08, 2010 11:45 AM  
To: Archer, Stephanie (NIH/NICHD) [E]; [wcarlo@peds.uab.edu](mailto:wcarlo@peds.uab.edu); Neil 'Finer'  
Cc: Higgins, Rosemary (NIH/NICHD) [E]  
Subject: RE: Boilerplate | SUPPORT

Hi Stephanie--please see below---sorry, they helped with both of the studies--Laura Grau goes only under the pulse ox/ ROP one and not CPAP--thanks--pablo

University of Texas Southwestern Medical Center at Dallas Parkland Health & Hospital System and Children's Medical Center Dallas (U10 HD40689, GCRC M01 RR633) - Charles R. Rosenfeld, MD; Walid A. Salhab, MD; Alicia Guzman; Gaynelle Hensley, RN; Melissa H. Lepps, RN; Nancy A. Miller, RN.

Diana M Vasil, RNC, NIC, James Allen, RRT, Araceli Solis, RRT, Melissa Martin, RN, Kerry Wilder, RN, Laura Grau, RN

>>> "Archer, Stephanie (NIH/NICHD) [E]" <[archerst@mail.nih.gov](mailto:archerst@mail.nih.gov)> 3/5/10 9:13 AM >>>  
Pablo,

Please send us your complete list of names.

At the moment, I believe both manuscripts include:

University of Texas Southwestern Medical Center at Dallas Parkland Health & Hospital System and Children's Medical Center Dallas (U10 HD40689, GCRC M01 RR633) - Charles R. Rosenfeld, MD; Walid A. Salhab, MD; Alicia Guzman; Gaynelle Hensley, RN; Melissa H. Lepps, RN; Nancy A. Miller, RN.

When we get the galleys, we will add:  
Diana M Vasil, RNC, NIC

-----Original Message-----

From: Finer, Neil [<mailto:nfiner@ucsd.edu>]  
Sent: Thursday, March 04, 2010 7:16 PM  
To: Pablo Sanchez; Archer, Stephanie (NIH/NICHD) [E]; [wcarlo@peds.uab.edu](mailto:wcarlo@peds.uab.edu)

Cc: Higgins, Rosemary (NIH/NICHD) [E]  
Subject: RE: Boilerplate | SUPPORT

I think we can add this to the galleys - It will not add length to the manuscript  
Neil

-----Original Message-----

From: Pablo Sanchez [mailto:Pablo.Sanchez@UTSouthwestern.edu]  
Sent: Thursday, March 04, 2010 2:07 PM  
To: archerst@mail.nih.gov; wcarlo@peds.uab.edu; Finer, Neil  
Cc: higginsr@mail.nih.gov  
Subject: Re: Boilerplate | SUPPORT

Actually, I have been meaning to e-mail you about this-please include her in both-also if not too late, need to add a couple of others-sorry-pablo

Pablo -sent from Blackberry  
214-648-3753 (office)  
214-621-(b) (cell)  
972-206-(b) (beeper)

-----Original Message-----

From: "Archer, Stephanie (NIH/NICHD) [E]" <archerst@mail.nih.gov>  
Cc: Rosemary (NIH/NICHD) [E] Higgins <higginsr@mail.nih.gov>  
To: Wally Carlo(wcarlo@peds.uab.edu) <wcarlo@peds.uab.edu>  
To: Neil Finer (nfiner@ucsd.edu) <nfiner@ucsd.edu>  
Cc: Pablo Sanchez <Pablo.Sanchez@UTSouthwestern.edu>

Sent: 3/4/2010 3:42:23 PM  
Subject: RE: Boilerplate | SUPPORT

Hi Wally and Neil,

Were you able to add Diana to the boilerplate in the final versions of the NEJM papers?

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: Archer, Stephanie (NIH/NICHD) [E]  
Sent: Tuesday, February 02, 2010 2:43 PM  
To: Wally Carlo (wcarlo@peds.uab.edu); Neil Finer (nfiner@ucsd.edu)  
Cc: Higgins, Rosemary (NIH/NICHD) [E]; 'Pablo Sanchez (Pablo.Sanchez@UTSouthwestern.edu)'; Archer, Stephanie (NIH/NICHD) [E]  
Subject: Boilerplate | SUPPORT

Hi Wally and Neil,

Pablo would like to add "Diana M Vasil, RNC, NIC" to the list of people in the acknowledgements for UT Southwestern.

When you get the galleys back, I can review the boilerplate information for you.

Thanks,

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:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**To:** [Archer, Stephanie \(NIH/NICHD\) \[E\]](#)  
**Subject:** RE: Author for SUPPORT FROM HOUSTON  
**Date:** Wednesday, March 10, 2010 10:39:00 AM

---

This is almost fixed – We have all the letters and will send them this afternoon.

Rose

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network

---

**From:** Archer, Stephanie (NIH/NICHD) [E]  
**Sent:** Sunday, March 07, 2010 8:14 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Author for SUPPORT FROM HOUSTON

Sorry about this. I had Kathleen's name on the title page list I sent to Neil. He must not have made the changes on his draft. I should have checked it.

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Friday, March 05, 2010 5:03 PM  
**To:** Archer, Stephanie (NIH/NICHD) [E]; 'Georgia.E.McDavid@uth.tmc.edu'; 'Kathleen.A.Kennedy@uth.tmc.edu'; 'Jon.E.Tyson@uth.tmc.edu'; 'nfiner@ucsd.edu'  
**Subject:** Re: Author for SUPPORT FROM HOUSTON

The paper currently list Brenda on both. I see the email trail below- an error must have been made to not have Kathleen on one of the papers. We will need to contact NEJM about switching the UT Houston author on the CPAP paper.

Sorry for the confusion.

Kathleen - i will find the authorship forms and get them to you asap  
Rose

---

**From:** Archer, Stephanie (NIH/NICHD) [E]  
**To:** 'Georgia.E.McDavid@uth.tmc.edu' <Georgia.E.McDavid@uth.tmc.edu>; Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Fri Mar 05 16:30:12 2010  
**Subject:** Re: Author for SUPPORT FROM HOUSTON

Hi Georgia,

I'm not in the office today, but that is how the authorship was in the last versions of the papers I saw.  
Rose, can you double check, please?

Thanks,  
Steph

---

**From:** Mcdavid, Georgia E <Georgia.E.McDavid@uth.tmc.edu>  
**To:** Archer, Stephanie (NIH/NICHD) [E]  
**Sent:** Fri Mar 05 16:06:28 2010  
**Subject:** FW: Author for SUPPORT FROM HOUSTON

Here are the series of confusing emails about it. ☺

---

**From:** Kennedy, Kathleen A  
**Sent:** Friday, March 05, 2010 2:24 PM  
**To:** Mcdavid, Georgia E  
**Subject:** FW: Author for SUPPORT FROM HOUSTON

This is the last email about it. Brenda should be in the authors on the oximetry/ROP paper (Wally's) and I should be an author on the CPAP/BPD (Neil's) paper. Each of us should be in the boilerplate for the one on which we're not listed as an author.

Kathleen A. Kennedy, MD, MPH  
Richard W. Mithoff Professor of Pediatrics  
Director, Division of Neonatal-Perinatal Medicine  
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:** Monday, November 16, 2009 9:00 AM  
**To:** Kennedy, Kathleen A  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Author for SUPPORT FROM HOUSTON

I'll swap them.

---

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:** Kennedy, Kathleen A [mailto:Kathleen.A.Kennedy@uth.tmc.edu]  
**Sent:** Monday, November 16, 2009 9:47 AM  
**To:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** Re: Author for SUPPORT FROM HOUSTON

That was the email I couldn't find! Thanks. Brenda spent a lot of time working on oximetry compliance so I'm now thinking it would be better to name her on that one, but either way would be fair.

Kathleen A. Kennedy, MD, MPH  
Director, Neonatal-Perinatal Division  
Director, MS in Clinical Research Degree Program

---

**From:** Archer, Stephanie (NIH/NICHD) [E] <archerst@mail.nih.gov>  
**To:** Kennedy, Kathleen A

**Cc:** Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov>; Archer, Stephanie (NIH/NICHD) [E] <archerst@mail.nih.gov>  
**Sent:** Mon Nov 16 08:42:44 2009  
**Subject:** FW: Author for SUPPORT FROM HOUSTON

Hi Kathleen,

Per your email below, you had requested previously that you would be on the CPAP and Brenda would be on Oximetry, but I can certainly switch it if you prefer.

Please let me know for sure which way you want it.

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:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Tuesday, October 13, 2009 1:54 PM  
**To:** 'Kennedy, Kathleen A'; Tyson, Jon E  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: Author for SUPPORT FROM HOUSTON

Sounds good  
Thanks  
Rose

---

**From:** Kennedy, Kathleen A [<mailto:Kathleen.A.Kennedy@uth.tmc.edu>]  
**Sent:** Tuesday, October 13, 2009 1:52 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Tyson, Jon E  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: Author for SUPPORT FROM HOUSTON

Brenda did a lot of work on this study before she left. I took over then. I think it would be fair to include her as the site PI for the vent/CPAP arm paper and then I would be the site PI for the oximetry arm paper.

Kathleen A. Kennedy, MD, MPH  
Richard W. Mithoff Professor of Pediatrics  
Director, Division of Neonatal-Perinatal Medicine  
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 13, 2009 11:05 AM

**To:** Tyson, Jon E; Kennedy, Kathleen A

**Cc:** Archer, Stephanie (NIH/NICHD) [E]

**Subject:** RE: Author for SUPPORT FROM HOUSTON

I will tell you that two sites are having one author for the ventilation arm paper and another author for the oximetry arm paper.

Rose

---

**From:** Tyson, Jon E [mailto:Jon.E.Tyson@uth.tmc.edu]

**Sent:** Tuesday, October 13, 2009 11:53 AM

**To:** Higgins, Rosemary (NIH/NICHD) [E]; Kennedy, Kathleen A

**Subject:** RE: Author for SUPPORT FROM HOUSTON

Brenda did a lot of work but up to Kathleen

Jon E. Tyson, MD, MPH  
Center for Clinical Research & Evidence-Based Medicine  
UT Medical School at Houston  
6431 Fannin St., MSB 2.106  
Houston, TX 77030  
voice 713-500-5651  
fax 713-500-0519

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]

**Sent:** Tuesday, October 13, 2009 10:46 AM

**To:** Kennedy, Kathleen A; Tyson, Jon E

**Cc:** Archer, Stephanie (NIH/NICHD) [E]

**Subject:** Author for SUPPORT FROM HOUSTON

Hi,

We are working on the authorship for the SUPPORT main trial papers (one for vent arm, one for oximetry arm). We originally had Brenda Morris as the site PI for SUPPORT. Shall we list her on the paper or do you wish to designate a different investigator from UT Houston – let me know

Thanks

Rose

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network  
Pregnancy and Perinatology Branch  
Center for Developmental Biology and Perinatal Medicine  
Eunice Kennedy Shriver National Institute of Child Health and Human Development  
National Institutes of Health  
6100 Executive Blvd., Room 4B03  
MSC 7510  
Bethesda, MD 20892  
For overnight delivery use Rockville, MD 20852

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301-496-5575  
301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Irene, Amanda"  
**Cc:** "Wallace, Dennis"  
**Subject:** RE: BPD/Oximetry minutes  
**Date:** Wednesday, March 10, 2010 9:52:00 AM  
**Attachments:** [Follow Up ON BPD and Oximeters02March2010.ai.doc](#)

---

Amanda, Please have Dennis look at these for accuracy. Also, change the title to SUPPORT SUBCOMMITTEE CALL.

Thanks  
Rose

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network

---

**From:** Irene, Amanda [mailto:airene@rti.org]  
**Sent:** Wednesday, March 10, 2010 9:30 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** BPD/Oximetry minutes

Hi Rose,

I've attached the minutes from the BPD/Oximetry call last week. Let me know if there are any changes!

Thanks!  
Amanda

**SUPPORT SUBCOMMITTEE TELECONFERENCE Follow-Up ON BPD and Oximeters  
March 2, 2010**

**Participants:** Neil Finer, Michelle Walsh, Rose Higgins, Kurt Schibler, Wade Rich, Wally Carlo, Roger Faix, Dennis Wallace, Meg Cunningham, Kris Zaterka-Baxter Amanda Irene, Stephanie Archer,

- The ad-hoc conference call was convened to discuss whether the evidence regarding potential bias in the use study oximeter for diagnosis BPD based on oxygen use or test for the physiologic challenge was sufficient to require modification of the SUPPORT papers
- Only three of the 4616 centers used the study oximeter to conduct the physiologic challenge
- Analyses conducted Dr. Gantz clearly demonstrated that any differences in outcome associated with the type of oximeter were clearly confounded with any center differences, so the impact of oximeter type cannot be distinguished from other center characteristics.
- Dr. Wallace explained that there is some potential for bias in the analysis; Dr. Gantz's models looked at treatment and the type of oximeter used for analysis.
  - No interaction was found to show that there was a differential risk ratio between the two treatment arms as a function of which oximeter was used; there was a p-value of 0.25 so there was nothing suggestive of that effect.
  - Furthermore, the effect of any bias appears to be away from the null. Since the effect is currently not significant, any control for bias would just make the effect less significant, meaning that any changes will not substantively affect the conclusions of the manuscripts.
- While this particular analysis was underpowered, no clinically important impact was seen based on oximeter use; additionally, oximeter use is confounded with center and the study controlled for center in the primary analysis.
- Dr. Wallace indicated that the potential biases would not have affected the conclusions of the manuscript, there is no need to highlight the issue in the manuscript, as it would simply detract from the key conclusions of the study.
- Dr. Finer asked whether additional analyses done on oximeter use would be best stated in the manuscript currently underway by Walsh et al. Dr. Walsh indicated that this analyses may be an entirely different paper those agreed by all that these further analyses are needed.

**Clarifications and summary:**

- Within the 2 saturation arms, there is more BPD in the high saturation arm but looking at the physiological definition alone there is no difference between the arms.
- NEJM has asked that death + phys def BPD (not BPD by oxygen be used as primary outcome as that appeared to be the intent from the protocol provided)
- The subcommittee agrees that based on Dr. Wallace's explanation; this is a non significant results that may be biased against the null and would only add confusion therefore should not be addressed in the paper.
- Dr. Higgins will call Dr. Tyson to discuss the committee consensus on the matter above; a conversation between Dr. Tyson and Dr. Wallace may be set up.

**Comment [a1]:** Do you have the 4 bullets that you summarized at the end of the call? Neither Kris nor myself have them. Thanks!

**Formatted:** Bullets and Numbering

**Further Comments:**

- Dr. Carlo has not heard from the NEJM as of yet. He is not expecting any further comments.

**From:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**To:** [Archer, Stephanie \(NIH/NICHD\) \[E\]](#)  
**Subject:** RE: Boilerplate | Shankaran, Hypothermia 6-7 yr FU  
**Date:** Wednesday, March 10, 2010 9:27:00 AM

---

WE need to check the journal directions - I can look this afternoon - we did this for SUPPORT and I think there is some statement as to a Conflict with the current manuscript.

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network

-----Original Message-----

From: Archer, Stephanie (NIH/NICHD) [E]  
Sent: Wednesday, March 10, 2010 9:23 AM  
To: Higgins, Rosemary (NIH/NICHD) [E]  
Subject: RE: Boilerplate | Shankaran, Hypothermia 6-7 yr FU

Should I leave this in the boilerplate file for now?

-----Original Message-----

From: Higgins, Rosemary (NIH/NICHD) [E]  
Sent: Wednesday, March 10, 2010 9:22 AM  
To: Archer, Stephanie (NIH/NICHD) [E]  
Subject: RE: Boilerplate | Shankaran, Hypothermia 6-7 yr FU

They have to be current (or within the guideline of past COI - usually 1-3 years). All authors will be asked to fill out the IJMCE form. We will need to ask folks again, but only for the authors, and we need to check the journal instructions. There was a major change in 2006 which occurred after the primary hypothermia paper was published.

Thanks  
Rose

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network

-----Original Message-----

From: Archer, Stephanie (NIH/NICHD) [E]  
Sent: Wednesday, March 10, 2010 9:19 AM  
To: Higgins, Rosemary (NIH/NICHD) [E]  
Subject: RE: Boilerplate | Shankaran, Hypothermia 6-7 yr FU

The original boilerplate also had some COIs listed:

(b) (6)



Should these remain, even if the relationships have changed? I need to check whether this or any new COIs exist, although that should appear outside of the acknowledgements.

-----Original Message-----

From: Higgins, Rosemary (NIH/NICHD) [E]



Sent: Tuesday, March 09, 2010 4:03 PM  
To: Archer, Stephanie (NIH/NICHD) [E]  
Subject: RE: Boilerplate | Shankaran, Hypothermia 6-7 yr FU

Marian started on the DSMC in 2004-2005, so this study ended in May 2003 - she was not involved. We do not need the DSMC for this boilerplate as the 6-7 year FU was "observational data" collected. The intervention had ended.

Thanks  
Rose

-----Original Message-----

From: Archer, Stephanie (NIH/NICHD) [E]  
Sent: Tuesday, March 09, 2010 3:16 PM  
To: Higgins, Rosemary (NIH/NICHD) [E]  
Subject: RE: Boilerplate | Shankaran, Hypothermia 6-7 yr FU

For the Extended Hypothermia boilerplate, I was starting with the original paper's acknowledgements and adding FU examiners.

The original paper included the DSMC, but Marian isn't on the list. Was this intentional, or should she be on it now?

**From:** Walsh, Michele  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** Re: Follow Up ON BPD and Oximeters  
**Date:** Tuesday, March 09, 2010 6:57:57 AM

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I'm covering the del rm. Will try to call you

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**From:** Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov>  
**To:** Walsh, Michele  
**Sent:** Mon Mar 08 18:30:11 2010  
**Subject:** Re: Follow Up ON BPD and Oximeters

I called him last week after the SUPPORT subcommittee call and told him we would write a secondary paper on BPD. I told him you were taking the lead for this paper. I am happy to discuss with you. I am attending the vbac consensus conference in the morning (3/9) and will likely be in the office for part of the afternoon. Shall i try to call you?

Rose

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**From:** Walsh, Michele <Michele.Walsh@UHhospitals.org>  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Mon Mar 08 17:20:56 2010  
**Subject:** FW: Follow Up ON BPD and Oximeters

See below: Jon is driving me nuts. I do not understand why he thinks  
This is my issue?

Michele Walsh  
beeper (b) (6)  
Ph 216 844 3759

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**From:** Tyson, Jon E [mailto:Jon.E.Tyson@uth.tmc.edu]  
**Sent:** Monday, March 08, 2010 1:56 PM  
**To:** Walsh, Michele  
**Subject:** RE: Follow Up ON BPD and Oximeters

I tried to call but couldn't reach you today to try to understand our differences. You are talking about Wally's paper, not Neil's, right? If so, I don't see how use of study oximeter at 36 weeks is a bias toward the null rather than a bias toward identifying a higher BPD rate in the higher saturation goal group (who would systematically more likely to receive supplemental oxygen). Such a bias could account for significantly increased rate of BPD by O2 delivery (and the nearly significant increase in either death or BPD by O2 delivery; upper limit of 95% upper limit = 1.01) reported in Wally's paper where BPD by O2 saturation. If I am right, I don't see how you will identify this problem later without being in the uncomfortable position of prompting criticism of how the Network designed the trial (an inadvertent oversight) and particularly how it reported the trial (an openly discussed decision).

Jon E. Tyson, MD, MPH  
Center for Clinical Research & Evidence-Based Medicine  
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6431 Fannin St., MSB 2.106  
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fax 713-500-0519

---

**From:** Walsh, Michele [mailto:Michele.Walsh@UHhospitals.org]  
**Sent:** Friday, March 05, 2010 10:59 AM  
**To:** Tyson, Jon E  
**Subject:** RE: Follow Up ON BPD and Oximeters

Jon: I too am somewhat concerned that this was dropped into my assignment- and I have not agreed to accept such an assignment. I do not find that this topic is well discussed by email. After reading your Concerns I would be pleased to discuss further, but currently I do not feel That this is a significant source of bias which was worthy of disclosure. I believe that the direction of the bias would be toward the null of no difference, Which is what we have already concluded. I do not draw the inference that you did Below: that the bias is not important, just that it does not change our conclusion.

Michele Walsh  
beeper (b) (6)  
Ph 216 844 3759

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**From:** Tyson, Jon E [mailto:Jon.E.Tyson@uth.tmc.edu]  
**Sent:** Thursday, March 04, 2010 8:08 PM  
**To:** Walsh, Michele  
**Cc:** Wally Carlo, M.D.  
**Subject:** FW: Follow Up ON BPD and Oximeters

Michele and Wally, this is a note of dismay from me and concern for you as good friends and respected colleagues.

Michele, I understand from Rose that you are on the hot seat in a later paper that will address the oximeters as a likely source of bias for an important predefined secondary outcome (which BPD by O2 administration certainly is). In my view, this puts you in the difficult position of being on the receiving end of being asked why this source of bias was not even mentioned in the primary paper. As for any other potential source of bias in a study in evaluating an important secondary outcome—loss to follow-up, administration of the treatment to controls, inability to blind caregivers, inability to blind outcome assessors, or any other recognized potential source of ascertainment bias—the reviewers, editors, and readers expect us to report it, whether or not there was a significant or near significant outcome difference between groups in the outcome and whether or not we assessed or found any interaction or other statistical evidence that this potential source of bias affected the results.

While I certainly have no doubt about the integrity or sincerity of the subcommittee members, it is hard to believe that any of us, including the subcommittee members, really understand the analyses, given the complexities involved in measuring and interpreting statistical interactions, the limited information about even what data were available and analyzed, whether those data were reliably recorded and properly interpreted, and the limited and confusing explanations of the analyses so far. The questions I raised below have not been answered, and the explanation to date—which seems to be: Center differences are big, the effect of using the study oximeter can't be disentangled from center differences, therefore the effect of using the study oximeter must not be big or important—makes no sense to me.

Hopefully I am wrong but I fear that when they read your paper Michele, it will be difficult to convince sophisticated readers—the people whose respect we most want and need to earn—that the Network made a good decision and that it didn't instead chose not to disclose an important potential source of bias that was not well evaluated in assessing an important secondary outcome.

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**From:** Tyson, Jon E

**Sent:** Friday, February 26, 2010 5:28 PM

**To:** 'Wallace, Dennis'; Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpointex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; Stevenson David (E-mail); Finer, Neil; Rich, Wade; Gantz, Marie

**Cc:** Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]

**Subject:** RE: Follow Up ON BPD and Oximeters

I don't understand your statement "Controlling for center adjusts for differences between centers including differences in the BPD oximeter used." To simplify the discussion, suppose every center always used the study oximeter in designating who had BPD by oxygen saturation. Because the true saturation that would prompt oxygen administration would differ in the two treatment groups, there would be systematic bias toward administering oxygen to more infants in the high sat group than in the low sat group. This is inherent in the study design. Whatever differences there were between centers, this bias would occur in every center and would not be eliminated by controlling for center. And if I understand the analysis, there would be no interaction between treatment oximeter and BPD oximeter because they would be the same in every baby in every center.

You indicate that 5 centers used the study oximeter in almost every baby. In saying "it's not possible to tease out the effect of the BPD oximeter from other between-center differences" (a statement that I certainly accept), aren't you saying that the effect of the study oximeter on the difference in the incidence of BPD by oxygen administration between high and low sat groups (i.e., the bias) can not be distinguished from the effect of the myriad of other factors in those centers that might affect that difference in incidence? If so, why would you expect to be able to discern that bias (the signal) from all the noise resulting from other factors? I understand from what you said that the same approach was used in virtually all infants in each center which makes the effective n to be based on the number of centers rather than the number of babies. As I understand the analysis, the power to assess an interaction would then be quite low.

The issue here is whether is simply whether to report somewhere in the paper (which could be noted under the table and wouldn't increase the word count for the text) a bias in evaluating a secondary outcome. This can be done with no delay in submitting the manuscript or waiting for Maria to return. *If we had other real or potential sources of bias—say, a breaking of the blind for some infants, open label administration of a study drug to the control group, or differential loss to follow-up, we would certainly report it as a matter of course, whether or not there was a significant or near significant difference in the outcome and without testing and whether or not we assessed or found any interaction or other statistical evidence that this potential source of bias affected the results!*

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---

**From:** Wallace, Dennis [mailto:dwallace@rti.org]  
**Sent:** Friday, February 26, 2010 1:56 PM  
**To:** Wallace, Dennis; Tyson, Jon E; Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; Stevenson David (E-mail); Finer, Neil; Rich, Wade; Gantz, Marie  
**Cc:** Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: Follow Up ON BPD and Oximeters

Hello all,

I accidentally hit the send button before finishing editing this response so ignore the earlier e-mail and see the response below.

Dennis

Dennis Wallace  
Senior Research Statistician  
Cox 241  
RTI International  
3040 Cornwallis Rd  
Research Triangle Park, NC 27709-2104  
Voice: 919-541-6271  
Fax: 919-541-6416

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**From:** Wallace, Dennis  
**Sent:** Friday, February 26, 2010 2:53 PM  
**To:** 'Tyson, Jon E'; Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; 'Stevenson David (E-mail)'; 'Finer, Neil'; Rich, Wade; Gantz, Marie  
**Cc:** Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: Follow Up ON BPD and Oximeters

Jon,

Marie flew out on a long-scheduled vacation after completing these analyses late Tuesday evening and has very limited e-mail and cell phone access. However, she has taken time to provide a preliminary response that I've outlined below with some added thoughts of my own in red font below. Based on these responses, I do believe that the critical concerns about bias have been addressed sufficiently for this initial manuscript, but if you think we need to have a more full discussion, we can talk after Marie returns next week. Because the programming for these outcome measures is relatively complicated, I'm hesitant to try to do any additional analyses

prior to her return. However, as I indicated above, I don't think that we need to delay any submissions while trying to iron on the small details.

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-----Original Message-----

From: Tyson, Jon E [mailto:Jon.E.Tyson@uth.tmc.edu]  
Sent: Thursday, February 25, 2010 12:45 AM  
To: Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; Wallace, Dennis; cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; 'Stevenson David (E-mail)'; 'Finer, Neil'; Rich, Wade; Gantz, Marie  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]  
Subject: RE: Follow Up ON BPD and Oximeters

Rose, before we can understand and interpret this information noted in the mail, we really need to know more about what was done and answers to questions like those below:

1. Which trial result was addressed - whether the evaluation of BPD was biased in the analyses of CPAP/limited ventilation vs. surfactant/conventional ventilation arm (not the analysis for which there is concern) or the analyses of the high vs. low oxygen saturation goal.

Although models were run for the different arms of the factorial design, the trial result that was addressed in the earlier e-mail was the impact of different oximeters on the comparison of the effects high vs. low oxygen saturation targets on BPD and BPD/death outcomes, which we believe is the question of interest.

2. Do we have reliable data to know whether individual infants were monitored on the study oximeter or on the clinical oximeter on the day the infant was 36 weeks and 0 and whether the oximeter was changed part way through that 24 hour period? What was done if the infant was switched on that day. As I understand it, the diagnosis of BPD was based on the entire 24 hours the day the infant was 36 weeks 0 days. Though the results of the survey weren't distributed, my impression from responses to my earlier e mails was that even the procedure usually followed in individual centers was not necessarily clear.

We can determine from form PHY02 what oximeter was used to determine the physiologic definition of BPD, but we do not have the detailed level of information that you described. However, based on the survey results, we do know that only 5 sites used the study oximeter for an oxygen-based definition, and only 3 used the study oximeter for challenge.

3. What variables in the model when the BPD oximeter was added? What variables were in the model when a BPD oximeter x study treatment group was added?

Variables in the model were treatment oximeter (low vs. high), center, GA group. Familial clustering was adjusted for as a random effect. I added BPD oximeter and also looked at the interaction between BPD oximeter and treatment oximeter. These factors were identical to the factors used in the models for which secondary outcomes were reported in the manuscript.

4. Do I understand Maria and you to conclude that because centers tended to be consistent in their oximeter use, controlling for center would prevent a biased assessment of the effect on BPD by oxygen administration?

This comment makes me wonder if the analysis was done for the wrong comparison. This conclusion would be correct for analyses of the effect of CPAP/limited ventilation vs. surfactant/ conventional ventilation on BPD by oxygen delivery (because each treatment arm would contain equal numbers of infants in the high and low sat groups). However, this isn't the comparison in question. This conclusion would certainly not be correct in analyzing the effect of high vs low sat goals on BPD. In this analysis, centers that used the study oximeter would be systematically more likely to administer oxygen to the high sat group than to the low sat group. The problem wouldn't go away by controlling for center, and the more centers that used the study oximeter, the more biased the result would be. How many centers were there that used the study oximeter?

Controlling for center adjusts for differences between centers including differences in the BPD oximeter used. Thus, adding a covariate for BPD oximeter does not change the estimates for the treatment oximeter effect. We are not arguing that the BPD oximeter used did not have an impact. We did find that BPD oximeter was significant in the models, as was center. However, since center and BPD oximeter are strongly confounded (in fact we have almost complete aliasing of center and clinical/study oximeter), it's not possible to tease out the effect of the BPD oximeter from other between-center differences. In addition, the interaction between BPD oximeter and treatment oximeter was not significant. This indicates that the impact of treatment oximeter on the BPD outcomes was not significantly different in the centers that used the study oximeters to determine BPD and those that used the clinical oximeters.

5. What is the basis for believing that there would be anything near reasonable power to assess a oximeter x treatment group interaction?

Clearly, these analyses were conducted from a post-hoc perspective, and the study was never designed to have the power to determine that the interaction in our data set is statistically significant for a pre-specified interaction effect size. But, that is not a shortcoming unless the magnitude of the interaction effect is such that it represents an important scientific bias in study interpretation. Our preliminary analyses indicate that biases of such magnitude are not present in this data set. We can do more detailed analyses of the level of bias that might have been introduced after Marie returns from vacation, but nothing in the analyses conducted to date suggest that those magnitudes warrant delay of submission of this manuscript.

I know that everyone is anxious to get this paper submitted. While I have an external advisory committee tomorrow, I will try to respond tomorrow night if the information requested above is sent tomorrow during the day.

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From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]  
Sent: Wednesday, February 24, 2010 7:53 AM  
To: Tyson, Jon E; 'Cunningham, Meg'; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; Wallace, Dennis; cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; 'Stevenson David (E-mail)'; 'Finer, Neil'; Rich, Wade; Gantz, Marie  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]  
Subject: Follow Up ON BPD and Oximeters

Hi all -

In Follow up to yesterday's discussion, Marie spent a great deal of time last evening running additional analyses to address (and now alleviate) Jon's concern as described:

We have looked into the question of whether the oximeter used to determine BPD impacted the BPD and death/BPD outcomes by adding a covariate for the BPD oximeter (study or clinical) to the statistical models. We found that the effect of the BPD oximeter was significant; however, the interaction between BPD oximeter and treatment oximeter (low or high SpO2 target range) was not significant in any model, indicating that, if there was a BPD oximeter effect, it was not different in the two treatment groups. In addition, it should be noted that BPD oximeter is confounded with center (centers tended to be consistent in their use of the study or clinical oximeters to determine BPD). Therefore, by including center in the original models, we have already accounted for the effect of the BPD oximeter the center chose to use. Finally, because center and BPD oximeter are confounded, we cannot know whether the significant BPD oximeter effect is due to the BPD oximeters themselves or other characteristics that differ between centers.

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From: Tyson, Jon E [mailto:Jon.E.Tyson@uth.tmc.edu]  
Sent: Tuesday, February 23, 2010 4:33 PM  
To: Higgins, Rosemary (NIH/NICHD) [E]; 'Cunningham, Meg'; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; Wallace, Dennis; cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; bbatton@siumed.edu  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; lmoore@med.wayne.edu; pamela.neville@duke.edu; gonza025@mc.duke.edu; Smith, Nancy M; Brenda Vecchio; msumner@peds.uab.edu; Archer, Stephanie (NIH/NICHD) [E]  
Subject: RE: Steering Committee Call Tomorrow

While it may seem that I am fixated on an unimportant issue regarding a not quite significant difference, I think we undermine the credibility of Network studies if we are not completely forthright about problems in measuring what everyone would agree is an important secondary outcome. Not reporting that the assessment of BPD by oxygen administration could be biased by continued use of the study oximeters would seem to be in the category of not reporting protocol deviations and not something that is in the Network's best interest. Why not just put a footnote under the table describing the problem?

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---

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
Sent: Tuesday, February 23, 2010 2:11 PM  
To: 'Cunningham, Meg'; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; Wallace, Dennis; cotte010@mc.duke.edu; Tyson, Jon E; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; bbatton@siumed.edu  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; lmoore@med.wayne.edu; pamela.neville@duke.edu; gonza025@mc.duke.edu; Smith, Nancy M; Brenda Vecchio; msumner@peds.uab.edu; Archer, Stephanie (NIH/NICHD) [E]  
Subject: RE: Steering Committee Call Tomorrow

If you joined the call already in progress, please send us an email so we can count your attendance.



Rose

From: Cunningham, Meg [mailto:mcunningham@rti.org]  
Sent: Monday, February 22, 2010 9:59 AM  
To: [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward;  
bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; Higgins, Rosemary  
(NIH/NICHD) [E]; ifrantz@tuftsmedicalcenter.org;  
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e.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; Wallace, Dennis;  
cotte010@mc.duke.edu; jon.e.tyson@uth.tmc.edu; Bradley Yoder;  
rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; bbatton@siumed.edu  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman,  
Jamie; lmoore@med.wayne.edu; pamela.neville@duke.edu; gonza025@mc.duke.edu;  
Nancy.M.Smith@uth.tmc.edu; Brenda Vecchio; msumner@peds.uab.edu; Archer,  
Stephanie (NIH/NICHD) [E]  
Subject: Steering Committee Call Tomorrow

Dear All -

The next standing Steering Committee call is scheduled for tomorrow, Tuesday,  
February 23rd at 3:00pm ET.

Please Dial:  
Outside the USA 1-203-310-0094  
or Within the USA 866-675-3256  
Then, enter Participant Passcode: 560152 #

Steering Committee Conference Call Agenda 02/23/2010

1. Early BP discussion (attached are a brief description of the time limited data collection proposal and a draft of the form which would be used.)
2. SUPPORT manuscript discussion and update
3. New Business

Thanks,  
Meg

Meg Cunningham  
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fax: 202-728-2095  
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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. Visit us at [www.UHhospitals.org](http://www.UHhospitals.org).

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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:** Phelps, Dale  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu  
**Subject:** RE: cpap manuscript  
**Date:** Friday, March 05, 2010 8:31:18 PM

---

Hi Rose and Neil,  
Yes, Nirupama was the site PI, and is the author listed in the author list.

I have asked Tim whether his leadership of the Wheezing SUPPORT Secondary study involved him enough with the primary study that he thinks he should be listed in the acknowledgments. He has also been the Medical Director of our unit, and in that role facilitated the CPAP/Oximeter study. I could go either way, and will wait to see what he says. If I don't hear from him by Monday, I will drop the thought.

Dale

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Friday, March 05, 2010 3:58 PM  
**To:** Phelps, Dale; 'nfiner@ucsd.edu'  
**Subject:** Re: cpap manuscript

For the boilerplate, the individuals listed need to have been involved with the primary study. If Tim Stevens was involved with the primary study, let us know. I had previously thought Nirupama was the site PI. Help us to give credit where credit is due.

Thanks  
Rose

---

**From:** Phelps, Dale <Dale\_Phelps@URMC.Rochester.edu>  
**To:** Finer, Neil <nfiner@ucsd.edu>  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Fri Mar 05 18:45:11 2010  
**Subject:** cpap manuscript

Hi Neil,  
I really enjoyed reading through the 'final' manuscript. Thank you for your great efforts.

I noted two things in going through: maybe you can save this for when you're proofing galleys.

1. Reference 18 in regard to the definition of Type 1 ROP should be the manuscript where that was described. Since it was not defined and described until the post hoc analysis, it is only in the results paper. Your current reference is the Design paper. I suggest you change to:

ETROP Cooperative Group. Revised indications for the treatment of retinopathy of prematurity: results of the early treatment for retinopathy of prematurity randomized trial. Archives of Ophthalmology 2003; 121(12):1684-1694.

2. In the legend for the Figure, the superscripts for "240/7 and 276/7" weeks were lost.  
I did not receive the Figure, so I can not comment on the figure itself.

One last thing:

I wanted to know what you would think of my adding Tim Stevens to the Univ. of Rochester acknowledgments section? Although he was not directly involved in the CPAP study per se, his project

on the longer term wheezing study would seem to warrant this.

Be well,

*Dale*

Dale Phelps

Professor of Pediatrics

30250 S. Highway 1

Gualala, CA 95445

Ph. (707) 897-9063

**From:** Archer, Stephanie (NIH/NICHD) [E]  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** Re: Author for SUPPORT FROM HOUSTON  
**Date:** Friday, March 05, 2010 5:38:41 PM

---

Just out. (b) (6)

(b) (6)

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Archer, Stephanie (NIH/NICHD) [E]  
**Sent:** Fri Mar 05 17:20:16 2010  
**Subject:** RE: Author for SUPPORT FROM HOUSTON

We will get this fixed. (b) (6)

Take Care  
Rose

---

**From:** Archer, Stephanie (NIH/NICHD) [E]  
**Sent:** Friday, March 05, 2010 4:30 PM  
**To:** 'Georgia.E.McDavid@uth.tmc.edu'; Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** Re: Author for SUPPORT FROM HOUSTON

Hi Georgia,

I'm not in the office today, but that is how the authorship was in the last versions of the papers I saw.  
Rose, can you double check, please?

Thanks,  
Steph

---

**From:** Mcdavid, Georgia E <Georgia.E.McDavid@uth.tmc.edu>  
**To:** Archer, Stephanie (NIH/NICHD) [E]  
**Sent:** Fri Mar 05 16:06:28 2010  
**Subject:** FW: Author for SUPPORT FROM HOUSTON

Here are the series of confusing emails about it. ☺

---

**From:** Kennedy, Kathleen A  
**Sent:** Friday, March 05, 2010 2:24 PM  
**To:** Mcdavid, Georgia E  
**Subject:** FW: Author for SUPPORT FROM HOUSTON

This is the last email about it. Brenda should be in the authors on the oximetry/ROP paper (Wally's) and I should be an author on the CPAP/BPD (Neil's) paper. Each of us should be in the boilerplate for the one on which we're not listed as an author.

Kathleen A. Kennedy, MD, MPH  
Richard W. Mithoff Professor of Pediatrics  
Director, Division of Neonatal-Perinatal Medicine

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:** Monday, November 16, 2009 9:00 AM  
**To:** Kennedy, Kathleen A  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Author for SUPPORT FROM HOUSTON

I'll swap them.

---

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:** Kennedy, Kathleen A [mailto:Kathleen.A.Kennedy@uth.tmc.edu]  
**Sent:** Monday, November 16, 2009 9:47 AM  
**To:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** Re: Author for SUPPORT FROM HOUSTON

That was the email I couldn't find! Thanks. Brenda spent a lot of time working on oximetry compliance so I'm now thinking it would be better to name her on that one, but either way would be fair.

Kathleen A. Kennedy, MD, MPH  
Director, Neonatal-Perinatal Division  
Director, MS in Clinical Research Degree Program

---

**From:** Archer, Stephanie (NIH/NICHD) [E] <archerst@mail.nih.gov>  
**To:** Kennedy, Kathleen A  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov>; Archer, Stephanie (NIH/NICHD) [E] <archerst@mail.nih.gov>  
**Sent:** Mon Nov 16 08:42:44 2009  
**Subject:** FW: Author for SUPPORT FROM HOUSTON

Hi Kathleen,

Per your email below, you had requested previously that you would be on the CPAP and Brenda would be on Oximetry, but I can certainly switch it if you prefer.

Please let me know for sure which way you want it.

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:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Tuesday, October 13, 2009 1:54 PM  
**To:** 'Kennedy, Kathleen A'; Tyson, Jon E  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: Author for SUPPORT FROM HOUSTON

Sounds good  
Thanks  
Rose

---

**From:** Kennedy, Kathleen A [<mailto:Kathleen.A.Kennedy@uth.tmc.edu>]  
**Sent:** Tuesday, October 13, 2009 1:52 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Tyson, Jon E  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: Author for SUPPORT FROM HOUSTON

Brenda did a lot of work on this study before she left. I took over then. I think it would be fair to include her as the site PI for the vent/CPAP arm paper and then I would be the site PI for the oximetry arm paper.

Kathleen A. Kennedy, MD, MPH  
Richard W. Mithoff Professor of Pediatrics  
Director, Division of Neonatal-Perinatal Medicine  
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 13, 2009 11:05 AM  
**To:** Tyson, Jon E; Kennedy, Kathleen A  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: Author for SUPPORT FROM HOUSTON

I will tell you that two sites are having one author for the ventilation arm paper and another author for the oximetry arm paper.

Rose

---

**From:** Tyson, Jon E [<mailto:Jon.E.Tyson@uth.tmc.edu>]  
**Sent:** Tuesday, October 13, 2009 11:53 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Kennedy, Kathleen A

**Subject:** RE: Author for SUPPORT FROM HOUSTON

Brenda did a lot of work but up to Kathleen

Jon E. Tyson, MD, MPH  
Center for Clinical Research & Evidence-Based Medicine  
UT Medical School at Houston  
6431 Fannin St., MSB 2.106  
Houston, TX 77030  
voice 713-500-5651  
fax 713-500-0519

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Tuesday, October 13, 2009 10:46 AM  
**To:** Kennedy, Kathleen A; Tyson, Jon E  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** Author for SUPPORT FROM HOUSTON

Hi,

We are working on the authorship for the SUPPORT main trial papers (one for vent arm, one for oximetry arm). We originally had Brenda Morris as the site PI for SUPPORT. Shall we list her on the paper or do you wish to designate a different investigator from UT Houston – let me know

Thanks  
Rose

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network  
Pregnancy and Perinatology Branch  
Center for Developmental Biology and Perinatal Medicine  
Eunice Kennedy Shriver National Institute of Child Health and Human Development  
National Institutes of Health  
6100 Executive Blvd., Room 4B03  
MSC 7510  
Bethesda, MD 20892  
For overnight delivery use Rockville, MD 20852  
301-496-5575  
301-496-3790 (FAX)  
higginsr@mail.nih.gov



**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Finer, Neil"; "Duara, Shahnaz"; "Phelps, Dale"; "Michael O` Shea"; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; "Abhik Das"; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); "Brenda Poindexter"; "Carlo Waldemar (E-mail)"; cotte010@mc.duke.edu; "Dennis Wallace"; "Ed Bell"; "Ed Donovan"; "Ehrenkranz Richard (E-mail)"; Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; "Kristi Watterberg"; Kurt Schibler [kurt.schibler@cchmc.org]; "Matthew Bizzarro"; "Michelle Walsh"; "Mickey Caplan"; "Oh William (E-mail)"; "Pablo Sanchez"; "Poole Kenneth (E-mail)"; "Roger Faix"; "Ronald Goldberg"; "Seetha Shankaran"; "Stevenson David (E-mail)"; "Stoll Barbara (E-mail)"; "Tyson Jon (E-mail)"; VanMeurs, Krisa  
**Cc:** "Zaterka-Baxter, Kristin"  
**Subject:** \*\*\*\*Important NEJM acknowledgements\*\*\*\*\*  
**Date:** Friday, March 05, 2010 9:17:00 AM  
**Attachments:** CarloSUPPORTFINAL (2).doc  
FinerSUPPORTFinal (2).doc

---

Hi,

It was brought to our attention that at least one site has a staff member missing on the acknowledgements section of the SUPPORT papers. I spoke with Brendan Abel, editorial assistant at NEJM this morning and we will be permitted to insert additional names into the acknowledgements section. He pointed out that no changes can be made to the manuscript without the approval of the editor so the attached papers are final.

**Therefore, I am requesting that each Steering Committee PI (from both cycles of the NRN involved in the study) review the two acknowledgement sections and send me any additional person(s) that deserve to be listed by *Monday March 8*. If someone is an author on the paper, they should not appear in the boilerplate. Further, please check to insure that all of the hospitals that your site recruited from are listed and that all of your staff/hospitals are correctly spelled in the documents.**

The acknowledgements begin on page 20 for the CPAP/surf paper and on page 21 for the oxygen saturation paper.

Thanks for all your help and remember to keep the manuscripts confidential as NEJM

has a very strict embargo policy.

**Rose**

Rosemary D. Higgins, MD

Program Scientist for the Neonatal Research Network

Pregnancy and Perinatology Branch

Center for Developmental Biology and Perinatal Medicine

Eunice Kennedy Shriver National Institute of Child Health and Human Development

National Institutes of Health

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For overnight delivery use Rockville, MD 20852

301-496-5575

301-496-3790 (FAX)

[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "nfiner@ucsd.edu"; "wcarlo@peds.uab.edu"  
**Subject:** Re: Boilerplate | SUPPORT  
**Date:** Friday, March 05, 2010 6:26:21 AM

---

Yes - i can call him this am to see if he is ok with this and then tell folks to respond by monday.

We sent the boilerplate out several times and i spefically sent emails.

I certainly want to recognize the site staff.

Thanks

Rose

----- Original Message -----

From: Finer, Neil <nfiner@ucsd.edu>  
To: Higgins, Rosemary (NIH/NICHD) [E]; wcarlo@peds.uab.edu <wcarlo@peds.uab.edu>  
Sent: Thu Mar 04 22:00:18 2010  
Subject: FW: Boilerplate | SUPPORT

Rose

Do you think we could send a revision to Brendan with just the new Boilerplate?

He seems very reasonable.

Neil

-----Original Message-----

From: Pablo Sanchez [mailto:Pablo.Sanchez@UTSouthwestern.edu]  
Sent: Thursday, March 04, 2010 4:18 PM  
To: Finer, Neil  
Subject: Re: Boilerplate | SUPPORT

Thanks, Neil-will do it tonight-currently in nyc...and congratulations-great job! -pablo

Pablo -sent from Blackberry

214-648-3753 (office)

214-621-(b) (cell)

972-206-(b) (beeper)

-----Original Message-----

From: "Finer, Neil" <nfiner@ucsd.edu>  
To: archerst@mail.nih.gov <archerst@mail.nih.gov>  
Cc: higginsr@mail.nih.gov <higginsr@mail.nih.gov>  
To: wcarlo@peds.uab.edu <wcarlo@peds.uab.edu>  
To: Pablo Sanchez <Pablo.Sanchez@UTSouthwestern.edu>

Sent: 3/4/2010 6:16:23 PM

Subject: RE: Boilerplate | SUPPORT

I think we can add this to the galleys - It will not add length to the manuscript

Neil

-----Original Message-----

From: Pablo Sanchez [mailto:Pablo.Sanchez@UTSouthwestern.edu]  
Sent: Thursday, March 04, 2010 2:07 PM  
To: archerst@mail.nih.gov; wcarlo@peds.uab.edu; Finer, Neil  
Cc: higginsr@mail.nih.gov  
Subject: Re: Boilerplate | SUPPORT

Actually, I have been meaning to e-mail you about this-please include her in both-also if not too late, need to add a

couple of others-sorry-pablo  
Pablo -sent from Blackberry  
214-648-3753 (office)  
214-621-(b) (cell)  
972-206-(b) (beeper)

-----Original Message-----

From: "Archer, Stephanie (NIH/NICHD) [E]" <archerst@mail.nih.gov>  
Cc: Rosemary (NIH/NICHD) [E] Higgins <higginsr@mail.nih.gov>  
To: Wally Carlo(wcarlo@peds.uab.edu) <wcarlo@peds.uab.edu>  
To: Neil Finer (nfiner@ucsd.edu) <nfiner@ucsd.edu>  
Cc: Pablo Sanchez <Pablo.Sanchez@UTSouthwestern.edu>

Sent: 3/4/2010 3:42:23 PM  
Subject: RE: Boilerplate | SUPPORT

Hi Wally and Neil,

Were you able to add Diana to the boilerplate in the final versions of the NEJM papers?

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: Archer, Stephanie (NIH/NICHD) [E]  
Sent: Tuesday, February 02, 2010 2:43 PM  
To: Wally Carlo (wcarlo@peds.uab.edu); Neil Finer (nfiner@ucsd.edu)  
Cc: Higgins, Rosemary (NIH/NICHD) [E]; 'Pablo Sanchez (Pablo.Sanchez@UTSouthwestern.edu)'; Archer, Stephanie (NIH/NICHD) [E]  
Subject: Boilerplate | SUPPORT

Hi Wally and Neil,

Pablo would like to add "Diana M Vasil, RNC, NIC" to the list of people in the acknowledgements for UT Southwestern.

When you get the galleys back, I can review the boilerplate information for you.

Thanks,

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

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Sincerely yours,

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

New England Journal of Medicine  
10 Shattuck Street  
Boston, MA 02115  
(617) 734-9800  
Fax: (617) 739-9864  
<http://www.nejm.org>

**From:** [Spong, Catherine \(NIH/NICHD\) \[E\]](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Subject:** RE: New England Journal of Medicine 09-11783.R3  
**Date:** Wednesday, March 03, 2010 2:26:31 PM

---

CONGRATULATIONS!

Catherine Y Spong MD  
Chief, Pregnancy and Perinatology Branch  
Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health  
6100 Executive Blvd, Rm 4B03, MSC 7510  
Bethesda MD 20892 (express mail: Rockville MD 20852)  
Phone 301 435 6894 or 301 496 5575  
Fax 301 496 3790  
email [spongcc@mail.nih.gov](mailto:spongcc@mail.nih.gov)

-----Original Message-----

From: Higgins, Rosemary (NIH/NICHD) [E]  
Sent: Wednesday, March 03, 2010 2:18 PM  
To: Spong, Catherine (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]; Blaisdell, Carol (NIH/NHLBI) [E]; Gail, Dorothy (NIH/NHLBI) [E]  
Subject: FW: New England Journal of Medicine 09-11783.R3

Here's the acceptance for the second paper!!!!

Thanks for all your help

Rose

-----Original Message-----

From: [onbehalfof+editorial+nejm.org@manuscriptcentral.com](mailto:onbehalfof+editorial+nejm.org@manuscriptcentral.com)  
[<mailto:onbehalfof+editorial+nejm.org@manuscriptcentral.com>] On Behalf Of [editorial@nejm.org](mailto:editorial@nejm.org)  
Sent: Wednesday, March 03, 2010 2:09 PM  
To: [nfiner@ucsd.edu](mailto:nfiner@ucsd.edu); [wcarlo@peds.uab.edu](mailto:wcarlo@peds.uab.edu); [michele.walsh@cwru.edu](mailto:michele.walsh@cwru.edu); [wrich@ucsd.edu](mailto:wrich@ucsd.edu); [mgantz@rti.org](mailto:mgantz@rti.org); [alaptook@wihri.org](mailto:alaptook@wihri.org); [Bradley.yoder@hsc.utah.edu](mailto:Bradley.yoder@hsc.utah.edu); [roger.faix@has.utah.edu](mailto:roger.faix@has.utah.edu); [adas@rti.org](mailto:adas@rti.org); [poo@rti.org](mailto:poo@rti.org); [nambalavanan@peds.uab.edu](mailto:nambalavanan@peds.uab.edu); (b) (6); [edward.donovan@cchmc.org](mailto:edward.donovan@cchmc.org); [vivek.narendran@cchmc.org](mailto:vivek.narendran@cchmc.org); [nxs5@cwru.edu](mailto:nxs5@cwru.edu); [ifrantz@tuftsmedicalcenter.org](mailto:ifrantz@tuftsmedicalcenter.org); [Pablo.Sanchez@UTSouthwestern.edu](mailto:Pablo.Sanchez@UTSouthwestern.edu); [susie.buchter@oz.ped.emory.edu](mailto:susie.buchter@oz.ped.emory.edu); (b) (6); [nirupama\\_laroia@urmc.rochester.edu](mailto:nirupama_laroia@urmc.rochester.edu); [bpointex@iupui.edu](mailto:bpointex@iupui.edu); [cotte010@mc.duke.edu](mailto:cotte010@mc.duke.edu); [vanmeurs@leland.stanford.edu](mailto:vanmeurs@leland.stanford.edu); [bsood@med.wayne.edu](mailto:bsood@med.wayne.edu); [sduara@med.miami.edu](mailto:sduara@med.miami.edu); [moshea@wfubmc.edu](mailto:moshea@wfubmc.edu); [edward-bell@uiowa.edu](mailto:edward-bell@uiowa.edu); [vineet.bhandari@yale.edu](mailto:vineet.bhandari@yale.edu); [kwatterberg@salud.unm.edu](mailto:kwatterberg@salud.unm.edu); Higgins, Rosemary (NIH/NICHD) [E]; (b) (6)  
Subject: New England Journal of Medicine 09-11783.R3

Dear Dr. Finer and co-authors,

Thank you for the article, "Early CPAP versus Surfactant in Extremely Preterm Infants," which the Journal is pleased to accept for publication.

This acceptance is made with the understanding that neither the article itself nor any part of its essential substance, tables or figures has been published or will be submitted for publication elsewhere before it appears in the Journal. The acceptance is also made with the understanding that all the authors, the data, and its presentation meet the requirements as described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals ([www.icmje.org](http://www.icmje.org)).

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Sincerely yours,

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New England Journal of Medicine  
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Harvard Medical School

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Boston, MA 02115  
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Fax: (617) 739-9864  
<http://www.nejm.org>

**From:** Fanaroff, Avroy  
**To:** rae2@email.med.yale.edu; Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Luc.Brion@UTSouthwestern.edu; rohls@unm.edu; aaf2@po.cwru.edu; adas@rti.org; alaptook@wihri.org; ambal@uab.edu; Bradley.yoder@hsc.utah.edu; bpoindex@iupui.edu; wcarlo@peds.uab.edu; cotte010@mc.duke.edu; dwallace@rti.org; Edward-bell@uiowa.edu; edward.donovan@cchmc.org; richard.ehrenkranz@yale.edu; ifrantz@tuftsmedicalcenter.org; Kathleen.A.Kennedy@uth.tmc.edu; kwatterberg@salud.unm.edu; kurt.schibler@cchmc.org; matthew.bizzarro@yale.edu; mcw3@po.cwru.edu; mcaplan@northshore.org; william\_oh@brown.edu; Pablo.Sanchez@UTSouthwestern.edu; poo@rti.org; Roger.Faix@hsc.utah.edu; goldb008@mc.duke.edu; sshankar@med.wayne.edu; dstevenson@stanford.edu; barbara\_stoll@oz.ped.emory.edu; Jon.E.Tyson@uth.tmc.edu; vanmeurs@leland.stanford.edu; kzaterka@rti.org  
**Subject:** Re: FW: CONFIDENTIAL New England Journal of Medicine 09-11781.R2  
**Date:** Wednesday, March 03, 2010 4:47:14 PM

---

Congrats  
Another kudos in the Network cap  
Av

----- Original Message -----

From: rae2@email.med.yale.edu <rae2@email.med.yale.edu>  
To: Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov>  
Cc: (Luc.Brion@UTSouthwestern.edu) <Luc.Brion@UTSouthwestern.edu>; (rohls@unm.edu) <rohls@unm.edu>; aaf2@po.cwru.edu <aaf2@po.cwru.edu>; Abhik Das <adas@rti.org>; alaptook@WIHRI.org <alaptook@WIHRI.org>; Ambal (ambal@uab.edu) <ambal@uab.edu>; Brad Yoder (Bradley.yoder@hsc.utah.edu) <Bradley.yoder@hsc.utah.edu>; Brenda Poindexter <bpoindex@iupui.edu>; Carlo Waldemar (E-mail) <wcarlo@peds.uab.edu>; cotte010@mc.duke.edu <cotte010@mc.duke.edu>; Dennis Wallace <dwallace@rti.org>; Ed Bell <Edward-bell@uiowa.edu>; Ed Donovan <edward.donovan@cchmc.org>; Ehrenkranz Richard (E-mail) <richard.ehrenkranz@yale.edu>; Ivan Frantz (ifrantz@tuftsmedicalcenter.org) <ifrantz@tuftsmedicalcenter.org>; Kennedy, Kathleen A <Kathleen.A.Kennedy@uth.tmc.edu>; Kristi Watterberg <kwatterberg@salud.unm.edu>; Kurt Schibler [kurt.schibler@cchmc.org] <kurt.schibler@cchmc.org>; Matthew Bizzarro <matthew.bizzarro@yale.edu>; Michelle Walsh <mcw3@po.cwru.edu>; Mickey Caplan <mcaplan@northshore.org>; Oh William (E-mail) <william\_oh@brown.edu>; Pablo Sanchez <Pablo.Sanchez@UTSouthwestern.edu>; Poole Kenneth (E-mail) <poo@rti.org>; Roger Faix <Roger.Faix@hsc.utah.edu>; Ronald GOLDBERG <goldb008@mc.duke.edu>; Seetha Shankaran <sshankar@med.wayne.edu>; Stevenson David (E-mail) <dstevenson@stanford.edu>; Stoll Barbara (E-mail) <barbara\_stoll@oz.ped.emory.edu>; Tyson Jon (E-mail) <Jon.E.Tyson@uth.tmc.edu>; VanMeurs, Krisa <vanmeurs@leland.stanford.edu>; 'Zaterka-Baxter, Kristin' <kzaterka@rti.org>; 'Cunningham, Meg' <mcunningham@rti.org>; Archer, Stephanie (NIH/NICHD) [E] <archerst@mail.nih.gov>; 'Huitema, Carolyn Petrie' <petrie@rti.org>  
Sent: Wed Mar 03 13:30:48 2010  
Subject: Re: FW: CONFIDENTIAL New England Journal of Medicine 09-11781.R2

Fantastic!!! Congratulations to all!  
Richard

Quoting "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>:

> CONGRATULATIONS!!!!  
> Remember, the embargo policy is quite strict, so keep this in mind.  
>  
> THANKS TO EVERYONE FOR ALL THE HARD WORK!!!  
> ROSE  
>

> -----Original Message-----

> From: onbehalfof+editorial+nejm.org@manuscriptcentral.com  
> [mailto:onbehalfof+editorial+nejm.org@manuscriptcentral.com] On Behalf Of  
> editorial@nejm.org



> Sent: Wednesday, March 03, 2010 12:26 PM  
> To: wcarlo@peds.uab.edu; nfiner@ucsd.edu; michele.walsh@cwru.edu;  
> wrich@ucsd.edu; mgantz@rti.org; alaptook@wihri.org;  
> Bradley.yoder@hsc.utah.edu; roger.faix@hsc.utah.edu; adas@rti.org;  
> poo@rti.org; kurt.schibler@cchmc.org; Nancy.Newman@UHhospitals.org;  
> nambalavanan@peds.uab.edu; (b) (6) ifrantz@tuftsmedicalcenter.org;  
> Pablo.Sanchez@UTSouthwestern.edu; anthony\_piazza@oz.ped.emory.edu;  
> (b) (6) nirupama\_laroia@urmc.rochester.edu;  
> dale\_phelps@urmc.rochester.edu; bpointex@iupui.edu; cotte010@mc.duke.edu;  
> vanmeurs@stanford.edu; sduara@med.miami.edu; vivek.narendran@cchmc.org;  
> bsood@med.wayne.edu; moshea@wfubmc.edu; edward-bell@uiowa.edu;  
> richard.ehrenkranz@yale.edu; kwatterberg@salud.unm.edu; Higgins, Rosemary  
> (NIH/NICHD) [E](b) (6)  
> Subject: New England Journal of Medicine 09-11781.R2

> Dear Dr. Carlo and co-authors,

> Thank you for the article, "A Randomized Trial of Oxygen Saturation Targets  
> in Extremely Preterm Infants," which the Journal is pleased to accept for  
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> published or will be submitted for publication elsewhere before it appears in  
> the Journal. The acceptance is also made with the understanding that all the  
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**From:** Gail, Dorothy (NIH/NHLBI) [E]  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: New England Journal of Medicine 09-11783.R3  
**Date:** Wednesday, March 03, 2010 2:55:28 PM

---

Congratulations Rose. You kept this trial on track and produced a very high quality study. I'll see you in New Orleans! Dorothy

-----Original Message-----

From: Higgins, Rosemary (NIH/NICHD) [E]  
Sent: Wednesday, March 03, 2010 2:18 PM  
To: Spong, Catherine (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]; Blaisdell, Carol (NIH/NHLBI) [E]; Gail, Dorothy (NIH/NHLBI) [E]  
Subject: FW: New England Journal of Medicine 09-11783.R3

Here's the acceptance for the second paper!!!!

Thanks for all your help

Rose

-----Original Message-----

From: onbehalfof+editorial+nejm.org@manuscriptcentral.com  
[mailto:onbehalfof+editorial+nejm.org@manuscriptcentral.com] On Behalf Of editorial@nejm.org  
Sent: Wednesday, March 03, 2010 2:09 PM  
To: nfiner@ucsd.edu; wcarlo@peds.uab.edu; michele.walsh@cwru.edu; wrich@ucsd.edu; mgantz@rti.org; alaptook@wihri.org; Bradley.yoder@hsc.utah.edu; roger.faix@has.utah.edu; adas@rti.org; poo@rti.org; nambalavanan@peds.uab.edu; (b) (6) edward.donovan@cchmc.org; vivek.narendran@cchmc.org; nxs5@cwru.edu; ifrantz@tuftsmedicalcenter.org; Pablo.Sanchez@UTSouthwestern.edu; susie.buchter@oz.ped.emory.edu; (b) (6) nirupama\_laroia@urmc.rochester.edu; bpointex@iupui.edu; cotte010@mc.duke.edu; vanmeurs@leland.stanford.edu; bsood@med.wayne.edu; sduara@med.miami.edu; moshea@wfubmc.edu; edward-bell@uiowa.edu; vineet.bhandari@yale.edu; kwatterberg@salud.unm.edu; Higgins, Rosemary (NIH/NICHD) [E]; (b) (6)  
Subject: New England Journal of Medicine 09-11783.R3

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**From:** [Blaisdell, Carol \(NIH/NHLBI\) \[E\]](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Spong, Catherine \(NIH/NICHD\) \[E\]](#); [Bock, Robert \(NIH/NICHD\) \[E\]](#); [Gail, Dorothy \(NIH/NHLBI\) \[E\]](#)  
**Subject:** RE: New England Journal of Medicine 09-11783.R3  
**Date:** Wednesday, March 03, 2010 2:44:10 PM

---

Fabulous!!

Carol  
(301) 435-0222 phone

-----Original Message-----

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Wednesday, March 03, 2010 2:18 PM  
**To:** Spong, Catherine (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]; Blaisdell, Carol (NIH/NHLBI) [E]; Gail, Dorothy (NIH/NHLBI) [E]  
**Subject:** FW: New England Journal of Medicine 09-11783.R3

Here's the acceptance for the second paper!!!!

Thanks for all your help

Rose

-----Original Message-----

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**Sent:** Wednesday, March 03, 2010 2:09 PM  
**To:** [nfiner@ucsd.edu](mailto:nfiner@ucsd.edu); [wcarlo@peds.uab.edu](mailto:wcarlo@peds.uab.edu); [michele.walsh@cwru.edu](mailto:michele.walsh@cwru.edu); [wrich@ucsd.edu](mailto:wrich@ucsd.edu); [mgantz@rti.org](mailto:mgantz@rti.org); [alaptook@wihri.org](mailto:alaptook@wihri.org); [Bradley.yoder@hsc.utah.edu](mailto:Bradley.yoder@hsc.utah.edu); [roger.faix@has.utah.edu](mailto:roger.faix@has.utah.edu); [adas@rti.org](mailto:adas@rti.org); [poo@rti.org](mailto:poo@rti.org); [nambalavanan@peds.uab.edu](mailto:nambalavanan@peds.uab.edu); (b) (6); [edward.donovan@cchmc.org](mailto:edward.donovan@cchmc.org); [vivek.narendran@cchmc.org](mailto:vivek.narendran@cchmc.org); [nxs5@cwru.edu](mailto:nxs5@cwru.edu); [ifrantz@tuftsmedicalcenter.org](mailto:ifrantz@tuftsmedicalcenter.org); [Pablo.Sanchez@UTSouthwestern.edu](mailto:Pablo.Sanchez@UTSouthwestern.edu); [susie.buchter@oz.ped.emory.edu](mailto:susie.buchter@oz.ped.emory.edu); (b) (6); [nirupama\\_laroya@urmc.rochester.edu](mailto:nirupama_laroya@urmc.rochester.edu); [bpointex@iupui.edu](mailto:bpointex@iupui.edu); [cotte010@mc.duke.edu](mailto:cotte010@mc.duke.edu); [vanmeurs@leland.stanford.edu](mailto:vanmeurs@leland.stanford.edu); [bsood@med.wayne.edu](mailto:bsood@med.wayne.edu); [sduara@med.miami.edu](mailto:sduara@med.miami.edu); [moshea@wfubmc.edu](mailto:moshea@wfubmc.edu); [edward-bell@uiowa.edu](mailto:edward-bell@uiowa.edu); [vineet.bhandari@yale.edu](mailto:vineet.bhandari@yale.edu); [kwatterberg@salud.unm.edu](mailto:kwatterberg@salud.unm.edu); Higgins, Rosemary (NIH/NICHD) [E]; (b) (6)  
**Subject:** New England Journal of Medicine 09-11783.R3

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Fax: (617) 739-9864  
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**From:** Bock, Robert (NIH/NICHD) [E]  
**To:** Blaisdell, Carol (NIH/NHLBI) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Gail, Dorothy (NIH/NHLBI) [E]  
**Subject:** RE: New England Journal of Medicine 09-11781.R2  
**Date:** Wednesday, March 03, 2010 2:16:42 PM

---

Surely. I've worked with Susan many times in the past and would be more than happy to work with her again.

-----Original Message-----

**From:** Blaisdell, Carol (NIH/NHLBI) [E]  
**Sent:** Wednesday, March 03, 2010 2:02 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]; Gail, Dorothy (NIH/NHLBI) [E]  
**Subject:** RE: New England Journal of Medicine 09-11781.R2

Congratulations Rose.

A lot of hard work went into this trial with you at the reins!

If a press release is considered, please be sure Robert Bock works with our media office at NHLBI, Susan Dambrasukas. As we talked about if the NEJM publication date is around the PAS meeting it would be great to coordinate a press release at that time, maintaining the embargo as NEJM requires.

Carol

Carol J. Blaisdell, M.D.  
Medical Officer  
Lung Developmental Biology and  
Pediatric Pulmonary Diseases  
Division of Lung Diseases, NHLBI/NIH  
(301) 435-0222 phone

-----Original Message-----

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Wednesday, March 03, 2010 12:38 PM  
**To:** Spong, Catherine (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]; Blaisdell, Carol (NIH/NHLBI) [E]; Gail, Dorothy (NIH/NHLBI) [E]  
**Subject:** FW: New England Journal of Medicine 09-11781.R2  
**Importance:** High

Here is one of the SUPPORT papers - accepted!!!!

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**To:** wcarlo@peds.uab.edu; nfiner@ucsd.edu; michele.walsh@cwru.edu; wrich@ucsd.edu; mgantz@rti.org; alaptook@wihri.org; Bradley.yoder@hsc.utah.edu; roger.faix@hsc.utah.edu; adas@rti.org; poo@rti.org; kurt.schibler@cchmc.org; Nancy.Newman@UHHospitals.org; nambalavanan@peds.uab.edu; a(b) (6) ifrantz@tuftsmedicalcenter.org; Pablo.Sanchez@UTSouthwestern.edu; anthony\_piazza@oz.ped.emory.edu; (b) (6) nirupama\_laroia@urmc.rochester.edu; dale\_phelps@urmc.rochester.edu; bpointex@iupui.edu; cotte010@mc.duke.edu; vanmeurs@stanford.edu; sduara@med.miami.edu; vivek.narendran@cchmc.org; bsood@med.wayne.edu; moshea@wfubmc.edu; edward-bell@uiowa.edu; richard.ehrenkranz@yale.edu; kwatterberg@salud.unm.edu; Higgins, Rosemary (NIH/NICHD) [E]; (b) (6)  
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**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Finer, Neil"; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; "Abhik Das"; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); "Brenda Poindexter"; "Carlo Waldemar (E-mail)"; cotte010@mc.duke.edu; "Dennis Wallace"; "Ed Bell"; "Ed Donovan"; "Ehrenkranz Richard (E-mail)"; Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; "Kristi Watterberg"; Kurt Schibler (kurt.schibler@cchmc.org); "Matthew Bizzarro"; "Michelle Walsh"; "Mickey Caplan"; "Oh William (E-mail)"; "Pablo Sanchez"; "Poole Kenneth (E-mail)"; "Roger Faix"; "Ronald Goldberg"; "Seetha Shankaran"; "Stevenson David (E-mail)"; "Stoll Barbara (E-mail)"; "Tyson Jon (E-mail)"; VanMeurs, Krisa  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; "Zaterka-Baxter, Kristin"; "Cunningham, Meg"; "Dennis Wallace"; "Huitema, Carolyn Petrie"  
**Subject:** FW: New England Journal of Medicine 09-11783.R3  
**Date:** Wednesday, March 03, 2010 2:16:00 PM  
**Attachments:** FinerSUPPORTFinal.doc  
Embargo-Guidelines-11-07.pdf

---

CONGRATULATIONS!!!!

Remember, the embargo policy is quite strict, so keep this in mind.

THANKS TO EVERYONE FOR ALL THE HARD WORK!!!

ROSE

-----Original Message-----

From: onbehalfof+editorial+nejm.org@manuscriptcentral.com

[mailto:onbehalfof+editorial+nejm.org@manuscriptcentral.com] On Behalf Of editorial@nejm.org

Sent: Wednesday, March 03, 2010 2:09 PM

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Subject: New England Journal of Medicine 09-11783.R3

Dear Dr. Finer and co-authors,

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Editor-in-Chief  
New England Journal of Medicine  
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Harvard Medical School

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**From:** [Spong, Catherine \(NIH/NICHD\) \[E\]](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Bock, Robert \(NIH/NICHD\) \[E\]](#); [Blaisdell, Carol \(NIH/NHLBI\) \[E\]](#); [Gail, Dorothy \(NIH/NHLBI\) \[E\]](#)  
**Subject:** RE: New England Journal of Medicine 09-11781.R2  
**Date:** Wednesday, March 03, 2010 2:13:30 PM

---

CONGRATULATIONS!

Catherine Y Spong MD  
Chief, Pregnancy and Perinatology Branch  
Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health  
6100 Executive Blvd, Rm 4B03, MSC 7510  
Bethesda MD 20892 (express mail: Rockville MD 20852)  
Phone 301 435 6894 or 301 496 5575  
Fax 301 496 3790  
email [spongca@mail.nih.gov](mailto:spongca@mail.nih.gov)

-----Original Message-----

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Wednesday, March 03, 2010 12:38 PM  
**To:** Spong, Catherine (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]; Blaisdell, Carol (NIH/NHLBI) [E]; Gail, Dorothy (NIH/NHLBI) [E]  
**Subject:** FW: New England Journal of Medicine 09-11781.R2  
**Importance:** High

Here is one of the SUPPORT papers - accepted!!!!

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**Sent:** Wednesday, March 03, 2010 12:26 PM  
**To:** [wcarlo@peds.uab.edu](mailto:wcarlo@peds.uab.edu); [nfiner@ucsd.edu](mailto:nfiner@ucsd.edu); [michele.walsh@cwru.edu](mailto:michele.walsh@cwru.edu); [wrich@ucsd.edu](mailto:wrich@ucsd.edu); [mgantz@rti.org](mailto:mgantz@rti.org); [alaptook@wihri.org](mailto:alaptook@wihri.org); [Bradley.yoder@hsc.utah.edu](mailto:Bradley.yoder@hsc.utah.edu); [roger.faix@hsc.utah.edu](mailto:roger.faix@hsc.utah.edu); [adas@rti.org](mailto:adas@rti.org); [poo@rti.org](mailto:poo@rti.org); [kurt.schibler@cchmc.org](mailto:kurt.schibler@cchmc.org); [Nancy.Newman@UHhospitals.org](mailto:Nancy.Newman@UHhospitals.org); [nambalavanan@peds.uab.edu](mailto:nambalavanan@peds.uab.edu); (b) (6); [ifrantz@tuftsmedicalcenter.org](mailto:ifrantz@tuftsmedicalcenter.org); [Pablo.Sanchez@UTSouthwestern.edu](mailto:Pablo.Sanchez@UTSouthwestern.edu); [anthony\\_piazza@oz.ped.emory.edu](mailto:anthony_piazza@oz.ped.emory.edu); (b) (6); [nirupama\\_laroia@urmc.rochester.edu](mailto:nirupama_laroia@urmc.rochester.edu); [dale\\_phelps@urmc.rochester.edu](mailto:dale_phelps@urmc.rochester.edu); [bpoindex@iupui.edu](mailto:bpoindex@iupui.edu); [cotte010@mc.duke.edu](mailto:cotte010@mc.duke.edu); [vanmeurs@stanford.edu](mailto:vanmeurs@stanford.edu); [sduara@med.miami.edu](mailto:sduara@med.miami.edu); [vivek.narendran@cchmc.org](mailto:vivek.narendran@cchmc.org); [bsood@med.wayne.edu](mailto:bsood@med.wayne.edu); [moshea@wfubmc.edu](mailto:moshea@wfubmc.edu); [edward-bell@uiowa.edu](mailto:edward-bell@uiowa.edu); [richard.ehrenkranz@yale.edu](mailto:richard.ehrenkranz@yale.edu); [kwatterberg@salud.unm.edu](mailto:kwatterberg@salud.unm.edu); Higgins, Rosemary (NIH/NICHD) [E]; (b) (6)  
**Subject:** New England Journal of Medicine 09-11781.R2

Dear Dr. Carlo and co-authors,

Thank you for the article, "A Randomized Trial of Oxygen Saturation Targets in Extremely Preterm Infants," which the Journal is pleased to accept for publication.

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**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Spong, Catherine (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]; Blaisdell, Carol (NIH/NHLBI) [E]; Gail, Dorothy (NIH/NHLBI) [E]  
**Subject:** FW: New England Journal of Medicine 09-11783.R3  
**Date:** Wednesday, March 03, 2010 2:17:00 PM  
**Attachments:** FinerSUPPORTFinal.doc  
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---

Here's the acceptance for the second paper!!!!

Thanks for all your help

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**From:** [Pablo Sanchez](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Subject:** Re: Breathing Outcomes - prelim data request  
**Date:** Wednesday, March 03, 2010 4:53:39 PM

---

I don't think that I voted---just saw your e-mail..but I agreed with many of the comments that we should not provide data for an ongoing study that data collection is ongoing and remains blinded (at least in part)...pablo

>>> "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> 2/16/10 3:43 PM >>>

Hi,

Tim Stevens is preparing a revision to his school age breathing outcomes study protocol and would like the following information from the school age SUPPORT trial for the 6 and 12 month visits.

Pease let me know by February 23 if the data can be given at this time. Some of the infants have not yet completed the 12 month assessment.

Thanks

Rose



**From:** onbehalfof+editorial+nejm.org@manuscriptcentral.com on behalf of editorial@nejm.org  
**To:** nfiner@ucsd.edu; wcarlo@peds.uab.edu; michele.walsh@cwru.edu; wrich@ucsd.edu; mgantz@rti.org; alaptook@wihri.org; Bradley.yoder@hsc.utah.edu; roger.faix@has.utah.edu; adas@rti.org; poo@rti.org; nambalayanan@peds.uab.edu; (b) (6) edward.donovan@cchmc.org; vivek.narendran@cchmc.org; nxs5@cwru.edu; ifrantz@tuftsmedicalcenter.org; Pablo.Sanchez@UTSouthwestern.edu; susie.buchter@oz.ped.emory.edu; (b) (6) nirupama\_larola@umc.rochester.edu; bpoindex@iupui.edu; cotte010@mc.duke.edu; vanmeurs@leland.stanford.edu; bsood@med.wayne.edu; sduara@med.miami.edu; moshea@wfubmc.edu; edward-bell@uiowa.edu; vineet.bhandari@yale.edu; kwatterberg@salud.unm.edu; Higgins, Rosemary (NIH/NICHD) [E]; (b) (6)  
**Subject:** New England Journal of Medicine 09-11783.R3  
**Date:** Wednesday, March 03, 2010 2:09:23 PM  
**Attachments:** FinerSUPPORTFinal.doc  
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**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Subject:** RE: New England Journal of Medicine 09-11781.R2  
**Date:** Wednesday, March 03, 2010 12:49:00 PM

---

Up to you, I am fine by phone.

-----Original Message-----

From: Bock, Robert (NIH/NICHD) [E]  
Sent: Wednesday, March 03, 2010 12:49 PM  
To: Higgins, Rosemary (NIH/NICHD) [E]  
Subject: RE: New England Journal of Medicine 09-11781.R2

OK. Do we need to meet on the second paper, or should we just discuss it on the phone?

-----Original Message-----

From: Higgins, Rosemary (NIH/NICHD) [E]  
Sent: Wednesday, March 03, 2010 12:48 PM  
To: Bock, Robert (NIH/NICHD) [E]  
Subject: RE: New England Journal of Medicine 09-11781.R2

NO - (b) (5)

-----Original Message-----

From: Bock, Robert (NIH/NICHD) [E]  
Sent: Wednesday, March 03, 2010 12:46 PM  
To: Higgins, Rosemary (NIH/NICHD) [E]  
Subject: RE: New England Journal of Medicine 09-11781.R2

It would seem that (b) (5)

(b)

Do we need to meet on the second paper, or should we just discuss it on the phone?

-----Original Message-----

From: Higgins, Rosemary (NIH/NICHD) [E]  
Sent: Wednesday, March 03, 2010 12:43 PM  
To: Bock, Robert (NIH/NICHD) [E]  
Subject: RE: New England Journal of Medicine 09-11781.R2

No, (b) (5)

We should hear about the second paper within the next day or two. DO you think we should meet to discuss??

-----Original Message-----

From: Bock, Robert (NIH/NICHD) [E]  
Sent: Wednesday, March 03, 2010 12:42 PM  
To: Higgins, Rosemary (NIH/NICHD) [E]  
Subject: RE: New England Journal of Medicine 09-11781.R2

Thanks. Could you have (b) (5)

-----Original Message-----

From: Higgins, Rosemary (NIH/NICHD) [E]  
Sent: Wednesday, March 03, 2010 12:38 PM  
To: Spong, Catherine (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]; Blaisdell, Carol (NIH/NHLBI) [E]; Gail, Dorothy (NIH/NHLBI) [E]  
Subject: FW: New England Journal of Medicine 09-11781.R2  
Importance: High

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Sent: Wednesday, March 03, 2010 12:26 PM  
To: wcarlo@peds.uab.edu; nfiner@ucsd.edu; michele.walsh@cwru.edu; wrich@ucsd.edu; mgantz@rti.org; alaptook@wihri.org; Bradley.yoder@hsc.utah.edu; roger.faix@hsc.utah.edu; adas@rti.org; poo@rti.org; kurt.schibler@cchmc.org; Nancy.Newman@UHhospitals.org; nambalavanan@peds.uab.edu; (b) (6); ifrantz@tuftsmedicalcenter.org; Pablo.Sanchez@UTSouthwestern.edu; anthony\_piazza@oz.ped.emory.edu; (b) (6); nirupama\_laroya@urmc.rochester.edu; dale\_phelps@urmc.rochester.edu; bpoindex@iupui.edu; cotte010@mc.duke.edu; vanmeurs@stanford.edu; sduara@med.miami.edu; vivek.narendran@cchmc.org; bsood@med.wayne.edu; moshea@wfubmc.edu; edward-bell@uiowa.edu; richard.ehrenkranz@yale.edu; kwatterberg@salud.unm.edu; Higgins, Rosemary (NIH/NICHD) [E]; (b) (6)  
Subject: New England Journal of Medicine 09-11781.R2

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Sincerely yours,

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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<http://www.nejm.org>

**From:** Evans, Patricia W  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Kennedy, Kathleen A  
**Subject:** FW: SUPPORT FU  
**Date:** Wednesday, March 03, 2010 12:39:02 PM

---

We are going to try some additional incentives with Pt (b) Will let you know.

Patricia Wilder Evans, MD  
Assistant Professor of Pediatrics, Division of Neonatology  
The University of Texas Medical School at Houston  
713.500.5311 Office  
713.500.5794 Fax  
Patricia.W.Evans@uth.tmc.edu

---

**From:** Poundstone, Margaret  
**Sent:** Tuesday, March 02, 2010 3:58 PM  
**To:** Evans, Patricia W  
**Subject:** RE: SUPPORT FU

Pt (b) is a year out of her window. Do I still continue to pursue her? Why can't people just be compliant?  
Pt (b) is coming tomorrow.

---

**From:** Evans, Patricia W  
**Sent:** Monday, February 22, 2010 10:47 AM  
**To:** Poundstone, Margaret  
**Subject:** FW: SUPPORT FU  
**Importance:** High

Happy Monday!

Patricia W. Evans, MD  
Assistant Professor of Pediatrics, Division of Neonatology  
The University of Texas Medical School at Houston  
713-500-5311 (office)  
713-500-5794 (fax)  
Patricia.W.Evans@uth.tmc.edu (e-mail)

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Monday, February 22, 2010 9:23 AM  
**To:** Kennedy, Kathleen A; Evans, Patricia W; Mcdavid, Georgia E  
**Cc:** Gantz, Marie  
**Subject:** SUPPORT FU  
**Importance:** High

Hi,  
We are missing the following primary outcomes for the SUPPORT FU study. Let us know how you are doing.

Thanks for all the effort!!

Rose

CENTER	NETWORK	FU_message
18	(b)	FU window has closed but NF05 and NF09a have not been completed.
18	(b)	FU window has closed but NF05 and NF09a have not been completed.

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network  
Pregnancy and Perinatology Branch

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Bethesda, MD 20892  
For overnight delivery use Rockville, MD 20852  
301-496-5575  
301-496-3790 (FAX)  
higginsr@mail.nih.gov



**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Spong, Catherine (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]; Blaisdell, Carol (NIH/NHLBI) [E]; Gail, Dorothy (NIH/NHLBI) [E]  
**Subject:** FW: New England Journal of Medicine 09-11781.R2  
**Date:** Wednesday, March 03, 2010 12:37:00 PM  
**Attachments:** CarloSUPPORTFINAL.doc  
Embargo-Guidelines-11-07.pdf  
**Importance:** High

---

Here is one of the SUPPORT papers - accepted!!!!

-----Original Message-----

From: onbehalfof+editorial+nejm.org@manuscriptcentral.com  
[mailto:onbehalfof+editorial+nejm.org@manuscriptcentral.com] On Behalf Of editorial@nejm.org  
Sent: Wednesday, March 03, 2010 12:26 PM  
To: wcarlo@peds.uab.edu; nfiner@ucsd.edu; michele.walsh@cwru.edu; wrich@ucsd.edu; mgantz@rti.org; alaptook@wihri.org; Bradley.yoder@hsc.utah.edu; roger.faix@hsc.utah.edu; adas@rti.org; poo@rti.org; kurt.schibler@cchmc.org; Nancy.Newman@UHhospitals.org; nambalavanan@peds.uab.edu; (b) (6) ifrantz@tuftsmedicalcenter.org; Pablo.Sanchez@UTSouthwestern.edu; anthony\_piazza@oz.ped.emory.edu; (b) (6); nirupama\_laroia@urmc.rochester.edu; dale\_phelps@urmc.rochester.edu; bpoindex@iupui.edu; cotte010@mc.duke.edu; vanmeurs@stanford.edu; sduara@med.miami.edu; vivek.narendran@cchmc.org; bsood@med.wayne.edu; moshea@wfubmc.edu; edward-bell@uiowa.edu; richard.ehrenkranz@yale.edu; kwatterberg@salud.unm.edu; Higgins, Rosemary (NIH/NICHD) [E]; (b) (6)  
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will be your next opportunity to make changes. In the meantime, please do not make any changes or send any new material to us. Once the manuscript is in press, changes become increasingly difficult and should be limited to the correction of errors. Thank you for your contribution to the Journal.

Sincerely yours,

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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Email: mediasupport@nejm.org

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; "Abhik Das"; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); "Brenda Poindexter"; "Carlo Waldemar (E-mail)"; cotte010@mc.duke.edu; "Dennis Wallace"; "Ed Bell"; "Ed Donovan"; "Ehrenkranz Richard (E-mail)"; Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; "Kristi Watterberg"; Kurt Schibler [kurt.schibler@cchmc.org]; "Matthew Bizzarro"; "Michelle Walsh"; "Mickey Caplan"; "Oh William (E-mail)"; "Pablo Sanchez"; "Poole Kenneth (E-mail)"; "Roger Faix"; "Ronald GOLDBERG"; "Seetha Shankaran"; "Stevenson David (E-mail)"; "Stoll Barbara (E-mail)"; "Tyson Jon (E-mail)"; VanMeurs, Krisa  
**Cc:** "Zaterka-Baxter, Kristin"; "Cunningham, Meg"; Archer, Stephanie (NIH/NICHD) [E]; "Huitema, Carolyn Petrie"; "Dennis Wallace"  
**Subject:** FW: CONFIDENTIAL New England Journal of Medicine 09-11781.R2  
**Date:** Wednesday, March 03, 2010 12:36:00 PM  
**Attachments:** CarloSUPPORTFINAL.doc  
Embargo-Guidelines-11-07.pdf  
**Importance:** High

---

CONGRATULATIONS!!!!

Remember, the embargo policy is quite strict, so keep this in mind.

THANKS TO EVERYONE FOR ALL THE HARD WORK!!!

ROSE

-----Original Message-----

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Sent: Wednesday, March 03, 2010 12:26 PM

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**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Laptook, Abbot"  
**Subject:** RE: \*\*\*\*\* Important -Follow Up ON BPD and Oximeters\*\*\*\*\*  
**Date:** Tuesday, March 02, 2010 3:12:00 PM

---

Abbot  
No problem.  
Rose

---

**From:** Laptook, Abbot [mailto:ALaptook@WIHRI.org]  
**Sent:** Tuesday, March 02, 2010 3:12 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** Re: \*\*\*\*\* Important -Follow Up ON BPD and Oximeters\*\*\*\*\*

I will be traveling and unable to be on a call. AL

Sent from my iPhone

On Mar 2, 2010, at 10:11 AM, "Higgins, Rosemary (NIH/NICHD) [E]"  
<[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)> wrote:

**I would like to have a brief call this afternoon to discuss with the subcommittee.**

**Let me know if you could join a call sometime between 330-5 PM TODAY, let me know ASAP.**

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Monday, March 01, 2010 11:00 AM  
**To:** 'Wally Carlo, M.D.'; 'Finer, Neil'; [alaptook@WIHRI.org](mailto:alaptook@WIHRI.org); [Roger.Faix@hsc.utah.edu](mailto:Roger.Faix@hsc.utah.edu); Bradley Yoder; [kurt.schibler@cchmc.org](mailto:kurt.schibler@cchmc.org); [adas@rti.org](mailto:adas@rti.org); nancy newman; Rich, Wade; Gantz, Marie; [mcw3@case.edu](mailto:mcw3@case.edu); Dennis Wallace  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin  
**Subject:** \*\*\*\*\* Important -Follow Up ON BPD and Oximeters\*\*\*\*\*  
**Importance:** High

To the SUPPORT Subcommittee

Given the email exchange, the subcommittee will need to ascertain whether or not to indicate in the SUPPORT papers whether or not a bias could have existed in reporting the secondary outcome of BPD based on oximeter. Previously the subcommittee had reviewed the oximeter use on a conference call and decided to defer this to a secondary paper. There

has been discussion on the SC call and via email subsequently.

**Therefore, please send me a yes/no vote to include this in the paper by March 2.**

Thanks  
Rose

---

**From:** Tyson, Jon E [mailto:Jon.E.Tyson@uth.tmc.edu]

**Sent:** Friday, February 26, 2010 6:28 PM

**To:** Wallace, Dennis; Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; Stevenson David (E-mail); Finer, Neil; Rich, Wade; Gantz, Marie

**Cc:** Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]

**Subject:** RE: Follow Up ON BPD and Oximeters

I don't understand your statement "Controlling for center adjusts for differences between centers including differences in the BPD oximeter used." To simplify the discussion, suppose every center always used the study oximeter in designating who had BPD by oxygen saturation. Because the true saturation that would prompt oxygen administration would differ in the two treatment groups, there would be systematic bias toward administering oxygen to more infants in the high sat group than in the low sat group. This is inherent in the study design. Whatever differences there were between centers, this bias would occur in every center and would not be eliminated by controlling for center. And if I understand the analysis, there would be no interaction between treatment oximeter and BPD oximeter because they would be the same in every baby in every center.

You indicate that 5 centers used the study oximeter in almost every baby. In saying "it's not possible to tease out the effect of the BPD oximeter from other between-center differences" (a statement that I certainly accept), aren't you saying that the effect of the study oximeter on the difference in the incidence of BPD by oxygen administration between high and low sat groups (i.e., the bias) can not be distinguished from the effect of the myriad of other factors in those centers that might affect that difference in incidence? If so, why would you expect to be able to discern that bias (the signal) from all the noise resulting from other factors? I understand from what you said that the same approach was used in virtually all infants in each center which makes the effective n to be based on the number of centers rather than the number of babies. As I understand the analysis, the power to assess an interaction would then be quite low.

The issue here is whether is simply whether to report somewhere in the paper (which could be noted under the table and wouldn't increase the word count for the text) a bias in evaluating a secondary outcome. This can be done with no delay in submitting the manuscript or waiting for Maria to return. *If we had other real or potential sources of bias—say, a breaking of the blind for some infants, open label administration of a study drug to the control group, or differential loss to follow-up, we would certainly report it as a matter of course, whether or not there*



*was a significant or near significant difference in the outcome and without testing and whether or not we assessed or found any interaction or other statistical evidence that this potential source of bias affected the results!*

Jon E. Tyson, MD, MPH  
Center for Clinical Research & Evidence-Based Medicine  
UT Medical School at Houston  
6431 Fannin St., MSB 2.106  
Houston, TX 77030  
voice 713-500-5651  
fax 713-500-0519

---

**From:** Wallace, Dennis [<mailto:dwallace@rti.org>]  
**Sent:** Friday, February 26, 2010 1:56 PM  
**To:** Wallace, Dennis; Tyson, Jon E; Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara; [alaptook@WIHRI.org](mailto:alaptook@WIHRI.org); Bell, Edward; [bpointindex@iupui.edu](mailto:bpointindex@iupui.edu); Das, Abhik; [goldb008@mc.duke.edu](mailto:goldb008@mc.duke.edu); [ifrantz@tuftsmedicalcenter.org](mailto:ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; [kurt.schibler@cchmc.org](mailto:kurt.schibler@cchmc.org); [kwatterberg@salud.unm.edu](mailto:kwatterberg@salud.unm.edu); [matthew.bizzarro@yale.edu](mailto:matthew.bizzarro@yale.edu); [mcw3@cwru.edu](mailto:mcw3@cwru.edu); [mcaplan@northshore.org](mailto:mcaplan@northshore.org); [Pablo.Sanchez@UTSouthwestern.edu](mailto:Pablo.Sanchez@UTSouthwestern.edu); [richard.ehrenkranz@yale.edu](mailto:richard.ehrenkranz@yale.edu); [Roger.Faix@hsc.utah.edu](mailto:Roger.Faix@hsc.utah.edu); [sshankar@med.wayne.edu](mailto:sshankar@med.wayne.edu); [vanmeurs@leland.stanford.edu](mailto:vanmeurs@leland.stanford.edu); Wally Carlo, M.D.; [cotte010@mc.duke.edu](mailto:cotte010@mc.duke.edu); Bradley Yoder; [rohls@salud.unm.edu](mailto:rohls@salud.unm.edu); [Luc.Brion@utsouthwestern.edu](mailto:Luc.Brion@utsouthwestern.edu); Stevenson David (E-mail); Finer, Neil; Rich, Wade; Gantz, Marie  
**Cc:** Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: Follow Up ON BPD and Oximeters

Hello all,

I accidentally hit the send button before finishing editing this response so ignore the earlier e-mail and see the response below.

Dennis

Dennis Wallace  
Senior Research Statistician  
Cox 241  
RTI International  
3040 Cornwallis Rd  
Research Triangle Park, NC 27709-2104  
Voice: 919-541-6271  
Fax: 919-541-6416

---

**From:** Wallace, Dennis  
**Sent:** Friday, February 26, 2010 2:53 PM  
**To:** 'Tyson, Jon E'; Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara; [alaptook@WIHRI.org](mailto:alaptook@WIHRI.org); Bell, Edward; [bpointindex@iupui.edu](mailto:bpointindex@iupui.edu); Das, Abhik; [goldb008@mc.duke.edu](mailto:goldb008@mc.duke.edu); [ifrantz@tuftsmedicalcenter.org](mailto:ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; [kurt.schibler@cchmc.org](mailto:kurt.schibler@cchmc.org); [kwatterberg@salud.unm.edu](mailto:kwatterberg@salud.unm.edu); [matthew.bizzarro@yale.edu](mailto:matthew.bizzarro@yale.edu); [mcw3@cwru.edu](mailto:mcw3@cwru.edu); [mcaplan@northshore.org](mailto:mcaplan@northshore.org); [Pablo.Sanchez@UTSouthwestern.edu](mailto:Pablo.Sanchez@UTSouthwestern.edu); [richard.ehrenkranz@yale.edu](mailto:richard.ehrenkranz@yale.edu); [Roger.Faix@hsc.utah.edu](mailto:Roger.Faix@hsc.utah.edu); [sshankar@med.wayne.edu](mailto:sshankar@med.wayne.edu); [vanmeurs@leland.stanford.edu](mailto:vanmeurs@leland.stanford.edu); Wally Carlo, M.D.; [cotte010@mc.duke.edu](mailto:cotte010@mc.duke.edu); Bradley Yoder; [rohls@salud.unm.edu](mailto:rohls@salud.unm.edu); [Luc.Brion@utsouthwestern.edu](mailto:Luc.Brion@utsouthwestern.edu); 'Stevenson David (E-mail)'; 'Finer, Neil'; Rich, Wade; Gantz, Marie  
**Cc:** Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: Follow Up ON BPD and Oximeters

Jon,

Marie flew out on a long-scheduled vacation after completing these analyses late Tuesday evening and has very limited e-mail and cell phone access. However, she has taken time to provide a preliminary response that I've outlined below with some added thoughts of my own in red font below. Based on these responses, I do believe that the critical concerns about bias have been addressed sufficiently for this initial manuscript, but if you think we need to have a more full discussion, we can talk after Marie returns next week. Because the programming for these outcome measures is relatively complicated, I'm hesitant to try to do any additional analyses prior to her return. However, as I indicated above, I don't think that we need to delay any submissions while trying to iron on the small details.

Dennis Wallace

Senior Research Statistician

Cox 241

RTI International

3040 Cornwallis Rd

Research Triangle Park, NC 27709-2104

Voice: 919-541-6271

Fax: 919-541-6416

-----Original Message-----

From: Tyson, Jon E [mailto:Jon.E.Tyson@uth.tmc.edu]  
Sent: Thursday, February 25, 2010 12:45 AM  
To: Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara; [alaptook@WIHRI.org](mailto:alaptook@WIHRI.org); Bell, Edward; [bpoindex@iupui.edu](mailto:bpoindex@iupui.edu); Das, Abhik; [goldb008@mc.duke.edu](mailto:goldb008@mc.duke.edu); [ifrantz@tuftsmedicalcenter.org](mailto:ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; [kurt.schibler@cchmc.org](mailto:kurt.schibler@cchmc.org); [kwatterberg@salud.unm.edu](mailto:kwatterberg@salud.unm.edu); [matthew.bizzarro@yale.edu](mailto:matthew.bizzarro@yale.edu); [mcw3@cwru.edu](mailto:mcw3@cwru.edu); [mcaplan@northshore.org](mailto:mcaplan@northshore.org); [Pablo.Sanchez@UTSouthwestern.edu](mailto:Pablo.Sanchez@UTSouthwestern.edu); [richard.ehrenkranz@yale.edu](mailto:richard.ehrenkranz@yale.edu); [Roger.Faix@hsc.utah.edu](mailto:Roger.Faix@hsc.utah.edu); [sshankar@med.wayne.edu](mailto:sshankar@med.wayne.edu); [vanmeurs@leland.stanford.edu](mailto:vanmeurs@leland.stanford.edu); Wally Carlo, M.D.; Wallace, Dennis; [cotte010@mc.duke.edu](mailto:cotte010@mc.duke.edu); Bradley Yoder; [rohls@salud.unm.edu](mailto:rohls@salud.unm.edu); [Luc.Brion@utsouthwestern.edu](mailto:Luc.Brion@utsouthwestern.edu); 'Stevenson David (E-mail)'; 'Finer, Neil'; Rich, Wade; Gantz, Marie  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]  
Subject: RE: Follow Up ON BPD and Oximeters

Rose, before we can understand and interpret this information noted in the mail, we really need to know more about what was done and answers to questions like those below:

1. Which trial result was addressed - whether the evaluation of BPD was biased in the analyses of CPAP/limited ventilation

vs. surfactant/conventional ventilation arm (not the analysis for which there is concern) or the analyses of the high vs. low oxygen saturation goal.

Although models were run for the different arms of the factorial design, the trial result that was addressed in the earlier e-mail was the impact of different oximeters on the comparison of the effects high vs. low oxygen saturation targets on BPD and BPD/death outcomes, which we believe is the question of interest.

2. Do we have reliable data to know whether individual infants were monitored on the study oximeter or on the clinical oximeter on the day the infant was 36 weeks and 0 and whether the oximeter was changed part way through that 24 hour period? What was done if the infant was switched on that day. As I understand it, the diagnosis of BPD was based on the entire 24 hours the day the infant was 36 weeks 0 days. Though the results of the survey weren't distributed, my impression from responses to my earlier e-mails was that even the procedure usually followed in individual centers was not necessarily clear.

We can determine from form PHY02 what oximeter was used to determine the physiologic definition of BPD, but we do not have the detailed level of information that you described. However, based on the survey results, we do know that only 5 sites used the study oximeter for an oxygen-based definition, and only 3 used the study oximeter for challenge.

3. What variables in the model when the BPD oximeter was added? What variables were in the model when a BPD oximeter x study treatment group was added?

Variables in the model were treatment oximeter (low vs. high), center, GA group. Familial clustering was adjusted for as a random effect. I added BPD oximeter and also looked at the interaction between BPD oximeter and treatment oximeter. These factors were identical to the factors used in the models for which secondary outcomes were reported in the manuscript.

4. Do I understand Maria and you to conclude that because centers tended to be consistent in their oximeter use, controlling for center would prevent a biased assessment of the effect on BPD by oxygen administration?

This comment makes me wonder if the analysis was done for the wrong

comparison, This conclusion would be correct for analyses of the effect of CPAP/limited ventilation vs. surfactant/ conventional ventilation on BPD by oxygen delivery (because each treatment arm would contain equal numbers of infants in the high and low sat groups). However, this isn't the comparison in question. This conclusion would certainly not be correct in analyzing the effect of high vs low sat goals on BPD. In this analysis, centers that used the study oximeter would be systematically more likely to administer oxygen to the high sat group than to the low sat group. The problem wouldn't go away by controlling for center, and the more centers that used the study oximeter, the more biased the result would be. How many centers were there that used the study oximeter?

Controlling for center adjusts for differences between centers including differences in the BPD oximeter used. Thus, adding a covariate for BPD oximeter does not change the estimates for the treatment oximeter effect. We are not arguing that the BPD oximeter used did not have an impact. We did find that BPD oximeter was significant in the models, as was center. However, since center and BPD oximeter are strongly confounded (in fact we have almost complete aliasing of center and clinical/study oximeter), it's not possible to tease out the effect of the BPD oximeter from other between-center differences. In addition, the interaction between BPD oximeter and treatment oximeter was not significant. This indicates that the impact of treatment oximeter on the BPD outcomes was not significantly different in the centers that used the study oximeters to determine BPD and those that used the clinical oximeters.

5. What is the basis for believing that there would be anything near reasonable power to assess a oximeter x treatment group interaction?

Clearly, these analyses were conducted from a post-hoc perspective, and the study was never designed to have the power to determine that the interaction in our data set is statistically significant for a pre-specified interaction effect size. But, that is not a shortcoming unless the magnitude of the interaction effect is such that it represents an important scientific bias in study interpretation. Our preliminary analyses indicate that biases of such magnitude are not present in this data set. We can do more detailed analyses of the level of bias that might have been introduced after Marie returns from vacation, but nothing in the analyses conducted to date suggest that those magnitudes warrant delay of submission of this manuscript.

I know that everyone is anxious to get this paper submitted. While I have an external advisory committee tomorrow, I will try to respond tomorrow night if the information requested above is sent tomorrow during the day.

---

From: Higgins, Rosemary (NIH/NICHD) [E] [[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)]

Sent: Wednesday, February 24, 2010 7:53 AM

To: Tyson, Jon E; 'Cunningham, Meg'; [SCRN] Stoll, Barbara; [alaptook@WIHRI.org](mailto:alaptook@WIHRI.org); Bell, Edward; [bpoindex@iupui.edu](mailto:bpoindex@iupui.edu); Das, Abhik; [goldb008@mc.duke.edu](mailto:goldb008@mc.duke.edu); [ifrantz@tuftsmedicalcenter.org](mailto:ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; [kurt.schibler@cchmc.org](mailto:kurt.schibler@cchmc.org); [kwatterberg@salud.unm.edu](mailto:kwatterberg@salud.unm.edu); [matthew.bizzarro@yale.edu](mailto:matthew.bizzarro@yale.edu); [mcw3@cwru.edu](mailto:mcw3@cwru.edu); [mcaplan@northshore.org](mailto:mcaplan@northshore.org); [Pablo.Sanchez@UTSouthwestern.edu](mailto:Pablo.Sanchez@UTSouthwestern.edu); [richard.ehrenkranz@yale.edu](mailto:richard.ehrenkranz@yale.edu); [Roger.Faix@hsc.utah.edu](mailto:Roger.Faix@hsc.utah.edu); [sshankar@med.wayne.edu](mailto:sshankar@med.wayne.edu); [vanmeurs@leland.stanford.edu](mailto:vanmeurs@leland.stanford.edu); Wally Carlo, M.D.; Wallace, Dennis; [cotte010@mc.duke.edu](mailto:cotte010@mc.duke.edu); Bradley Yoder; [rohls@salud.unm.edu](mailto:rohls@salud.unm.edu); [Luc.Brion@utsouthwestern.edu](mailto:Luc.Brion@utsouthwestern.edu); 'Stevenson David (E-mail)'; 'Finer, Neil'; Rich, Wade; Gantz, Marie

Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]

Subject: Follow Up ON BPD and Oximeters

Hi all -

In Follow up to yesterday's discussion, Marie spent a great deal of time last evening running additional analyses to address (and now alleviate) Jon's concern as described:

We have looked into the question of whether the oximeter used to determine BPD impacted the BPD and death/BPD outcomes by adding a covariate for the BPD oximeter (study or clinical) to the statistical models. We found that the effect of the BPD oximeter was significant; however, the interaction between BPD oximeter and treatment oximeter (low or high SpO2 target range) was not significant in any model, indicating that, if there was a BPD oximeter effect, it was not different in the two treatment groups. In addition, it should be noted that BPD oximeter is confounded with center (centers tended to be consistent in their use of the study or clinical oximeters to determine BPD). Therefore, by including center in the original models, we have already accounted for the effect of the BPD oximeter the center chose to use. Finally, because center and BPD oximeter are confounded, we cannot know whether the significant BPD oximeter effect is due to the BPD oximeters themselves or other characteristics that differ between centers.

---

From: Tyson, Jon E [<mailto:Jon.E.Tyson@uth.tmc.edu>]

Sent: Tuesday, February 23, 2010 4:33 PM

To: Higgins, Rosemary (NIH/NICHD) [E]; 'Cunningham, Meg'; [SCRN] Stoll, Barbara; [alaptook@WIHRI.org](mailto:alaptook@WIHRI.org); Bell, Edward; [bpoindex@iupui.edu](mailto:bpoindex@iupui.edu); Das, Abhik; [goldb008@mc.duke.edu](mailto:goldb008@mc.duke.edu); [ifrantz@tuftsmedicalcenter.org](mailto:ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; [kurt.schibler@cchmc.org](mailto:kurt.schibler@cchmc.org); [kwatterberg@salud.unm.edu](mailto:kwatterberg@salud.unm.edu); [matthew.bizzarro@yale.edu](mailto:matthew.bizzarro@yale.edu); [mcw3@cwru.edu](mailto:mcw3@cwru.edu); [mcaplan@northshore.org](mailto:mcaplan@northshore.org); [Pablo.Sanchez@UTSouthwestern.edu](mailto:Pablo.Sanchez@UTSouthwestern.edu); [richard.ehrenkranz@yale.edu](mailto:richard.ehrenkranz@yale.edu); [Roger.Faix@hsc.utah.edu](mailto:Roger.Faix@hsc.utah.edu); [sshankar@med.wayne.edu](mailto:sshankar@med.wayne.edu); [vanmeurs@leland.stanford.edu](mailto:vanmeurs@leland.stanford.edu); Wally Carlo, M.D.; Wallace, Dennis; [cotte010@mc.duke.edu](mailto:cotte010@mc.duke.edu); Bradley Yoder; [rohls@salud.unm.edu](mailto:rohls@salud.unm.edu); [Luc.Brion@utsouthwestern.edu](mailto:Luc.Brion@utsouthwestern.edu); [bbatton@siu.edu](mailto:bbatton@siu.edu)

Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; [lmoore@med.wayne.edu](mailto:lmoore@med.wayne.edu); [pamela.neville@duke.edu](mailto:pamela.neville@duke.edu); [gonza025@mc.duke.edu](mailto:gonza025@mc.duke.edu); Smith, Nancy M; Brenda Vecchio; [msumner@peds.uab.edu](mailto:msumner@peds.uab.edu); Archer, Stephanie (NIH/NICHD) [E]

Subject: RE: Steering Committee Call Tomorrow

While it may seem that I am fixated on an unimportant issue regarding a not quite significant difference, I think we undermine the credibility of Network studies if we are not completely forthright about problems in measuring what everyone would agree is an important secondary outcome. Not reporting that the assessment of BPD by oxygen administration could be biased by continued use of the study oximeters would seem to be in the category of not reporting protocol deviations and not something that is in the Network's best interest. Why not just put a footnote under the table describing the problem?

Jon E. Tyson, MD, MPH

Center for Clinical Research & Evidence-Based Medicine

UT Medical School at Houston

6431 Fannin St., MSB 2.106

Houston, TX 77030

voice 713-500-5651

fax 713-500-0519

---

From: Higgins, Rosemary (NIH/NICHD) [E]  
[mailto:higginsr@mail.nih.gov]

Sent: Tuesday, February 23, 2010 2:11 PM

To: 'Cunningham, Meg'; [SCRN] Stoll, Barbara; [alaptook@WIHRI.org](mailto:alaptook@WIHRI.org); Bell, Edward; [bpoindex@iupui.edu](mailto:bpoindex@iupui.edu); Das, Abhik; [goldb008@mc.duke.edu](mailto:goldb008@mc.duke.edu); [ifrantz@tuftsmedicalcenter.org](mailto:ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; [kurt.schibler@cchmc.org](mailto:kurt.schibler@cchmc.org); [kwatterberg@salud.unm.edu](mailto:kwatterberg@salud.unm.edu); [matthew.bizzarro@yale.edu](mailto:matthew.bizzarro@yale.edu); [mcw3@cwru.edu](mailto:mcw3@cwru.edu); [mcaplan@northshore.org](mailto:mcaplan@northshore.org); [Pablo.Sanchez@UTSouthwestern.edu](mailto:Pablo.Sanchez@UTSouthwestern.edu); [richard.ehrenkranz@yale.edu](mailto:richard.ehrenkranz@yale.edu); [Roger.Faix@hsc.utah.edu](mailto:Roger.Faix@hsc.utah.edu); [sshankar@med.wayne.edu](mailto:sshankar@med.wayne.edu); [vanmeurs@leland.stanford.edu](mailto:vanmeurs@leland.stanford.edu); Wally Carlo, M.D.; Wallace, Dennis; [cotte010@mc.duke.edu](mailto:cotte010@mc.duke.edu); Tyson, Jon E; Bradley Yoder; [rohls@salud.unm.edu](mailto:rohls@salud.unm.edu); [Luc.Brion@utsouthwestern.edu](mailto:Luc.Brion@utsouthwestern.edu); [bbatton@siumed.edu](mailto:bbatton@siumed.edu)

Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; [lmoore@med.wayne.edu](mailto:lmoore@med.wayne.edu); [pamela.neville@duke.edu](mailto:pamela.neville@duke.edu); [gonza025@mc.duke.edu](mailto:gonza025@mc.duke.edu); Smith, Nancy M; Brenda Vecchio; [msummer@peds.uab.edu](mailto:msummer@peds.uab.edu); Archer, Stephanie (NIH/NICHD) [E]

Subject: RE: Steering Committee Call Tomorrow

If you joined the call already in progress, please send us an email so we can count your attendance.

Rose

---

From: Cunningham, Meg [mailto:mcunningham@rti.org]

Sent: Monday, February 22, 2010 9:59 AM

To: [SCRN] Stoll, Barbara; [alaptook@WIHRI.org](mailto:alaptook@WIHRI.org); Bell, Edward; [bpoindex@iupui.edu](mailto:bpoindex@iupui.edu); Das, Abhik; [goldb008@mc.duke.edu](mailto:goldb008@mc.duke.edu); Higgins, Rosemary (NIH/NICHD) [E]; [ifrantz@tuftsmedicalcenter.org](mailto:ifrantz@tuftsmedicalcenter.org); [Kathleen.A.Kennedy@uth.tmc.edu](mailto:Kathleen.A.Kennedy@uth.tmc.edu); [kurt.schibler@cchmc.org](mailto:kurt.schibler@cchmc.org); [kwatterberg@salud.unm.edu](mailto:kwatterberg@salud.unm.edu); [matthew.bizzarro@yale.edu](mailto:matthew.bizzarro@yale.edu); [mcw3@cwru.edu](mailto:mcw3@cwru.edu); [mcaplan@northshore.org](mailto:mcaplan@northshore.org); [Pablo.Sanchez@UTSouthwestern.edu](mailto:Pablo.Sanchez@UTSouthwestern.edu); [richard.ehrenkranz@yale.edu](mailto:richard.ehrenkranz@yale.edu); [Roger.Faix@hsc.utah.edu](mailto:Roger.Faix@hsc.utah.edu); [sshankar@med.wayne.edu](mailto:sshankar@med.wayne.edu); [vanmeurs@leland.stanford.edu](mailto:vanmeurs@leland.stanford.edu); Wally Carlo, M.D.; Wallace, Dennis; [cotte010@mc.duke.edu](mailto:cotte010@mc.duke.edu); [jon.e.tyson@uth.tmc.edu](mailto:jon.e.tyson@uth.tmc.edu); Bradley Yoder; [rohls@salud.unm.edu](mailto:rohls@salud.unm.edu); [Luc.Brion@utsouthwestern.edu](mailto:Luc.Brion@utsouthwestern.edu); [bbatton@siumed.edu](mailto:bbatton@siumed.edu)

Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn; Petrie, Newman, Jamie; [lmoore@med.wayne.edu](mailto:lmoore@med.wayne.edu); [pamela.neville@duke.edu](mailto:pamela.neville@duke.edu); [gonza025@mc.duke.edu](mailto:gonza025@mc.duke.edu); [Nancy.M.Smith@uth.tmc.edu](mailto:Nancy.M.Smith@uth.tmc.edu); Brenda Vecchio; [msummer@peds.uab.edu](mailto:msummer@peds.uab.edu); Archer, Stephanie (NIH/NICHD) [E]

Subject: Steering Committee Call Tomorrow

Dear All -

The next standing Steering Committee call is scheduled for tomorrow, Tuesday, February 23rd at 3:00pm ET.

Please Dial:

Outside the USA 1-203-310-(b)

or Within the USA 866-675-(b)

Then, enter Participant Passcode: (b) (6)

Steering Committee Conference Call Agenda 02/23/2010

1. Early BP discussion (attached are a brief description of the time limited data collection proposal and a draft of the form which would be used.)
2. SUPPORT manuscript discussion and update
3. New Business

Thanks,

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Meg

Meg Cunningham

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**From:** Blaisdell, Carol (NIH/NHLBI) [E]  
**To:** Kiley, James (NIH/NHLBI) [E]; Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Dambruskas, Susan (NIH/NIDCD) [E]; Bock, Robert (NIH/NICHD) [E]; Gail, Dorothy (NIH/NHLBI) [E]  
**Subject:** Story on Session L4 at ATS International Conference  
**Date:** Tuesday, March 02, 2010 3:10:46 PM  
**Attachments:** Conference to Feature Sessions on Research Efforts, Clinical Trials.doc

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FYI Attached==Final draft of the newsletter that ATS plans to circulate with some content on SUPPORT (essentially like the previous draft we approved).

Carol

Carol J. Blaisdell, M.D.  
Medical Officer  
Lung Developmental Biology and  
Pediatric Pulmonary Diseases  
Division of Lung Diseases, NHLBI/NIH  
(301) 435-0222 phone

---

**From:** Susan Logan [mailto:slogan@thoracic.org]  
**Sent:** Tuesday, March 02, 2010 1:38 PM  
**To:** Blaisdell, Carol (NIH/NHLBI) [E]  
**Subject:** RE: Story on Session L4 at ATS International Conference

Thanks so much for your quick response. I've made this change in the attached document.

Best,

Suzy

Suzy Logan  
Senior Manager, Communications & Marketing  
American Thoracic Society  
61 Broadway, 4th Floor  
New York, NY 10006  
Phone: (212) 315-8631  
Fax: (212) 315-6471  
E-mail: [slogan@thoracic.org](mailto:slogan@thoracic.org)

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---

**From:** Blaisdell, Carol (NIH/NHLBI) [E] [mailto:blaisdellcj@nhlbi.nih.gov]  
**Sent:** Tuesday, March 02, 2010 1:35 PM  
**To:** Susan Logan  
**Subject:** RE: Story on Session L4 at ATS International Conference

Susan,  
This looks fine, except for the following.....

SUPPORT is an acronym for the study "the Surfactant Positive Airway Pressure and Pulse Oximetry Trial" so should be all caps as in "SUPPORT"

Carol

Carol J. Blaisdell, M.D.  
Medical Officer  
Lung Developmental Biology and  
Pediatric Pulmonary Diseases  
Division of Lung Diseases, NHLBI/NIH  
(301) 435-0222 phone

---

**From:** Susan Logan [mailto:slogan@thoracic.org]  
**Sent:** Tuesday, March 02, 2010 1:19 PM  
**To:** Blaisdell, Carol (NIH/NHLBI) [E]  
**Subject:** Story on Session L4 at ATS International Conference  
**Importance:** High

Dear Dr. Blaisdell,

Attached is a story written by Ascend Media about session L4, "The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight (ELBW) Infants," which will take place on Sunday, May 16, at the 2010 International Conference. This article is to appear in the electronic version of the Preview edition of the *ATS Daily Bulletin*, which will be distributed to about 30,000 clinicians and researchers by e-mail in the next two weeks.

Our editorial staff at the ATS has made edits to what Ascend originally wrote, and we wanted to be sure you are comfortable with how the text reads, before we finalize this. If you could take a look and let me know what you think—and whether you are comfortable with how you are quoted—I would greatly appreciate it. If you could get all changes back to me by **Friday, March 5**, we will still be on schedule. I have also sent this to Drs. Redline and Gergen for review.

Thanks so much,

Suzy

Suzy Logan  
Senior Manager, Communications & Marketing  
American Thoracic Society  
61 Broadway, 4th Floor  
New York, NY 10006  
Phone: (212) 315-8631  
Fax: (212) 315-6471  
E-mail: [slogan@thoracic.org](mailto:slogan@thoracic.org)

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## NO ART

### Conference to Feature Sessions on Research Efforts, Clinical Trials

Each year, many attendees come to the annual American Thoracic Society's International Conference for the latest clinical trial information because findings may have immediate or near-immediate implications for their practices.

With 21 sessions addressing topics as diverse as the connection between the urban environment and childhood asthma to using satellite remote sensors to study the environment and disease, ATS 2010 will be no exception. The one-hour noon sessions will be presented on Sunday, May 16, Monday, May 17 and Wednesday, May 19.

During one clinical trial session on Sunday, the National Heart, Lung, and Blood Institute (NHLBI) and National Institute of Child Health and Human Development (NICHD) will report the outcomes from their SUPPORT trial "The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight (ELBW) Infants."

"This is the largest study to date that is assessing early ventilation strategies and oximetry targets in extremely pre-term infants on outcomes of survival without bronchopulmonary dysplasia," said session chair Carol J. Blaisdell, M.D., medical officer at the NHLBI's Division of Lung Diseases. "Over 1,300 infants were enrolled through the Eunice Kennedy Shriver NICHD Neonatal Research Network (NRN), with co-funding from the NHLBI. This study is likely to impact care of the most immature pre-term infants."

Rosemary Higgins M.D., program scientist for the NICHD's NRN and Maternal Lifestyles Study, will serve as co-chair of this NHLBI-sponsored session.

A Wednesday symposium also sponsored by the NHLBI will look at "Candidate Gene Association Resource (CARE): Genetic Associations for Lung, Sleep and Obesity Phenotypes."

"Three years ago, the NHLBI, recognizing that very large sample sizes are needed for discovering genetic variants that predispose to chronic diseases, assembled a consortium of cohort studies that had collected extensive, well-characterized cardiovascular, pulmonary, sleep and blood phenotypes, and supported these cohorts to pool resources for the purposes of improving the power of genetic association studies," said session chair Susan S. Redline, M.D., M.P.H., professor of pediatrics, medicine, epidemiology and biostatistics at Case Western Reserve University's Center for Clinical Investigation in Shaker Heights, Ohio.

"Using a novel collaborative model, hundreds of phenotypes were shared and harmonized and genotyping was performed centrally on approximately 50,000 individuals. A series of working groups were assembled—with representatives from a large number of institutions with varied expertise—to analyze these data. The ATS symposium will present some of the representative work of this collaboration, specifically relating to lung function, sleep apnea and obesity," Dr. Redline said.

Michael Twery, Ph.D, director and branch chief of the NHLBI's National Center on Sleep Disorders Research in Bethesda, will serve as session co-chair.

The "Findings from Inner-City Anti-IgE Therapy for Asthma (ICATA)," will also be shared on Wednesday. Sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), the session will be co-chaired by Peter J. Gergen, M.D., M.P.H., medical officer of the NIAID's Division of Allergy, Immunology and Transplantation and Alkis Togias, M.D., section chief of the NIAID's Asthma and Inflammation Section.

"The ICATA evaluated the impact of adding omalizumab to guidelines base-therapy in moderate to severe persistent asthmatics," Dr. Gergen said. "Some very interesting findings dealing with allergen sensitization/exposure and the fall increase in asthma exacerbations will be presented."

In addition, a new composite score, the Asthma Burden Index (ABI), will be described, he said.

“The ABI incorporates both the level of control achieved and the amount of treatment needed to achieve that level of control.”

[SIDEBAR]

Below is a list of all of the clinical trial sessions to be held at ATS 2010 on Sunday, Monday and Tuesday:

**Noon to 1 p.m., Sunday, May 16**

- L1: “National Institute of Nursing Research: Funding Opportunities and Priorities”
- L2: “ALA Asthma Clinical Research Centers Clinical Trials”
- L3: “Update from CDC’s TB Trials Consortium and TB EPI Studies Consortium”
- L4: “Outcomes from the NHLBI-NICHD Support Trial: The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants”
- L5: “Update on Ongoing Clinical Trials in the NHLBI COPD Clinical Research Network”
- L6: “Management of Early Anti-Pseudomonal Airway Infection in Patients with Cystic Fibrosis (EPIC Study)”
- L7: “NHLBI Genome-Wide Association Studies in Asthma: Share-Asthma Resource Project (SHARP)”

**Noon to 1 p.m., Monday, May 17**

- L8: “Chronic Obstructive Pulmonary Disease Outcomes-Based Network for Clinical Effectiveness and Research Translation (CONCERT Consortium) Consensus Conference Recommendations”
- L9: “Gene Environment Interactions: NIEHS Exposure Biology Program”
- L10: “Coronary Artery Risk Development in Young Adults (CARDIA) Study and Multi-Ethnic Study of Atherosclerosis (MESA): Insights into Lung Function, Lung Disease and Cardiopulmonary Interactions”
- L11: “Translational Studies from NHLBI Acute Lung Injury Specialized Centers of Clinically Oriented Research (ALI-SCOR Program)”
- L12: “NHLBI Clinical Research Programs in Asthma: Research Findings Adjusting Therapy to Achieve and Maintain Asthma Control in Childhood Asthma”
- L13: “Idiopathic Pulmonary Fibrosis (IPF): Emerging Trends”
- L14: “Grant Funding Training Opportunities at NHLBI: Insights From a NHLBI Peer Reviewer and Mentor, NHLBI K23 Awardee, a NHLBI Program Officer and a NHLBI Scientific Review Officer.”

**Noon to 1 p.m., Wednesday, May 19**

- L15: “Findings from Inner-City ANTI-IGE Therapy for Asthma (ICATA)”
- L16: “Using NASA’s Satellite Remote Sensors for the Study of the Environment and Diseases”
- L17: “Pulmonary Update from the U.S. Food and Drug Administration”
- L18: “Update on NHLBI Acute Respiratory Distress Network (ARDSnet): Clinical Trials and Ancillary Studies”
- L19: “Candidate Gene Association Resource (CARE): Genetic Associations for Lung, Sleep and Obesity Phenotypes”
- L20: “The National Heart, Lung, and Blood Institute Lung HIV Study: A New Model for Collaborative Clinical and Translational Research”
- L21: “Prospective Investigation of Pulmonary Embolism Diagnosis III (PIOPED III)”

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; "Wally Carlo, M.D."; "Finer, Neil"; "alaptook@WIHRI.org"; "Roger.Faix@hsc.utah.edu"; "Bradley Yoder"; "kurt.schibler@cchmc.org"; "adas@rti.org"; "nancy newman"; "Rich, Wade"; "Gantz, Marie"; "mcw3@case.edu"; "Dennis Wallace"  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; "Zaterka-Baxter, Kristin"; "Cunningham, Meg"; "Huitema, Carolyn Petrie"  
**Subject:** RE: \*\*\*\*\* Important -Follow Up ON BPD and Oximeters\*\*\*\*\*  
**Date:** Tuesday, March 02, 2010 2:54:00 PM

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The question was raised regarding the specific term that was requested to be inserted on the table – I have cut and pasted a portion of Jon's email:

The issue here is whether is simply whether to report somewhere in the paper (which could be noted under the table and wouldn't increase the word count for the text) a bias in evaluating a secondary outcome. This can be done with no delay in submitting the manuscript or waiting for Maria to return. *If we had other real or potential sources of bias—say, a breaking of the blind for some infants, open label administration of a study drug to the control group, or differential loss to follow-up, we would certainly report it as a matter of course, whether or not there was a significant or near significant difference in the outcome and without testing and whether or not we assessed or found any interaction or other statistical evidence that this potential source of bias affected the results!*

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Tuesday, March 02, 2010 1:57 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; 'Wally Carlo, M.D.'; 'Finer, Neil'; 'alaptook@WIHRI.org'; 'Roger.Faix@hsc.utah.edu'; 'Bradley Yoder'; 'kurt.schibler@cchmc.org'; 'adas@rti.org'; 'nancy newman'; 'Rich, Wade'; 'Gantz, Marie'; 'mcw3@case.edu'; 'Dennis Wallace'  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; 'Zaterka-Baxter, Kristin'; 'Cunningham, Meg'; 'Huitema, Carolyn Petrie'  
**Subject:** RE: \*\*\*\*\* Important -Follow Up ON BPD and Oximeters\*\*\*\*\*  
**Importance:** High

Hi,  
We will have a BRIEF call at 430 PM ET.

Call in information  
866-675-(b) (6) with passcode (b) (6)

Thanks to everyone for the short notice.

Rose

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**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Tuesday, March 02, 2010 1:08 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; 'Wally Carlo, M.D.'; 'Finer, Neil'; 'alaptook@WIHRI.org'; 'Roger.Faix@hsc.utah.edu'; 'Bradley Yoder'; 'kurt.schibler@cchmc.org'; 'adas@rti.org'; 'nancy newman'; 'Rich, Wade'; 'Gantz, Marie'; 'mcw3@case.edu'; 'Dennis Wallace'  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; 'Zaterka-Baxter, Kristin'; 'Cunningham, Meg'  
**Subject:** RE: \*\*\*\*\* Important -Follow Up ON BPD and Oximeters\*\*\*\*\*

**I would like to have a brief call this afternoon to discuss with the subcommittee.**

## Let me know if you could join a call sometime between 330-5 PM TODAY, let me know ASAP.

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Monday, March 01, 2010 11:00 AM  
**To:** 'Wally Carlo, M.D.'; 'Finer, Neil'; alaptook@WIHRI.org; Roger.Faix@hsc.utah.edu; Bradley Yoder; kurt.schibler@cchmc.org; adas@rti.org; nancy newman; Rich, Wade; Gantz, Marie; mcw3@case.edu; Dennis Wallace  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin  
**Subject:** \*\*\*\*\* Important -Follow Up ON BPD and Oximeters\*\*\*\*\*  
**Importance:** High

To the SUPPORT Subcommittee

Given the email exchange, the subcommittee will need to ascertain whether or not to indicate in the SUPPORT papers whether or not a bias could have existed in reporting the secondary outcome of BPD based on oximeter. Previously the subcommittee had reviewed the oximeter use on a conference call and decided to defer this to a secondary paper. There has been discussion on the SC call and via email subsequently.

### Therefore, please send me a yes/no vote to include this in the paper by March 2.

Thanks  
Rose

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**From:** Tyson, Jon E [mailto:Jon.E.Tyson@uth.tmc.edu]  
**Sent:** Friday, February 26, 2010 6:28 PM  
**To:** Wallace, Dennis; Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; Stevenson David (E-mail); Finer, Neil; Rich, Wade; Gantz, Marie  
**Cc:** Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: Follow Up ON BPD and Oximeters

I don't understand your statement "Controlling for center adjusts for differences between centers including differences in the BPD oximeter used." To simplify the discussion, suppose every center always used the study oximeter in designating who had BPD by oxygen saturation. Because the true saturation that would prompt oxygen administration would differ in the two treatment groups, there would be systematic bias toward administering oxygen to more infants in the high sat group than in the low sat group. This is inherent in the study design. Whatever differences there were between centers, this bias would occur in every center and would not be eliminated

by controlling for center. And if I understand the analysis, there would be no interaction between treatment oximeter and BPD oximeter because they would be the same in every baby in every center.

You indicate that 5 centers used the study oximeter in almost every baby. In saying "it's not possible to tease out the effect of the BPD oximeter from other between-center differences" (a statement that I certainly accept), aren't you saying that the effect of the study oximeter on the difference in the incidence of BPD by oxygen administration between high and low sat groups (i.e., the bias) can not be distinguished from the effect of the myriad of other factors in those centers that might affect that difference in incidence? If so, why would you expect to be able to discern that bias (the signal) from all the noise resulting from other factors? I understand from what you said that the same approach was used in virtually all infants in each center which makes the effective n to be based on the number of centers rather than the number of babies. As I understand the analysis, the power to assess an interaction would then be quite low.

The issue here is whether is simply whether to report somewhere in the paper (which could be noted under the table and wouldn't increase the word count for the text) a bias in evaluating a secondary outcome. This can be done with no delay in submitting the manuscript or waiting for Maria to return. *If we had other real or potential sources of bias—say, a breaking of the blind for some infants, open label administration of a study drug to the control group, or differential loss to follow-up, we would certainly report it as a matter of course, whether or not there was a significant or near significant difference in the outcome and without testing and whether or not we assessed or found any interaction or other statistical evidence that this potential source of bias affected the results!*

Jon E. Tyson, MD, MPH  
Center for Clinical Research & Evidence-Based Medicine  
UT Medical School at Houston  
6431 Fannin St., MSB 2.106  
Houston, TX 77030  
voice 713-500-5651  
fax 713-500-0519

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**From:** Wallace, Dennis [mailto:dwallace@rti.org]  
**Sent:** Friday, February 26, 2010 1:56 PM  
**To:** Wallace, Dennis; Tyson, Jon E; Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; Stevenson David (E-mail); Finer, Neil; Rich, Wade; Gantz, Marie  
**Cc:** Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: Follow Up ON BPD and Oximeters

Hello all,

I accidentally hit the send button before finishing editing this response so ignore the earlier e-mail and see the response below.

Dennis

Dennis Wallace  
Senior Research Statistician  
Cox 241  
RTI International  
3040 Cornwallis Rd



Research Triangle Park, NC 27709-2104  
Voice: 919-541-6271  
Fax: 919-541-6416

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**From:** Wallace, Dennis  
**Sent:** Friday, February 26, 2010 2:53 PM  
**To:** 'Tyson, Jon E'; Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; 'Stevenson David (E-mail)'; 'Finer, Neil'; Rich, Wade; Gantz, Marie  
**Cc:** Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: Follow Up ON BPD and Oximeters

Jon,  
Marie flew out on a long-scheduled vacation after completing these analyses late Tuesday evening and has very limited e-mail and cell phone access. However, she has taken time to provide a preliminary response that I've outlined below with some added thoughts of my own in red font below. Based on these responses, I do believe that the critical concerns about bias have been addressed sufficiently for this initial manuscript, but if you think we need to have a more full discussion, we can talk after Marie returns next week. Because the programming for these outcome measures is relatively complicated, I'm hesitant to try to do any additional analyses prior to her return. However, as I indicated above, I don't think that we need to delay any submissions while trying to iron on the small details.

Dennis Wallace  
Senior Research Statistician  
Cox 241  
RTI International  
3040 Cornwallis Rd  
Research Triangle Park, NC 27709-2104  
Voice: 919-541-6271  
Fax: 919-541-6416

-----Original Message-----

**From:** Tyson, Jon E [mailto:Jon.E.Tyson@uth.tmc.edu]  
**Sent:** Thursday, February 25, 2010 12:45 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; Wallace, Dennis; cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; 'Stevenson David (E-mail)'; 'Finer, Neil'; Rich, Wade; Gantz, Marie  
**Cc:** Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: Follow Up ON BPD and Oximeters

Rose, before we can understand and interpret this information noted in the mail, we really need to know more about what was done and answers to questions like those below:

1. Which trial result was addressed - whether the evaluation of BPD was biased in the analyses of CPAP/limited ventilation vs. surfactant/conventional ventilation arm (not the analysis for which there is concern) or the analyses of the high vs. low oxygen saturation goal.

Although models were run for the different arms of the factorial design, the

trial result that was addressed in the earlier e-mail was the impact of different oximeters on the comparison of the effects high vs. low oxygen saturation targets on BPD and BPD/death outcomes, which we believe is the question of interest.

2. Do we have reliable data to know whether individual infants were monitored on the study oximeter or on the clinical oximeter on the day the infant was 36 weeks and 0 and whether the oximeter was changed part way through that 24 hour period? What was done if the infant was switched on that day. As I understand it, the diagnosis of BPD was based on the entire 24 hours the day the infant was 36 weeks 0 days. Though the results of the survey weren't distributed, my impression from responses to my earlier e-mails was that even the procedure usually followed in individual centers was not necessarily clear.

We can determine from form PHY02 what oximeter was used to determine the physiologic definition of BPD, but we do not have the detailed level of information that you described. However, based on the survey results, we do know that only 5 sites used the study oximeter for an oxygen-based definition, and only 3 used the study oximeter for challenge.

3. What variables in the model when the BPD oximeter was added? What variables were in the model when a BPD oximeter x study treatment group was added?

Variables in the model were treatment oximeter (low vs. high), center, GA group. Familial clustering was adjusted for as a random effect. I added BPD oximeter and also looked at the interaction between BPD oximeter and treatment oximeter. These factors were identical to the factors used in the models for which secondary outcomes were reported in the manuscript.

4. Do I understand Maria and you to conclude that because centers tended to be consistent in their oximeter use, controlling for center would prevent a biased assessment of the effect on BPD by oxygen administration?

This comment makes me wonder if the analysis was done for the wrong comparison. This conclusion would be correct for analyses of the effect of CPAP/limited ventilation vs. surfactant/ conventional ventilation on BPD by oxygen delivery (because each treatment arm would contain equal numbers of infants in the high and low sat groups). However, this isn't the comparison in question. This conclusion would certainly not be correct in analyzing the effect of high vs low sat goals on BPD. In this analysis, centers that used the study oximeter would be systematically more likely to administer oxygen to the high sat group than to the low sat group. The problem wouldn't go away by controlling for center, and the more centers that used the study oximeter, the more biased the result would be. How many centers were there that used the study oximeter?

Controlling for center adjusts for differences between centers including differences in the BPD oximeter used. Thus, adding a covariate for BPD oximeter does not change the estimates for the treatment oximeter effect. We are not arguing that the BPD oximeter used did not have an impact. We did find that BPD oximeter was significant in the models, as was center. However, since center and BPD oximeter are strongly confounded (in fact we have almost complete aliasing of center and clinical/study oximeter), it's not possible to tease out the effect of the BPD oximeter from other between-center differences. In addition, the interaction between BPD oximeter and treatment oximeter was not significant. This indicates that the impact of treatment oximeter on the BPD outcomes was not significantly different in the centers that used the study oximeters to determine BPD and those that used the clinical oximeters.

5. What is the basis for believing that there would be anything near reasonable power to assess a oximeter x treatment group interaction?

Clearly, these analyses were conducted from a post-hoc perspective, and the study was never designed to have the power to determine that the interaction in our data set is statistically significant for a pre-specified interaction effect size. But, that is not a shortcoming unless the magnitude of the

interaction effect is such that it represents an important scientific bias in study interpretation. Our preliminary analyses indicate that biases of such magnitude are not present in this data set. We can do more detailed analyses of the level of bias that might have been introduced after Marie returns from vacation, but nothing in the analyses conducted to date suggest that those magnitudes warrant delay of submission of this manuscript.

I know that everyone is anxious to get this paper submitted. While I have an external advisory committee tomorrow, I will try to respond tomorrow night if the information requested above is sent tomorrow during the day.

---

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]  
Sent: Wednesday, February 24, 2010 7:53 AM  
To: Tyson, Jon E; 'Cunningham, Meg'; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; Wallace, Dennis; cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; 'Stevenson David (E-mail)'; 'Finer, Neil'; Rich, Wade; Gantz, Marie  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]  
Subject: Follow Up ON BPD and Oximeters

Hi all -

In Follow up to yesterday's discussion, Marie spent a great deal of time last evening running additional analyses to address (and now alleviate) Jon's concern as described:

We have looked into the question of whether the oximeter used to determine BPD impacted the BPD and death/BPD outcomes by adding a covariate for the BPD oximeter (study or clinical) to the statistical models. We found that the effect of the BPD oximeter was significant; however, the interaction between BPD oximeter and treatment oximeter (low or high SpO2 target range) was not significant in any model, indicating that, if there was a BPD oximeter effect, it was not different in the two treatment groups. In addition, it should be noted that BPD oximeter is confounded with center (centers tended to be consistent in their use of the study or clinical oximeters to determine BPD). Therefore, by including center in the original models, we have already accounted for the effect of the BPD oximeter the center chose to use. Finally, because center and BPD oximeter are confounded, we cannot know whether the significant BPD oximeter effect is due to the BPD oximeters themselves or other characteristics that differ between centers.

---

From: Tyson, Jon E [mailto:Jon.E.Tyson@uth.tmc.edu]  
Sent: Tuesday, February 23, 2010 4:33 PM  
To: Higgins, Rosemary (NIH/NICHD) [E]; 'Cunningham, Meg'; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; Wallace, Dennis; cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; bbatton@siu.edu  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; lmoore@med.wayne.edu; pamela.neville@duke.edu; gonza025@mc.duke.edu; Smith, Nancy M; Brenda Vecchio; msumner@peds.uab.edu; Archer, Stephanie (NIH/NICHD) [E]  
Subject: RE: Steering Committee Call Tomorrow

While it may seem that I am fixated on an unimportant issue regarding a not quite significant difference, I think we undermine the credibility of Network studies if we are not completely forthright about problems in measuring what everyone would agree is an important secondary outcome. Not reporting that the assessment of BPD by oxygen administration could be

biased by continued use of the study oximeters would seem to be in the category of not reporting protocol deviations and not something that is in the Network's best interest. Why not just put a footnote under the table describing the problem?

Jon E. Tyson, MD, MPH  
Center for Clinical Research & Evidence-Based Medicine  
UT Medical School at Houston  
6431 Fannin St., MSB 2.106  
Houston, TX 77030  
voice 713-500-5651  
fax 713-500-0519

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
Sent: Tuesday, February 23, 2010 2:11 PM  
To: 'Cunningham, Meg'; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; Wallace, Dennis; cotte010@mc.duke.edu; Tyson, Jon E; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; bbatton@siumed.edu  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; lmoore@med.wayne.edu; pamela.neville@duke.edu; gonza025@mc.duke.edu; Smith, Nancy M; Brenda Vecchio; msumner@peds.uab.edu; Archer, Stephanie (NIH/NICHD) [E]  
Subject: RE: Steering Committee Call Tomorrow

If you joined the call already in progress, please send us an email so we can count your attendance.

Rose

From: Cunningham, Meg [mailto:mcunningham@rti.org]  
Sent: Monday, February 22, 2010 9:59 AM  
To: [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; Higgins, Rosemary (NIH/NICHD) [E]; ifrantz@tuftsmedicalcenter.org; Kathleen.A.Kennedy@uth.tmc.edu; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; Wallace, Dennis; cotte010@mc.duke.edu; jon.e.tyson@uth.tmc.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; bbatton@siumed.edu  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; lmoore@med.wayne.edu; pamela.neville@duke.edu; gonza025@mc.duke.edu; Nancy.M.Smith@uth.tmc.edu; Brenda Vecchio; msumner@peds.uab.edu; Archer, Stephanie (NIH/NICHD) [E]  
Subject: Steering Committee Call Tomorrow

Dear All -

The next standing Steering Committee call is scheduled for tomorrow, Tuesday, February 23rd at 3:00pm ET.

Please Dial:

Outside the USA 1-203-310-(b) (6)  
or Within the USA 866-675-(b) (6)

Then, enter Participant Passcode: (b) (6)

Steering Committee Conference Call Agenda 02/23/2010

1. Early BP discussion (attached are a brief description of the time limited data collection proposal and a draft of the form which would be used.)
2. SUPPORT manuscript discussion and update
3. New Business

Thanks,

Meg

Meg Cunningham  
RTI International  
701 13th St. NW, Ste. 750  
Washington, DC 20005  
tel: 202-974-7837  
fax: 202-728-2095  
www.rti.org<<http://www.rti.org>>

**From:** Bell, Edward  
**To:** Eastman, Diane; Acarregui, Michael  
**Cc:** Johnson, Karen; Higgins, Rosemary (NIH/NICHD) [E]; Segar, Jeffrey  
**Subject:** RE: SUPPORT trial f/u visits  
**Date:** Tuesday, March 02, 2010 2:47:11 PM

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Diane and Mike,

Thanks for your Herculean effort in getting these last two seen.

Ed

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**From:** Eastman, Diane  
**Sent:** Tuesday, March 02, 2010 1:30 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Bell, Edward; Johnson, Karen  
**Subject:** SUPPORT trial f/u visits

Rose,

The twins that we have been trying for months to do their f/u visit on, # (b) (6) we saw them yesterday!! So their data will be in soon. The weather finally cooperated and we went to see them. Diane

*Diane Eastman, ARNP*

*High Risk Infant Followup Program*

*Children's Hospital of Iowa*

*319-353-6880*

**From:** Walsh, Michele  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: \*\*\*\*\* Important -Follow Up ON BPD and Oximeters\*\*\*\*\*  
**Date:** Tuesday, March 02, 2010 2:38:41 PM

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Do we have the sentence that Jon wants to add to the table?  
Seems we need that to react too, else the call will just be  
All of us venting that we don't want to do this!

Michele Walsh  
beeper (b) (6)  
Ph 216 844 3759

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Tuesday, March 02, 2010 1:57 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; 'Wally Carlo, M.D.'; 'Finer, Neil'; 'alaptook@WIHRI.org'; 'Roger.Faix@hsc.utah.edu'; 'Bradley Yoder'; 'kurt.schibler@cchmc.org'; 'adas@rti.org'; 'nancy newman'; 'Rich, Wade'; 'Gantz, Marie'; 'mcw3@case.edu'; 'Dennis Wallace'  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; 'Zaterka-Baxter, Kristin'; 'Cunningham, Meg'; 'Huitema, Carolyn Petrie'  
**Subject:** RE: \*\*\*\*\* Important -Follow Up ON BPD and Oximeters\*\*\*\*\*  
**Importance:** High

Hi,  
We will have a BRIEF call at 430 PM ET.

Call in information  
866-675-(b) (6) with passcode (b) (6)

Thanks to everyone for the short notice.

Rose

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**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Tuesday, March 02, 2010 1:08 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; 'Wally Carlo, M.D.'; 'Finer, Neil'; 'alaptook@WIHRI.org'; 'Roger.Faix@hsc.utah.edu'; 'Bradley Yoder'; 'kurt.schibler@cchmc.org'; 'adas@rti.org'; 'nancy newman'; 'Rich, Wade'; 'Gantz, Marie'; 'mcw3@case.edu'; 'Dennis Wallace'  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; 'Zaterka-Baxter, Kristin'; Cunningham, Meg  
**Subject:** RE: \*\*\*\*\* Important -Follow Up ON BPD and Oximeters\*\*\*\*\*

**I would like to have a brief call this afternoon  
to discuss with the subcommittee.**

**Let me know if you could join a call sometime  
between 330-5 PM TODAY, let me know ASAP.**

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Monday, March 01, 2010 11:00 AM  
**To:** 'Wally Carlo, M.D.'; 'Finer, Neil'; alaptook@WIHRI.org; Roger.Faix@hsc.utah.edu; Bradley Yoder; kurt.schibler@cchmc.org; adas@rti.org; nancy newman; Rich, Wade; Gantz, Marie; mcw3@case.edu; Dennis Wallace  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin  
**Subject:** \*\*\*\*\* Important -Follow Up ON BPD and Oximeters\*\*\*\*\*  
**Importance:** High

To the SUPPORT Subcommittee

Given the email exchange, the subcommittee will need to ascertain whether or not to indicate in the SUPPORT papers whether or not a bias could have existed in reporting the secondary outcome of BPD based on oximeter. Previously the subcommittee had reviewed the oximeter use on a conference call and decided to defer this to a secondary paper. There has been discussion on the SC call and via email subsequently.

**Therefore, please send me a yes/no vote to include this in the paper by March 2.**

Thanks  
Rose

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**From:** Tyson, Jon E [mailto:Jon.E.Tyson@uth.tmc.edu]  
**Sent:** Friday, February 26, 2010 6:28 PM  
**To:** Wallace, Dennis; Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpointex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; Stevenson David (E-mail); Finer, Neil; Rich, Wade; Gantz, Marie  
**Cc:** Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: Follow Up ON BPD and Oximeters

I don't understand your statement "Controlling for center adjusts for differences between centers including differences in the BPD oximeter used." To simplify the discussion, suppose every center always used the study oximeter in designating who had BPD by oxygen saturation. Because the true saturation that would prompt oxygen administration would differ in the two treatment groups, there would be systematic bias toward administering oxygen to more infants in the high sat group than in the low sat group. This is inherent in the study design. Whatever differences there were between centers, this bias would occur in every center and would not be eliminated by controlling for center. And if I understand the analysis, there would be no interaction between treatment oximeter and BPD oximeter because they would be the same in every baby in every center.

You indicate that 5 centers used the study oximeter in almost every baby. In saying "it's not possible to tease out the effect of the BPD oximeter from other between-center differences" (a statement that I certainly accept), aren't you saying that the effect of the study oximeter on the difference in the incidence of BPD by oxygen administration between high and low sat groups (i.e., the bias) can not be distinguished from the effect of the



myriad of other factors in those centers that might affect that difference in incidence? If so, why would you expect to be able to discern that bias (the signal) from all the noise resulting from other factors? I understand from what you said that the same approach was used in virtually all infants in each center which makes the effective n to be based on the number of centers rather than the number of babies. As I understand the analysis, the power to assess an interaction would then be quite low.

The issue here is whether is simply whether to report somewhere in the paper (which could be noted under the table and wouldn't increase the word count for the text) a bias in evaluating a secondary outcome. This can be done with no delay in submitting the manuscript or waiting for Maria to return. *If we had other real or potential sources of bias—say, a breaking of the blind for some infants, open label administration of a study drug to the control group, or differential loss to follow-up, we would certainly report it as a matter of course, whether or not there was a significant or near significant difference in the outcome and without testing and whether or not we assessed or found any interaction or other statistical evidence that this potential source of bias affected the results!*

Jon E. Tyson, MD, MPH  
Center for Clinical Research & Evidence-Based Medicine  
UT Medical School at Houston  
6431 Fannin St., MSB 2.106  
Houston, TX 77030  
voice 713-500-5651  
fax 713-500-0519

---

**From:** Wallace, Dennis [mailto:dwallace@rti.org]

**Sent:** Friday, February 26, 2010 1:56 PM

**To:** Wallace, Dennis; Tyson, Jon E; Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; Stevenson David (E-mail); Finer, Neil; Rich, Wade; Gantz, Marie

**Cc:** Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]

**Subject:** RE: Follow Up ON BPD and Oximeters

Hello all,

I accidentally hit the send button before finishing editing this response so ignore the earlier e-mail and see the response below.

Dennis

Dennis Wallace  
Senior Research Statistician  
Cox 241  
RTI International  
3040 Cornwallis Rd  
Research Triangle Park, NC 27709-2104  
Voice: 919-541-6271  
Fax: 919-541-6416

---

**From:** Wallace, Dennis

**Sent:** Friday, February 26, 2010 2:53 PM

**To:** 'Tyson, Jon E'; Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara;

alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; 'Stevenson David (E-mail)'; 'Finer, Neil'; Rich, Wade; Gantz, Marie

**Cc:** Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]

**Subject:** RE: Follow Up ON BPD and Oximeters

Jon,

Marie flew out on a long-scheduled vacation after completing these analyses late Tuesday evening and has very limited e-mail and cell phone access. However, she has taken time to provide a preliminary response that I've outlined below with some added thoughts of my own in red font below. Based on these responses, I do believe that the critical concerns about bias have been addressed sufficiently for this initial manuscript, but if you think we need to have a more full discussion, we can talk after Marie returns next week. Because the programming for these outcome measures is relatively complicated, I'm hesitant to try to do any additional analyses prior to her return. However, as I indicated above, I don't think that we need to delay any submissions while trying to iron on the small details.

Dennis Wallace  
Senior Research Statistician  
Cox 241  
RTI International  
3040 Cornwallis Rd  
Research Triangle Park, NC 27709-2104  
Voice: 919-541-6271  
Fax: 919-541-6416

-----Original Message-----

From: Tyson, Jon E [mailto:Jon.E.Tyson@uth.tmc.edu]  
Sent: Thursday, February 25, 2010 12:45 AM  
To: Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; Wallace, Dennis; cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; 'Stevenson David (E-mail)'; 'Finer, Neil'; Rich, Wade; Gantz, Marie  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]  
Subject: RE: Follow Up ON BPD and Oximeters

Rose, before we can understand and interpret this information noted in the mail, we really need to know more about what was done and answers to questions like those below:

1. Which trial result was addressed - whether the evaluation of BPD was biased in the analyses of CPAP/limited ventilation vs. surfactant/conventional ventilation arm (not the analysis for which there is concern) or the analyses of the high vs. low oxygen saturation goal.

Although models were run for the different arms of the factorial design, the trial result that was addressed in the earlier e-mail was the impact of different oximeters on the comparison of the effects high vs. low oxygen saturation targets on BPD and BPD/death outcomes, which we believe is the question of interest.

2. Do we have reliable data to know whether individual infants were monitored on the study oximeter or on the clinical oximeter on the day the infant was 36 weeks and 0 and whether the oximeter was changed part way through that 24 hour period? What was done if the infant was switched on

that day. As I understand it, the diagnosis of BPD was based on the entire 24 hours the day the infant was 36 weeks 0 days. Though the results of the survey weren't distributed, my impression from responses to my earlier e mails was that even the procedure usually followed in individual centers was not necessarily clear.

We can determine from form PHY02 what oximeter was used to determine the physiologic definition of BPD, but we do not have the detailed level of information that you described. However, based on the survey results, we do know that only 5 sites used the study oximeter for an oxygen-based definition, and only 3 used the study oximeter for challenge.

3. What variables in the model when the BPD oximeter was added? What variables were in the model when a BPD oximeter x study treatment group was added?

Variables in the model were treatment oximeter (low vs. high), center, GA group. Familial clustering was adjusted for as a random effect. I added BPD oximeter and also looked at the interaction between BPD oximeter and treatment oximeter. These factors were identical to the factors used in the models for which secondary outcomes were reported in the manuscript.

4. Do I understand Maria and you to conclude that because centers tended to be consistent in their oximeter use, controlling for center would prevent a biased assessment of the effect on BPD by oxygen administration?

This comment makes me wonder if the analysis was done for the wrong comparison. This conclusion would be correct for analyses of the effect of CPAP/limited ventilation vs. surfactant/ conventional ventilation on BPD by oxygen delivery (because each treatment arm would contain equal numbers of infants in the high and low sat groups). However, this isn't the comparison in question. This conclusion would certainly not be correct in analyzing the effect of high vs low sat goals on BPD. In this analysis, centers that used the study oximeter would be systematically more likely to administer oxygen to the high sat group than to the low sat group. The problem wouldn't go away by controlling for center, and the more centers that used the study oximeter, the more biased the result would be. How many centers were there that used the study oximeter?

Controlling for center adjusts for differences between centers including differences in the BPD oximeter used. Thus, adding a covariate for BPD oximeter does not change the estimates for the treatment oximeter effect. We are not arguing that the BPD oximeter used did not have an impact. We did find that BPD oximeter was significant in the models, as was center. However, since center and BPD oximeter are strongly confounded (in fact we have almost complete aliasing of center and clinical/study oximeter), it's not possible to tease out the effect of the BPD oximeter from other between-center differences. In addition, the interaction between BPD oximeter and treatment oximeter was not significant. This indicates that the impact of treatment oximeter on the BPD outcomes was not significantly different in the centers that used the study oximeters to determine BPD and those that used the clinical oximeters.

5. What is the basis for believing that there would be anything near reasonable power to assess a oximeter x treatment group interaction?

Clearly, these analyses were conducted from a post-hoc perspective, and the study was never designed to have the power to determine that the interaction in our data set is statistically significant for a pre-specified interaction effect size. But, that is not a shortcoming unless the magnitude of the interaction effect is such that it represents an important scientific bias in study interpretation. Our preliminary analyses indicate that biases of such magnitude are not present in this data set. We can do more detailed analyses of the level of bias that might have been introduced after Marie returns from vacation, but nothing in the analyses conducted to date suggest that those magnitudes warrant delay of submission of this manuscript.

I know that everyone is anxious to get this paper submitted. While I have an external advisory committee tomorrow, I will try to respond tomorrow night if the information requested above is sent tomorrow during the day.

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]  
Sent: Wednesday, February 24, 2010 7:53 AM  
To: Tyson, Jon E; 'Cunningham, Meg'; [SCRN] Stoll, Barbara;  
alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik;  
goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A;  
kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu;  
matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org;  
Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu;  
Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu;  
vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; Wallace, Dennis;  
cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu;  
Luc.Brion@utsouthwestern.edu; 'Stevenson David (E-mail)'; 'Finer, Neil';  
Rich, Wade; Gantz, Marie  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman,  
Jamie; Archer, Stephanie (NIH/NICHD) [E]  
Subject: Follow Up ON BPD and Oximeters

Hi all -

In Follow up to yesterday's discussion, Marie spent a great deal of time last evening running additional analyses to address (and now alleviate) Jon's concern as described:

We have looked into the question of whether the oximeter used to determine BPD impacted the BPD and death/BPD outcomes by adding a covariate for the BPD oximeter (study or clinical) to the statistical models. We found that the effect of the BPD oximeter was significant; however, the interaction between BPD oximeter and treatment oximeter (low or high SpO2 target range) was not significant in any model, indicating that, if there was a BPD oximeter effect, it was not different in the two treatment groups. In addition, it should be noted that BPD oximeter is confounded with center (centers tended to be consistent in their use of the study or clinical oximeters to determine BPD). Therefore, by including center in the original models, we have already accounted for the effect of the BPD oximeter the center chose to use. Finally, because center and BPD oximeter are confounded, we cannot know whether the significant BPD oximeter effect is due to the BPD oximeters themselves or other characteristics that differ between centers.

From: Tyson, Jon E [mailto:Jon.E.Tyson@uth.tmc.edu]  
Sent: Tuesday, February 23, 2010 4:33 PM  
To: Higgins, Rosemary (NIH/NICHD) [E]; 'Cunningham, Meg'; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; Wallace, Dennis; cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; bbatton@siumed.edu  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; lmoore@med.wayne.edu; pamela.neville@duke.edu; gonza025@mc.duke.edu; Smith, Nancy M; Brenda Vecchio; msumner@peds.uab.edu; Archer, Stephanie (NIH/NICHD) [E]  
Subject: RE: Steering Committee Call Tomorrow

While it may seem that I am fixated on an unimportant issue regarding a not quite significant difference, I think we undermine the credibility of Network studies if we are not completely forthright about problems in measuring what everyone would agree is an important secondary outcome. Not reporting that the assessment of BPD by oxygen administration could be biased by continued use of the study oximeters would seem to be in the category of not reporting protocol deviations and not something that is in the Network's best interest. Why not just put a footnote under the table describing the problem?

Jon E. Tyson, MD, MPH  
Center for Clinical Research & Evidence-Based Medicine  
UT Medical School at Houston  
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voice 713-500-5651  
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From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
Sent: Tuesday, February 23, 2010 2:11 PM  
To: 'Cunningham, Meg'; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; Wallace, Dennis; cotte010@mc.duke.edu; Tyson, Jon E; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; bbatton@siumed.edu  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; lmoore@med.wayne.edu; pamela.neville@duke.edu; gonza025@mc.duke.edu; Smith, Nancy M; Brenda Vecchio; msumner@peds.uab.edu; Archer, Stephanie (NIH/NICHD) [E]  
Subject: RE: Steering Committee Call Tomorrow

If you joined the call already in progress, please send us an email so we can count your attendance.

Rose

From: Cunningham, Meg [mailto:mcunningham@rti.org]  
Sent: Monday, February 22, 2010 9:59 AM  
To: [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; Higgins, Rosemary (NIH/NICHD) [E]; ifrantz@tuftsmedicalcenter.org; Kathleen.A.Kennedy@uth.tmc.edu; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; Wallace, Dennis; cotte010@mc.duke.edu; jon.e.tyson@uth.tmc.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; bbatton@siumed.edu  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; lmoore@med.wayne.edu; pamela.neville@duke.edu; gonza025@mc.duke.edu; Nancy.M.Smith@uth.tmc.edu; Brenda Vecchio; msumner@peds.uab.edu; Archer, Stephanie (NIH/NICHD) [E]  
Subject: Steering Committee Call Tomorrow

Dear All -

The next standing Steering Committee call is scheduled for tomorrow, Tuesday, February 23rd at 3:00pm ET.

Please Dial:

Outside the USA 1-203-310-(b)  
or Within the USA 866-675-(b)  
Then, enter Participant Passcode: (b) (6)

Steering Committee Conference Call Agenda 02/23/2010

1. Early BP discussion (attached are a brief description of the time limited data collection proposal and a draft of the form which would be used.)
2. SUPPORT manuscript discussion and update
3. New Business

Thanks,  
Meg

Meg Cunningham  
RTI International  
701 13th St. NW, Ste. 750  
Washington, DC 20005  
tel: 202-974-7837  
fax: 202-728-2095  
www.rti.org<http://www.rti.org>

Visit us at [www.UHhospitals.org](http://www.UHhospitals.org).

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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:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Eastman, Diane"  
**Cc:** "Bell, Edward"; "Johnson, Karen"; "Gantz, Marie"  
**Subject:** RE: SUPPORT trial f/u visits  
**Date:** Tuesday, March 02, 2010 2:32:00 PM

---

AWESOME!!

---

**From:** Eastman, Diane [mailto:diane-eastman@uiowa.edu]  
**Sent:** Tuesday, March 02, 2010 2:30 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Bell, Edward; Johnson, Karen  
**Subject:** SUPPORT trial f/u visits

Rose,

The twins that we have been trying for months to do their f/u visit on, (b) (6) we saw them yesterday!! So their data will be in soon. The weather finally cooperated and we went to see them. Diane

*Diane Eastman, ARNP*

*High Risk Infant Followup Program*

*Children's Hospital of Iowa*

*319-353-6880*

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Laptook, Abbot"  
**Subject:** RE: \*\*\*\*\* Important -Follow Up ON BPD and Oximeters\*\*\*\*\*  
**Date:** Tuesday, March 02, 2010 2:31:00 PM

---

NO problem  
Your view will be shared on the call!  
Thanks  
Rose

---

**From:** Laptook, Abbot [mailto:ALaptook@WIHRI.org]  
**Sent:** Tuesday, March 02, 2010 2:18 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** Re: \*\*\*\*\* Important -Follow Up ON BPD and Oximeters\*\*\*\*\*

I will be traveling and unable to be on a call. AL

Sent from my iPhone

On Mar 2, 2010, at 10:11 AM, "Higgins, Rosemary (NIH/NICHD) [E]"  
<[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)> wrote:

**I would like to have a brief call this afternoon to discuss with the subcommittee.**

**Let me know if you could join a call sometime between 330-5 PM TODAY, let me know ASAP.**

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Monday, March 01, 2010 11:00 AM  
**To:** 'Wally Carlo, M.D.'; 'Finer, Neil'; [alaptook@WIHRI.org](mailto:alaptook@WIHRI.org); [Roger.Faix@hsc.utah.edu](mailto:Roger.Faix@hsc.utah.edu); Bradley Yoder; [kurt.schibler@cchmc.org](mailto:kurt.schibler@cchmc.org); [adas@rti.org](mailto:adas@rti.org); nancy newman; Rich, Wade; Gantz, Marie; [mcw3@case.edu](mailto:mcw3@case.edu); Dennis Wallace  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin  
**Subject:** \*\*\*\*\* Important -Follow Up ON BPD and Oximeters\*\*\*\*\*  
**Importance:** High

To the SUPPORT Subcommittee

Given the email exchange, the subcommittee will need to ascertain whether or not to indicate in the SUPPORT papers whether or not a bias could have existed in reporting the secondary outcome of BPD based on oximeter. Previously the subcommittee had reviewed the oximeter use on



a conference call and decided to defer this to a secondary paper. There has been discussion on the SC call and via email subsequently.

**Therefore, please send me a yes/no vote to include this in the paper by March 2.**

Thanks  
Rose

---

**From:** Tyson, Jon E [mailto:Jon.E.Tyson@uth.tmc.edu]  
**Sent:** Friday, February 26, 2010 6:28 PM  
**To:** Wallace, Dennis; Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara; [alaptook@WIHRI.org](mailto:alaptook@WIHRI.org); Bell, Edward; [bpoindex@iupui.edu](mailto:bpoindex@iupui.edu); Das, Abhik; [goldb008@mc.duke.edu](mailto:goldb008@mc.duke.edu); [ifrantz@tuftsmedicalcenter.org](mailto:ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; [kurt.schibler@cchmc.org](mailto:kurt.schibler@cchmc.org); [kwatterberg@salud.unm.edu](mailto:kwatterberg@salud.unm.edu); [matthew.bizzarro@yale.edu](mailto:matthew.bizzarro@yale.edu); [mcw3@cwru.edu](mailto:mcw3@cwru.edu); [mcaplan@northshore.org](mailto:mcaplan@northshore.org); [Pablo.Sanchez@UTSouthwestern.edu](mailto:Pablo.Sanchez@UTSouthwestern.edu); [richard.ehrenkranz@yale.edu](mailto:richard.ehrenkranz@yale.edu); [Roger.Faix@hsc.utah.edu](mailto:Roger.Faix@hsc.utah.edu); [sshankar@med.wayne.edu](mailto:sshankar@med.wayne.edu); [vanmeurs@leland.stanford.edu](mailto:vanmeurs@leland.stanford.edu); Wally Carlo, M.D.; [cotte010@mc.duke.edu](mailto:cotte010@mc.duke.edu); Bradley Yoder; [rohls@salud.unm.edu](mailto:rohls@salud.unm.edu); [Luc.Brion@utsouthwestern.edu](mailto:Luc.Brion@utsouthwestern.edu); Stevenson David (E-mail); Finer, Neil; Rich, Wade; Gantz, Marie  
**Cc:** Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: Follow Up ON BPD and Oximeters

I don't understand your statement "Controlling for center adjusts for differences between centers including differences in the BPD oximeter used." To simplify the discussion, suppose every center always used the study oximeter in designating who had BPD by oxygen saturation. Because the true saturation that would prompt oxygen administration would differ in the two treatment groups, there would be systematic bias toward administering oxygen to more infants in the high sat group than in the low sat group. This is inherent in the study design. Whatever differences there were between centers, this bias would occur in every center and would not be eliminated by controlling for center. And if I understand the analysis, there would be no interaction between treatment oximeter and BPD oximeter because they would be the same in every baby in every center.

You indicate that 5 centers used the study oximeter in almost every baby. In saying "it's not possible to tease out the effect of the BPD oximeter from other between-center differences" (a statement that I certainly accept), aren't you saying that the effect of the study oximeter on the difference in the incidence of BPD by oxygen administration between high and low sat groups (i.e., the bias) can not be distinguished from the effect of the myriad of other factors in those centers that might affect that difference in incidence? If so, why would you expect to be able to discern that bias (the signal) from all the noise resulting from other factors? I understand from what you said that the same approach was used in virtually all infants in each center which makes the effective n to be based on the number of centers rather than the number of babies. As I understand the analysis, the power to assess an interaction would then be quite low.

The issue here is whether is simply whether to report somewhere in the paper (which could be noted under the table and wouldn't increase the word count for the text) a bias in evaluating a secondary outcome. This can be done with no delay in submitting the manuscript or waiting for Maria to return. *If we had other real or potential sources of bias—say, a breaking of the blind for some infants, open label administration of a study drug to the control group, or differential loss to follow-up, we would*

*certainly report it as a matter of course, whether or not there was a significant or near significant difference in the outcome and without testing and whether or not we assessed or found any interaction or other statistical evidence that this potential source of bias affected the results!*

Jon E. Tyson, MD, MPH  
Center for Clinical Research & Evidence-Based Medicine  
UT Medical School at Houston  
6431 Fannin St., MSB 2.106  
Houston, TX 77030  
voice 713-500-5651  
fax 713-500-0519

---

**From:** Wallace, Dennis [mailto:[dwallace@rti.org](mailto:dwallace@rti.org)]

**Sent:** Friday, February 26, 2010 1:56 PM

**To:** Wallace, Dennis; Tyson, Jon E; Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara; [alaptook@WIHRI.org](mailto:alaptook@WIHRI.org); Bell, Edward; [bpointex@iupui.edu](mailto:bpointex@iupui.edu); Das, Abhik; [goldb008@mc.duke.edu](mailto:goldb008@mc.duke.edu); [ifrantz@tuftsmedicalcenter.org](mailto:ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; [kurt.schibler@cchmc.org](mailto:kurt.schibler@cchmc.org); [kwatterberg@salud.unm.edu](mailto:kwatterberg@salud.unm.edu); [matthew.bizzarro@yale.edu](mailto:matthew.bizzarro@yale.edu); [mcw3@cwru.edu](mailto:mcw3@cwru.edu); [mcaplan@northshore.org](mailto:mcaplan@northshore.org); [Pablo.Sanchez@UTSouthwestern.edu](mailto:Pablo.Sanchez@UTSouthwestern.edu); [richard.ehrenkranz@yale.edu](mailto:richard.ehrenkranz@yale.edu); [Roger.Faix@hsc.utah.edu](mailto:Roger.Faix@hsc.utah.edu); [sshankar@med.wayne.edu](mailto:sshankar@med.wayne.edu); [vanmeurs@leland.stanford.edu](mailto:vanmeurs@leland.stanford.edu); Wally Carlo, M.D.; [cotte010@mc.duke.edu](mailto:cotte010@mc.duke.edu); Bradley Yoder; [rohls@salud.unm.edu](mailto:rohls@salud.unm.edu); [Luc.Brion@utsouthwestern.edu](mailto:Luc.Brion@utsouthwestern.edu); Stevenson David (E-mail); Finer, Neil; Rich, Wade; Gantz, Marie

**Cc:** Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]

**Subject:** RE: Follow Up ON BPD and Oximeters

Hello all,

I accidentally hit the send button before finishing editing this response so ignore the earlier e-mail and see the response below.

Dennis

Dennis Wallace

<p class="Mso

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This e-mail and any files transmitted with it are confidential and intended solely for the use of the individual or entity to whom they are addressed. If you are not the intended recipient, you are hereby notified that any disclosure, copying, distribution or taking of any action in reliance on the information contained in this e-mail is prohibited. If you have received this e-mail in error, please notify sender by reply e-mail and delete this message and any attachment(s) immediately. Thank you for your consideration in this matter.

**From:** [Wallace, Dennis](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Wally Carlo, M.D.](#); [Finer, Neil](#); [alaptook@WIHRI.org](#); [Roger.Faix@hsc.utah.edu](#); [Bradley Yoder](#); [kurt.schibler@cchmc.org](#); [Das, Abhik](#); [nancy.newman](#); [Rich, Wade](#); [Gantz, Marie](#); [mcw3@case.edu](#)  
**Cc:** [Archer, Stephanie \(NIH/NICHD\) \[E\]](#); [Zaterka-Baxter, Kristin](#); [Cunningham, Meg](#); [Huitema, Carolyn Petrie](#)  
**Subject:** RE: \*\*\*\*\* Important -Follow Up ON BPD and Oximeters\*\*\*\*\*  
**Date:** Tuesday, March 02, 2010 2:17:28 PM

---

Thanks. I will be on the call.  
Dennis

Dennis Wallace  
Senior Research Statistician  
Cox 241  
RTI International  
3040 Cornwallis Rd  
Research Triangle Park, NC 27709-2104  
Voice: 919-541-6271  
Fax: 919-541-6416

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**From:** Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]  
**Sent:** Tuesday, March 02, 2010 1:57 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; 'Wally Carlo, M.D.'; 'Finer, Neil'; [alaptook@WIHRI.org](#); [Roger.Faix@hsc.utah.edu](#); 'Bradley Yoder'; [kurt.schibler@cchmc.org](#); Das, Abhik; 'nancy.newman'; 'Rich, Wade'; [Gantz, Marie](#); [mcw3@case.edu](#); Wallace, Dennis  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Cunningham, Meg; Huitema, Carolyn Petrie  
**Subject:** RE: \*\*\*\*\* Important -Follow Up ON BPD and Oximeters\*\*\*\*\*  
**Importance:** High

Hi,  
We will have a BRIEF call at 430 PM ET.

Call in information  
866-675-(b) (6) with passcode (b) (6)

Thanks to everyone for the short notice.

Rose

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Tuesday, March 02, 2010 1:08 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; 'Wally Carlo, M.D.'; 'Finer, Neil'; [alaptook@WIHRI.org](#); [Roger.Faix@hsc.utah.edu](#); 'Bradley Yoder'; [kurt.schibler@cchmc.org](#); [adas@rti.org](#); 'nancy.newman'; 'Rich, Wade'; [Gantz, Marie](#); [mcw3@case.edu](#); 'Dennis Wallace'  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Cunningham, Meg  
**Subject:** RE: \*\*\*\*\* Important -Follow Up ON BPD and Oximeters\*\*\*\*\*

**I would like to have a brief call this afternoon to discuss with the subcommittee.**

## Let me know if you could join a call sometime between 330-5 PM TODAY, let me know ASAP.

---

**From:** Higgins, Rosemary (NIH/NICHHD) [E]  
**Sent:** Monday, March 01, 2010 11:00 AM  
**To:** 'Wally Carlo, M.D.'; 'Finer, Neil'; alaptook@WIHRI.org; Roger.Faix@hsc.utah.edu; Bradley Yoder; kurt.schibler@cchmc.org; adas@rti.org; nancy newman; Rich, Wade; Gantz, Marie; mcw3@case.edu; Dennis Wallace  
**Cc:** Archer, Stephanie (NIH/NICHHD) [E]; Zaterka-Baxter, Kristin  
**Subject:** \*\*\*\*\* Important -Follow Up ON BPD and Oximeters\*\*\*\*\*  
**Importance:** High

To the SUPPORT Subcommittee

Given the email exchange, the subcommittee will need to ascertain whether or not to indicate in the SUPPORT papers whether or not a bias could have existed in reporting the secondary outcome of BPD based on oximeter. Previously the subcommittee had reviewed the oximeter use on a conference call and decided to defer this to a secondary paper. There has been discussion on the SC call and via email subsequently.

### Therefore, please send me a yes/no vote to include this in the paper by March 2.

Thanks  
Rose

---

**From:** Tyson, Jon E [mailto:Jon.E.Tyson@uth.tmc.edu]  
**Sent:** Friday, February 26, 2010 6:28 PM  
**To:** Wallace, Dennis; Higgins, Rosemary (NIH/NICHHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; Stevenson David (E-mail); Finer, Neil; Rich, Wade; Gantz, Marie  
**Cc:** Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHHD) [E]  
**Subject:** RE: Follow Up ON BPD and Oximeters

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Jon E. Tyson, MD, MPH  
Center for Clinical Research & Evidence-Based Medicine  
UT Medical School at Houston  
6431 Fannin St., MSB 2.106  
Houston, TX 77030  
voice 713-500-5651  
fax 713-500-0519

---

**From:** Wallace, Dennis [mailto:dwallace@rti.org]  
**Sent:** Friday, February 26, 2010 1:56 PM  
**To:** Wallace, Dennis; Tyson, Jon E; Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; Stevenson David (E-mail); Finer, Neil; Rich, Wade; Gantz, Marie  
**Cc:** Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: Follow Up ON BPD and Oximeters

Hello all,

I accidentally hit the send button before finishing editing this response so ignore the earlier e-mail and see the response below.

Dennis

Dennis Wallace  
Senior Research Statistician  
Cox 241  
RTI International  
3040 Cornwallis Rd

Research Triangle Park, NC 27709-2104  
Voice: 919-541-6271  
Fax: 919-541-6416

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**From:** Wallace, Dennis  
**Sent:** Friday, February 26, 2010 2:53 PM  
**To:** 'Tyson, Jon E'; Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; 'Stevenson David (E-mail)'; 'Finer, Neil'; Rich, Wade; Gantz, Marie  
**Cc:** Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: Follow Up ON BPD and Oximeters

Jon,

Marie flew out on a long-scheduled vacation after completing these analyses late Tuesday evening and has very limited e-mail and cell phone access. However, she has taken time to provide a preliminary response that I've outlined below with some added thoughts of my own in red font below. Based on these responses, I do believe that the critical concerns about bias have been addressed sufficiently for this initial manuscript, but if you think we need to have a more full discussion, we can talk after Marie returns next week. Because the programming for these outcome measures is relatively complicated, I'm hesitant to try to do any additional analyses prior to her return. However, as I indicated above, I don't think that we need to delay any submissions while trying to iron on the small details.

Dennis Wallace  
Senior Research Statistician  
Cox 241  
RTI International  
3040 Cornwallis Rd  
Research Triangle Park, NC 27709-2104  
Voice: 919-541-6271  
Fax: 919-541-6416

-----Original Message-----

From: Tyson, Jon E [mailto:Jon.E.Tyson@uth.tmc.edu]  
Sent: Thursday, February 25, 2010 12:45 AM  
To: Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; Wallace, Dennis; cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; 'Stevenson David (E-mail)'; 'Finer, Neil'; Rich, Wade; Gantz, Marie  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]  
Subject: RE: Follow Up ON BPD and Oximeters

Rose, before we can understand and interpret this information noted in the mail, we really need to know more about what was done and answers to questions like those below:

1. Which trial result was addressed - whether the evaluation of BPD was biased in the analyses of CPAP/limited ventilation vs. surfactant/conventional ventilation arm (not the analysis for which there is concern) or the analyses of the high vs. low oxygen saturation goal.

Although models were run for the different arms of the factorial design, the

trial result that was addressed in the earlier e-mail was the impact of different oximeters on the comparison of the effects high vs. low oxygen saturation targets on BPD and BPD/death outcomes, which we believe is the question of interest.

2. Do we have reliable data to know whether individual infants were monitored on the study oximeter or on the clinical oximeter on the day the infant was 36 weeks and 0 and whether the oximeter was changed part way through that 24 hour period? What was done if the infant was switched on that day. As I understand it, the diagnosis of BPD was based on the entire 24 hours the day the infant was 36 weeks 0 days. Though the results of the survey weren't distributed, my impression from responses to my earlier e-mails was that even the procedure usually followed in individual centers was not necessarily clear.

We can determine from form PHY02 what oximeter was used to determine the physiologic definition of BPD, but we do not have the detailed level of information that you described. However, based on the survey results, we do know that only 5 sites used the study oximeter for an oxygen-based definition, and only 3 used the study oximeter for challenge.

3. What variables in the model when the BPD oximeter was added? What variables were in the model when a BPD oximeter x study treatment group was added?

Variables in the model were treatment oximeter (low vs. high), center, GA group. Familial clustering was adjusted for as a random effect. I added BPD oximeter and also looked at the interaction between BPD oximeter and treatment oximeter. These factors were identical to the factors used in the models for which secondary outcomes were reported in the manuscript.

4. Do I understand Maria and you to conclude that because centers tended to be consistent in their oximeter use, controlling for center would prevent a biased assessment of the effect on BPD by oxygen administration?

This comment makes me wonder if the analysis was done for the wrong comparison. This conclusion would be correct for analyses of the effect of CPAP/limited ventilation vs. surfactant/ conventional ventilation on BPD by oxygen delivery (because each treatment arm would contain equal numbers of infants in the high and low sat groups). However, this isn't the comparison in question. This conclusion would certainly not be correct in analyzing the effect of high vs low sat goals on BPD. In this analysis, centers that used the study oximeter would be systematically more likely to administer oxygen to the high sat group than to the low sat group. The problem wouldn't go away by controlling for center, and the more centers that used the study oximeter, the more biased the result would be. How many centers were there that used the study oximeter?

Controlling for center adjusts for differences between centers including differences in the BPD oximeter used. Thus, adding a covariate for BPD oximeter does not change the estimates for the treatment oximeter effect. We are not arguing that the BPD oximeter used did not have an impact. We did find that BPD oximeter was significant in the models, as was center. However, since center and BPD oximeter are strongly confounded (in fact we have almost complete aliasing of center and clinical/study oximeter), it's not possible to tease out the effect of the BPD oximeter from other between-center differences. In addition, the interaction between BPD oximeter and treatment oximeter was not significant. This indicates that the impact of treatment oximeter on the BPD outcomes was not significantly different in the centers that used the study oximeters to determine BPD and those that used the clinical oximeters.

5. What is the basis for believing that there would be anything near reasonable power to assess a oximeter x treatment group interaction?

Clearly, these analyses were conducted from a post-hoc perspective, and the study was never designed to have the power to determine that the interaction in our data set is statistically significant for a pre-specified interaction effect size. But, that is not a shortcoming unless the magnitude of the

interaction effect is such that it represents an important scientific bias in study interpretation. Our preliminary analyses indicate that biases of such magnitude are not present in this data set. We can do more detailed analyses of the level of bias that might have been introduced after Marie returns from vacation, but nothing in the analyses conducted to date suggest that those magnitudes warrant delay of submission of this manuscript.

I know that everyone is anxious to get this paper submitted. While I have an external advisory committee tomorrow, I will try to respond tomorrow night if the information requested above is sent tomorrow during the day.

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]  
Sent: Wednesday, February 24, 2010 7:53 AM  
To: Tyson, Jon E; 'Cunningham, Meg'; [SCRN] Stoll, Barbara;  
alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik;  
goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A;  
kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu;  
matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org;  
Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu;  
Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu;  
vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; Wallace, Dennis;  
cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu;  
Luc.Brion@utsouthwestern.edu; 'Stevenson David (E-mail)'; 'Finer, Neil';  
Rich, Wade; Gantz, Marie  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman,  
Jamie; Archer, Stephanie (NIH/NICHD) [E]  
Subject: Follow Up ON BPD and Oximeters

Hi all -

In Follow up to yesterday's discussion, Marie spent a great deal of time last evening running additional analyses to address (and now alleviate) Jon's concern as described:

We have looked into the question of whether the oximeter used to determine BPD impacted the BPD and death/BPD outcomes by adding a covariate for the BPD oximeter (study or clinical) to the statistical models. We found that the effect of the BPD oximeter was significant; however, the interaction between BPD oximeter and treatment oximeter (low or high SpO2 target range) was not significant in any model, indicating that, if there was a BPD oximeter effect, it was not different in the two treatment groups. In addition, it should be noted that BPD oximeter is confounded with center (centers tended to be consistent in their use of the study or clinical oximeters to determine BPD). Therefore, by including center in the original models, we have already accounted for the effect of the BPD oximeter the center chose to use. Finally, because center and BPD oximeter are confounded, we cannot know whether the significant BPD oximeter effect is due to the BPD oximeters themselves or other characteristics that differ between centers.

From: Tyson, Jon E [mailto:Jon.E.Tyson@uth.tmc.edu]  
Sent: Tuesday, February 23, 2010 4:33 PM  
To: Higgins, Rosemary (NIH/NICHD) [E]; 'Cunningham, Meg'; [SCRN] Stoll,  
Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik;  
goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A;  
kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu;  
matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org;  
Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu;  
Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu;  
vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; Wallace, Dennis;  
cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu;  
Luc.Brion@utsouthwestern.edu; bbatton@siumed.edu  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman,  
Jamie; lmoore@med.wayne.edu; pamela.neville@duke.edu; gonza025@mc.duke.edu;  
Smith, Nancy M; Brenda Vecchio; msumner@peds.uab.edu; Archer, Stephanie  
(NIH/NICHD) [E]  
Subject: RE: Steering Committee Call Tomorrow

While it may seem that I am fixated on an unimportant issue regarding a not quite significant difference, I think we undermine the credibility of Network studies if we are not completely forthright about problems in measuring what everyone would agree is an important secondary outcome. Not reporting that the assessment of BPD by oxygen administration could be



biased by continued use of the study oximeters would seem to be in the category of not reporting protocol deviations and not something that is in the Network's best interest. Why not just put a footnote under the table describing the problem?

Jon E. Tyson, MD, MPH  
Center for Clinical Research & Evidence-Based Medicine  
UT Medical School at Houston  
6431 Fannin St., MSB 2.106  
Houston, TX 77030  
voice 713-500-5651  
fax 713-500-0519

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
Sent: Tuesday, February 23, 2010 2:11 PM  
To: 'Cunningham, Meg'; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; Wallace, Dennis; cotte010@mc.duke.edu; Tyson, Jon E; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; bbatton@siumed.edu  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; lmoore@med.wayne.edu; pamela.neville@duke.edu; gonza025@mc.duke.edu; Smith, Nancy M; Brenda Vecchio; msumner@peds.uab.edu; Archer, Stephanie (NIH/NICHD) [E]  
Subject: RE: Steering Committee Call Tomorrow

If you joined the call already in progress, please send us an email so we can count your attendance.

Rose

From: Cunningham, Meg [mailto:mcunningham@rti.org]  
Sent: Monday, February 22, 2010 9:59 AM  
To: [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; Higgins, Rosemary (NIH/NICHD) [E]; ifrantz@tuftsmedicalcenter.org; Kathleen.A.Kennedy@uth.tmc.edu; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; Wallace, Dennis; cotte010@mc.duke.edu; jon.e.tyson@uth.tmc.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; bbatton@siumed.edu  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; lmoore@med.wayne.edu; pamela.neville@duke.edu; gonza025@mc.duke.edu; Nancy.M.Smith@uth.tmc.edu; Brenda Vecchio; msumner@peds.uab.edu; Archer, Stephanie (NIH/NICHD) [E]  
Subject: Steering Committee Call Tomorrow

Dear All -

The next standing Steering Committee call is scheduled for tomorrow, Tuesday, February 23rd at 3:00pm ET.

Please Dial:

Outside the USA 1-203-310-(b) (6)  
or Within the USA 866-675-(b) (6)

Then, enter Participant Passcode: (b) (6)

Steering Committee Conference Call Agenda 02/23/2010

1. Early BP discussion (attached are a brief description of the time limited data collection proposal and a draft of the form which would be used.)
2. SUPPORT manuscript discussion and update
3. New Business

Thanks,

Meg

Meg Cunningham  
RTI International  
701 13th St. NW, Ste. 750  
Washington, DC 20005  
tel: 202-974-7837  
fax: 202-728-2095  
www.rti.org<<http://www.rti.org>>

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Cunningham, Meg"  
**Subject:** RE: \*\*\*\*\* Important -Follow Up ON BPD and Oximeters\*\*\*\*\*  
**Date:** Tuesday, March 02, 2010 1:34:00 PM

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probably

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**From:** Cunningham, Meg [mailto:mcunningham@rti.org]  
**Sent:** Tuesday, March 02, 2010 1:33 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: \*\*\*\*\* Important -Follow Up ON BPD and Oximeters\*\*\*\*\*

Do you want minutes on this discussion?

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**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Tuesday, March 02, 2010 1:30 PM  
**To:** Cunningham, Meg  
**Subject:** RE: \*\*\*\*\* Important -Follow Up ON BPD and Oximeters\*\*\*\*\*

I polled them – once I hear from Schibler we will be good to go –looking like 430 ET

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**From:** Cunningham, Meg [mailto:mcunningham@rti.org]  
**Sent:** Tuesday, March 02, 2010 1:28 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: \*\*\*\*\* Important -Follow Up ON BPD and Oximeters\*\*\*\*\*

Let me know if you want me to start calling some people!

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**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Tuesday, March 02, 2010 1:08 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; 'Wally Carlo, M.D.'; 'Finer, Neil'; 'alaptook@WIHRI.org'; 'Roger.Faix@hsc.utah.edu'; 'Bradley Yoder'; 'kurt.schibler@cchmc.org'; Das, Abhik; 'nancy newman'; 'Rich, Wade'; Gantz, Marie; 'mcw3@case.edu'; Wallace, Dennis  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Cunningham, Meg  
**Subject:** RE: \*\*\*\*\* Important -Follow Up ON BPD and Oximeters\*\*\*\*\*

**I would like to have a brief call this afternoon to discuss with the subcommittee.**

**Let me know if you could join a call sometime between 330-5 PM TODAY, let me know ASAP.**

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Monday, March 01, 2010 11:00 AM  
**To:** 'Wally Carlo, M.D.'; 'Finer, Neil'; alaptook@WIHRI.org; Roger.Faix@hsc.utah.edu; Bradley Yoder;

kurt.schibler@cchmc.org; adas@rti.org; nancy newman; Rich, Wade; Gantz, Marie; mcw3@case.edu;  
Dennis Wallace  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin  
**Subject:** \*\*\*\*\* Important -Follow Up ON BPD and Oximeters\*\*\*\*\*  
**Importance:** High

To the SUPPORT Subcommittee

Given the email exchange, the subcommittee will need to ascertain whether or not to indicate in the SUPPORT papers whether or not a bias could have existed in reporting the secondary outcome of BPD based on oximeter. Previously the subcommittee had reviewed the oximeter use on a conference call and decided to defer this to a secondary paper. There has been discussion on the SC call and via email subsequently.

**Therefore, please send me a yes/no vote to include this in the paper by March 2.**

Thanks  
Rose

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**From:** Tyson, Jon E [mailto:Jon.E.Tyson@uth.tmc.edu]  
**Sent:** Friday, February 26, 2010 6:28 PM  
**To:** Wallace, Dennis; Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; Stevenson David (E-mail); Finer, Neil; Rich, Wade; Gantz, Marie  
**Cc:** Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: Follow Up ON BPD and Oximeters

I don't understand your statement "Controlling for center adjusts for differences between centers including differences in the BPD oximeter used." To simplify the discussion, suppose every center always used the study oximeter in designating who had BPD by oxygen saturation. Because the true saturation that would prompt oxygen administration would differ in the two treatment groups, there would be systematic bias toward administering oxygen to more infants in the high sat group than in the low sat group. This is inherent in the study design. Whatever differences there were between centers, this bias would occur in every center and would not be eliminated by controlling for center. And if I understand the analysis, there would be no interaction between treatment oximeter and BPD oximeter because they would be the same in every baby in every center.

You indicate that 5 centers used the study oximeter in almost every baby. In saying "it's not possible to tease out the effect of the BPD oximeter from other between-center differences" (a statement that I certainly accept), aren't you saying that the effect of the study oximeter on the difference in the incidence of BPD by oxygen administration between high and low sat groups (i.e., the bias) can not be distinguished from the effect of the myriad of other factors in those centers that might affect that difference in incidence? If so, why would you expect to be able to discern that bias (the signal) from all the noise resulting from other factors? I understand from what you said that the same approach was used in virtually all infants in each center which makes the effective n to be based on the number of

centers rather than the number of babies. As I understand the analysis, the power to assess an interaction would then be quite low.

The issue here is whether is simply whether to report somewhere in the paper (which could be noted under the table and wouldn't increase the word count for the text) a bias in evaluating a secondary outcome. This can be done with no delay in submitting the manuscript or waiting for Maria to return. *If we had other real or potential sources of bias—say, a breaking of the blind for some infants, open label administration of a study drug to the control group, or differential loss to follow-up, we would certainly report it as a matter of course, whether or not there was a significant or near significant difference in the outcome and without testing and whether or not we assessed or found any interaction or other statistical evidence that this potential source of bias affected the results!*

Jon E. Tyson, MD, MPH  
Center for Clinical Research & Evidence-Based Medicine  
UT Medical School at Houston  
6431 Fannin St., MSB 2.106  
Houston, TX 77030  
voice 713-500-5651  
fax 713-500-0519

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**From:** Wallace, Dennis [mailto:dwallace@rti.org]  
**Sent:** Friday, February 26, 2010 1:56 PM  
**To:** Wallace, Dennis; Tyson, Jon E; Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; Stevenson David (E-mail); Finer, Neil; Rich, Wade; Gantz, Marie  
**Cc:** Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: Follow Up ON BPD and Oximeters

Hello all,

I accidentally hit the send button before finishing editing this response so ignore the earlier e-mail and see the response below.

Dennis

Dennis Wallace  
Senior Research Statistician  
Cox 241  
RTI International  
3040 Cornwallis Rd  
Research Triangle Park, NC 27709-2104  
Voice: 919-541-6271  
Fax: 919-541-6416

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**From:** Wallace, Dennis  
**Sent:** Friday, February 26, 2010 2:53 PM  
**To:** 'Tyson, Jon E'; Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu;

sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; 'Stevenson David (E-mail)'; 'Finer, Neil'; Rich, Wade; Gantz, Marie  
**Cc:** Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: Follow Up ON BPD and Oximeters

Jon,

Marie flew out on a long-scheduled vacation after completing these analyses late Tuesday evening and has very limited e-mail and cell phone access. However, she has taken time to provide a preliminary response that I've outlined below with some added thoughts of my own in red font below. Based on these responses, I do believe that the critical concerns about bias have been addressed sufficiently for this initial manuscript, but if you think we need to have a more full discussion, we can talk after Marie returns next week. Because the programming for these outcome measures is relatively complicated, I'm hesitant to try to do any additional analyses prior to her return. However, as I indicated above, I don't think that we need to delay any submissions while trying to iron on the small details.

Dennis Wallace  
Senior Research Statistician  
Cox 241  
RTI International  
3040 Cornwallis Rd  
Research Triangle Park, NC 27709-2104  
Voice: 919-541-6271  
Fax: 919-541-6416

-----Original Message-----

From: Tyson, Jon E [mailto:Jon.E.Tyson@uth.tmc.edu]  
Sent: Thursday, February 25, 2010 12:45 AM  
To: Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; Wallace, Dennis; cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; 'Stevenson David (E-mail)'; 'Finer, Neil'; Rich, Wade; Gantz, Marie  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]  
Subject: RE: Follow Up ON BPD and Oximeters

Rose, before we can understand and interpret this information noted in the mail, we really need to know more about what was done and answers to questions like those below:

1. Which trial result was addressed - whether the evaluation of BPD was biased in the analyses of CPAP/limited ventilation vs. surfactant/conventional ventilation arm (not the analysis for which there is concern) or the analyses of the high vs. low oxygen saturation goal.

Although models were run for the different arms of the factorial design, the trial result that was addressed in the earlier e-mail was the impact of different oximeters on the comparison of the effects high vs. low oxygen saturation targets on BPD and BPD/death outcomes, which we believe is the question of interest.

2. Do we have reliable data to know whether individual infants were monitored on the study oximeter or on the clinical oximeter on the day the infant was 36 weeks and 0 and whether the oximeter was changed part way through that 24 hour period? What was done if the infant was switched on that day. As I understand it, the diagnosis of BPD was based on the entire 24 hours the day the infant was 36 weeks 0 days. Though the results of the survey weren't distributed, my impression from responses to my earlier e mails was that even the procedure usually followed in individual centers was not necessarily clear.

We can determine from form PHY02 what oximeter was used to determine the physiologic definition of BPD, but we do not have the detailed level of information that you described. However, based on the survey results, we do know that only 5 sites used the study oximeter for an oxygen-based definition, and only 3 used the study oximeter for challenge.

3. What variables in the model when the BPD oximeter was added? What variables were in the model when a BPD oximeter x study treatment group was added?

Variables in the model were treatment oximeter (low vs. high), center, GA group. Familial clustering was adjusted for as a random effect. I added BPD oximeter and also looked at the interaction between BPD oximeter and treatment oximeter. These factors were identical to the factors used in the models for which secondary outcomes were reported in the manuscript.

4. Do I understand Maria and you to conclude that because centers tended to be consistent in their oximeter use, controlling for center would prevent a biased assessment of the effect on BPD by oxygen administration?

This comment makes me wonder if the analysis was done for the wrong comparison. This conclusion would be correct for analyses of the effect of CPAP/limited ventilation vs. surfactant/ conventional ventilation on BPD by oxygen delivery (because each treatment arm would contain equal numbers of infants in the high and low sat groups). However, this isn't the comparison in question. This conclusion would certainly not be correct in analyzing the effect of high vs low sat goals on BPD. In this analysis, centers that used the study oximeter would be systematically more likely to administer oxygen to the high sat group than to the low sat group. The problem wouldn't go away by controlling for center, and the more centers that used the study oximeter, the more biased the result would be. How many centers were there that used the study oximeter?

Controlling for center adjusts for differences between centers including differences in the BPD oximeter used. Thus, adding a covariate for BPD oximeter does not change the estimates for the treatment oximeter effect. We are not arguing that the BPD oximeter used did not have an impact. We did find that BPD oximeter was significant in the models, as was center. However, since center and BPD oximeter are strongly confounded (in fact we have almost complete aliasing of center and clinical/study oximeter), it's not possible to tease out the effect of the BPD oximeter from other between-center differences. In addition, the interaction between BPD oximeter and treatment oximeter was not significant. This indicates that the impact of treatment oximeter on the BPD outcomes was not significantly different in the centers that used the study oximeters to determine BPD and those that used the clinical oximeters.

5. What is the basis for believing that there would be anything near reasonable power to assess a oximeter x treatment group interaction?

Clearly, these analyses were conducted from a post-hoc perspective, and the study was never designed to have the power to determine that the interaction in our data set is statistically significant for a pre-specified interaction effect size. But, that is not a shortcoming unless the magnitude of the interaction effect is such that it represents an important scientific bias in study interpretation. Our preliminary analyses indicate that biases of such magnitude are not present in this data set. We can do more detailed analyses of the level of bias that might have been introduced after Marie returns from vacation, but nothing in the analyses conducted to date suggest that those magnitudes warrant delay of submission of this manuscript.

I know that everyone is anxious to get this paper submitted. While I have an external advisory committee tomorrow, I will try to respond tomorrow night if the information requested above is sent tomorrow during the day.

To: Tyson, Jon E; 'Cunningham, Meg'; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; Wallace, Dennis; cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; 'Stevenson David (E-mail)'; 'Finer, Neil'; Rich, Wade; Gantz, Marie  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]  
Subject: Follow Up ON BPD and Oximeters

Hi all -

In Follow up to yesterday's discussion, Marie spent a great deal of time last evening running additional analyses to address (and now alleviate) Jon's concern as described:

We have looked into the question of whether the oximeter used to determine BPD impacted the BPD and death/BPD outcomes by adding a covariate for the BPD oximeter (study or clinical) to the statistical models. We found that the effect of the BPD oximeter was significant; however, the interaction between BPD oximeter and treatment oximeter (low or high SpO2 target range) was not significant in any model, indicating that, if there was a BPD oximeter effect, it was not different in the two treatment groups. In addition, it should be noted that BPD oximeter is confounded with center (centers tended to be consistent in their use of the study or clinical oximeters to determine BPD). Therefore, by including center in the original models, we have already accounted for the effect of the BPD oximeter the center chose to use. Finally, because center and BPD oximeter are confounded, we cannot know whether the significant BPD oximeter effect is due to the BPD oximeters themselves or other characteristics that differ between centers.

---

From: Tyson, Jon E [mailto:Jon.E.Tyson@uth.tmc.edu]  
Sent: Tuesday, February 23, 2010 4:33 PM  
To: Higgins, Rosemary (NIH/NICHD) [E]; 'Cunningham, Meg'; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; Wallace, Dennis; cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; bbatton@siumed.edu  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; lmoore@med.wayne.edu; pamela.neville@duke.edu; gonza025@mc.duke.edu; Smith, Nancy M; Brenda Vecchio; msumner@peds.uab.edu; Archer, Stephanie (NIH/NICHD) [E]  
Subject: RE: Steering Committee Call Tomorrow

While it may seem that I am fixated on an unimportant issue regarding a not quite significant difference, I think we undermine the credibility of Network studies if we are not completely forthright about problems in measuring what everyone would agree is an important secondary outcome. Not reporting that the assessment of BPD by oxygen administration could be biased by continued use of the study oximeters would seem to be in the category of not reporting protocol deviations and not something that is in the Network's best interest. Why not just put a footnote under the table describing the problem?

Jon E. Tyson, MD, MPH  
Center for Clinical Research & Evidence-Based Medicine  
UT Medical School at Houston  
6431 Fannin St., MSB 2.106  
Houston, TX 77030  
voice 713-500-5651  
fax 713-500-0519

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From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]



Sent: Tuesday, February 23, 2010 2:11 PM  
To: 'Cunningham, Meg'; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; Wallace, Dennis; cotte010@mc.duke.edu; Tyson, Jon E; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; bbatton@siumed.edu  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; lmoore@med.wayne.edu; pamela.neville@duke.edu; gonza025@mc.duke.edu; Smith, Nancy M; Brenda Vecchio; msumner@peds.uab.edu; Archer, Stephanie (NIH/NICHD) [E]  
Subject: RE: Steering Committee Call Tomorrow

If you joined the call already in progress, please send us an email so we can count your attendance.

Rose

From: Cunningham, Meg [mailto:mcunningham@rti.org]  
Sent: Monday, February 22, 2010 9:59 AM  
To: [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; Higgins, Rosemary (NIH/NICHD) [E]; ifrantz@tuftsmedicalcenter.org; Kathleen.A.Kennedy@uth.tmc.edu; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; Wallace, Dennis; cotte010@mc.duke.edu; jon.e.tyson@uth.tmc.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; bbatton@siumed.edu  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; lmoore@med.wayne.edu; pamela.neville@duke.edu; gonza025@mc.duke.edu; Nancy.M.Smith@uth.tmc.edu; Brenda Vecchio; msumner@peds.uab.edu; Archer, Stephanie (NIH/NICHD) [E]  
Subject: Steering Committee Call Tomorrow

Dear All -

The next standing Steering Committee call is scheduled for tomorrow, Tuesday, February 23rd at 3:00pm ET.

Please Dial:

Outside the USA 1-203-310-(b)

or Within the USA 866-675-(b) (6)

Then, enter Participant Passcode: (b) (6)

Steering Committee Conference Call Agenda 02/23/2010

1. Early BP discussion (attached are a brief description of the time limited data collection proposal and a draft of the form which would be used.)
2. SUPPORT manuscript discussion and update
3. New Business

Thanks,  
Meg

Meg Cunningham  
RTI International  
701 13th St. NW, Ste. 750  
Washington, DC 20005  
tel: 202-974-7837  
fax: 202-728-2095  
www.rti.org<<http://www.rti.org>>

**From:** Walsh, Michele  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: \*\*\*\*\* Important -Follow Up ON BPD and Oximeters\*\*\*\*\*  
**Date:** Tuesday, March 02, 2010 1:33:55 PM

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Post call, wont be awake that long.

Michele Walsh  
beeper (b) (6)  
Ph 216 844 3759

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**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Tuesday, March 02, 2010 1:29 PM  
**To:** Walsh, Michele  
**Subject:** RE: \*\*\*\*\* Important -Follow Up ON BPD and Oximeters\*\*\*\*\*

Neil and Wally weren't available except 330-5. Could you do 430??

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**From:** Walsh, Michele [mailto:Michele.Walsh@UHhospitals.org]  
**Sent:** Tuesday, March 02, 2010 1:27 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: \*\*\*\*\* Important -Follow Up ON BPD and Oximeters\*\*\*\*\*

I think We all have the NEST call at 2p.  
Perhaps after that?

Michele Walsh  
beeper (b) (6)  
Ph 216 844 3759

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**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Tuesday, March 02, 2010 1:08 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; 'Wally Carlo, M.D.'; 'Finer, Neil'; 'alaptook@WIHRI.org'; 'Roger.Faix@hsc.utah.edu'; 'Bradley Yoder'; 'kurt.schibler@cchmc.org'; 'adas@rti.org'; 'nancy newman'; 'Rich, Wade'; 'Gantz, Marie'; 'mcw3@case.edu'; 'Dennis Wallace'  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; 'Zaterka-Baxter, Kristin'; Cunningham, Meg  
**Subject:** RE: \*\*\*\*\* Important -Follow Up ON BPD and Oximeters\*\*\*\*\*

**I would like to have a brief call this afternoon  
to discuss with the subcommittee.**

**Let me know if you could join a call sometime  
between 330-5 PM TODAY, let me know ASAP.**

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]

**Sent:** Monday, March 01, 2010 11:00 AM

**To:** 'Wally Carlo, M.D.'; 'Finer, Neil'; alaptook@WIHRI.org; Roger.Faix@hsc.utah.edu; Bradley Yoder; kurt.schibler@cchmc.org; adas@rti.org; nancy newman; Rich, Wade; Gantz, Marie; mcw3@case.edu; Dennis Wallace

**Cc:** Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin

**Subject:** \*\*\*\*\* Important -Follow Up ON BPD and Oximeters\*\*\*\*\*

**Importance:** High

To the SUPPORT Subcommittee

Given the email exchange, the subcommittee will need to ascertain whether or not to indicate in the SUPPORT papers whether or not a bias could have existed in reporting the secondary outcome of BPD based on oximeter. Previously the subcommittee had reviewed the oximeter use on a conference call and decided to defer this to a secondary paper. There has been discussion on the SC call and via email subsequently.

**Therefore, please send me a yes/no vote to include this in the paper by March 2.**

Thanks

Rose

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**From:** Tyson, Jon E [mailto:Jon.E.Tyson@uth.tmc.edu]

**Sent:** Friday, February 26, 2010 6:28 PM

**To:** Wallace, Dennis; Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpointex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; Stevenson David (E-mail); Finer, Neil; Rich, Wade; Gantz, Marie

**Cc:** Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]

**Subject:** RE: Follow Up ON BPD and Oximeters

I don't understand your statement "Controlling for center adjusts for differences between centers including differences in the BPD oximeter used." To simplify the discussion, suppose every center always used the study oximeter in designating who had BPD by oxygen saturation. Because the true saturation that would prompt oxygen administration would differ in the two treatment groups, there would be systematic bias toward administering oxygen to more infants in the high sat group than in the low sat group. This is inherent in the study design. Whatever differences there were between centers, this bias would occur in every center and would not be eliminated by controlling for center. And if I understand the analysis, there would be no interaction between treatment oximeter and BPD oximeter because they would be the same in every baby in every center.

You indicate that 5 centers used the study oximeter in almost every baby. In saying "it's not possible to tease out the effect of the BPD oximeter from other between-center differences" (a statement that I certainly accept), aren't you saying that the effect of the study oximeter on the difference in the incidence of BPD by oxygen administration between high and low sat groups (i.e., the bias) can not be distinguished from the effect of the myriad of other factors in those centers that might affect that difference in incidence? If so, why would you expect to be able to discern that bias (the signal) from all the noise resulting from other factors? I understand

from what you said that the same approach was used in virtually all infants in each center which makes the effective n to be based on the number of centers rather than the number of babies. As I understand the analysis, the power to assess an interaction would then be quite low.

The issue here is whether is simply whether to report somewhere in the paper (which could be noted under the table and wouldn't increase the word count for the text) a bias in evaluating a secondary outcome. This can be done with no delay in submitting the manuscript or waiting for Maria to return. *If we had other real or potential sources of bias—say, a breaking of the blind for some infants, open label administration of a study drug to the control group, or differential loss to follow-up, we would certainly report it as a matter of course, whether or not there was a significant or near significant difference in the outcome and without testing and whether or not we assessed or found any interaction or other statistical evidence that this potential source of bias affected the results!*

Jon E. Tyson, MD, MPH  
Center for Clinical Research & Evidence-Based Medicine  
UT Medical School at Houston  
6431 Fannin St., MSB 2.106  
Houston, TX 77030  
voice 713-500-5651  
fax 713-500-0519

---

**From:** Wallace, Dennis [mailto:dwallace@rti.org]

**Sent:** Friday, February 26, 2010 1:56 PM

**To:** Wallace, Dennis; Tyson, Jon E; Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; Stevenson David (E-mail); Finer, Neil; Rich, Wade; Gantz, Marie

**Cc:** Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]

**Subject:** RE: Follow Up ON BPD and Oximeters

Hello all,

I accidentally hit the send button before finishing editing this response so ignore the earlier e-mail and see the response below.

Dennis

Dennis Wallace  
Senior Research Statistician  
Cox 241  
RTI International  
3040 Cornwallis Rd  
Research Triangle Park, NC 27709-2104  
Voice: 919-541-6271  
Fax: 919-541-6416

---

**From:** Wallace, Dennis

**Sent:** Friday, February 26, 2010 2:53 PM

**To:** 'Tyson, Jon E'; Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org;

kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; 'Stevenson David (E-mail)'; 'Finer, Neil'; Rich, Wade; Gantz, Marie

**Cc:** Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]

**Subject:** RE: Follow Up ON BPD and Oximeters

Jon,

Marie flew out on a long-scheduled vacation after completing these analyses late Tuesday evening and has very limited e-mail and cell phone access. However, she has taken time to provide a preliminary response that I've outlined below with some added thoughts of my own in red font below. Based on these responses, I do believe that the critical concerns about bias have been addressed sufficiently for this initial manuscript, but if you think we need to have a more full discussion, we can talk after Marie returns next week. Because the programming for these outcome measures is relatively complicated, I'm hesitant to try to do any additional analyses prior to her return. However, as I indicated above, I don't think that we need to delay any submissions while trying to iron on the small details.

Dennis Wallace  
Senior Research Statistician  
Cox 241  
RTI International  
3040 Cornwallis Rd  
Research Triangle Park, NC 27709-2104  
Voice: 919-541-6271  
Fax: 919-541-6416

-----Original Message-----

From: Tyson, Jon E [mailto:Jon.E.Tyson@uth.tmc.edu]  
Sent: Thursday, February 25, 2010 12:45 AM  
To: Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; Wallace, Dennis; cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; 'Stevenson David (E-mail)'; 'Finer, Neil'; Rich, Wade; Gantz, Marie  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]  
Subject: RE: Follow Up ON BPD and Oximeters

Rose, before we can understand and interpret this information noted in the mail, we really need to know more about what was done and answers to questions like those below:

1. Which trial result was addressed - whether the evaluation of BPD was biased in the analyses of CPAP/limited ventilation vs. surfactant/conventional ventilation arm (not the analysis for which there is concern) or the analyses of the high vs. low oxygen saturation goal.

Although models were run for the different arms of the factorial design, the trial result that was addressed in the earlier e-mail was the impact of different oximeters on the comparison of the effects high vs. low oxygen saturation targets on BPD and BPD/death outcomes, which we believe is the question of interest.

2. Do we have reliable data to know whether individual infants were monitored on the study oximeter or on the clinical oximeter on the day the infant was 36 weeks and 0 and whether the oximeter was changed part way through that 24 hour period? What was done if the infant was switched on that day. As I understand it, the diagnosis of BPD was based on the entire 24 hours the day the infant was 36 weeks 0 days. Though the results of the survey weren't distributed, my impression from responses to my earlier e

mails was that even the procedure usually followed in individual centers was not necessarily clear.

We can determine from form PHY02 what oximeter was used to determine the physiologic definition of BPD, but we do not have the detailed level of information that you described. However, based on the survey results, we do know that only 5 sites used the study oximeter for an oxygen-based definition, and only 3 used the study oximeter for challenge.

3. What variables in the model when the BPD oximeter was added? What variables were in the model when a BPD oximeter x study treatment group was added?

Variables in the model were treatment oximeter (low vs. high), center, GA group. Familial clustering was adjusted for as a random effect. I added BPD oximeter and also looked at the interaction between BPD oximeter and treatment oximeter. These factors were identical to the factors used in the models for which secondary outcomes were reported in the manuscript.

4. Do I understand Maria and you to conclude that because centers tended to be consistent in their oximeter use, controlling for center would prevent a biased assessment of the effect on BPD by oxygen administration?

This comment makes me wonder if the analysis was done for the wrong comparison. This conclusion would be correct for analyses of the effect of CPAP/limited ventilation vs. surfactant/ conventional ventilation on BPD by oxygen delivery (because each treatment arm would contain equal numbers of infants in the high and low sat groups). However, this isn't the comparison in question. This conclusion would certainly not be correct in analyzing the effect of high vs low sat goals on BPD. In this analysis, centers that used the study oximeter would be systematically more likely to administer oxygen to the high sat group than to the low sat group. The problem wouldn't go away by controlling for center, and the more centers that used the study oximeter, the more biased the result would be. How many centers were there that used the study oximeter?

Controlling for center adjusts for differences between centers including differences in the BPD oximeter used. Thus, adding a covariate for BPD oximeter does not change the estimates for the treatment oximeter effect. We are not arguing that the BPD oximeter used did not have an impact. We did find that BPD oximeter was significant in the models, as was center. However, since center and BPD oximeter are strongly confounded (in fact we have almost complete aliasing of center and clinical/study oximeter), it's not possible to tease out the effect of the BPD oximeter from other between-center differences. In addition, the interaction between BPD oximeter and treatment oximeter was not significant. This indicates that the impact of treatment oximeter on the BPD outcomes was not significantly different in the centers that used the study oximeters to determine BPD and those that used the clinical oximeters.

5. What is the basis for believing that there would be anything near reasonable power to assess a oximeter x treatment group interaction?

Clearly, these analyses were conducted from a post-hoc perspective, and the study was never designed to have the power to determine that the interaction in our data set is statistically significant for a pre-specified interaction effect size. But, that is not a shortcoming unless the magnitude of the interaction effect is such that it represents an important scientific bias in study interpretation. Our preliminary analyses indicate that biases of such magnitude are not present in this data set. We can do more detailed analyses of the level of bias that might have been introduced after Marie returns from vacation, but nothing in the analyses conducted to date suggest that those magnitudes warrant delay of submission of this manuscript.

I know that everyone is anxious to get this paper submitted. While I have an external advisory committee tomorrow, I will try to respond tomorrow night if the information requested above is sent tomorrow during the day.

---

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]  
Sent: Wednesday, February 24, 2010 7:53 AM  
To: Tyson, Jon E; 'Cunningham, Meg'; [SCRN] Stoll, Barbara;  
alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik;  
goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A;  
kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu;  
matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org;  
Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu;  
Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu;  
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cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu;  
Luc.Brion@utsouthwestern.edu; 'Stevenson David (E-mail)'; 'Finer, Neil';  
Rich, Wade; Gantz, Marie  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman,  
Jamie; Archer, Stephanie (NIH/NICHD) [E]  
Subject: Follow Up ON BPD and Oximeters

Hi all -

In Follow up to yesterday's discussion, Marie spent a great deal of time last evening running additional analyses to address (and now alleviate) Jon's concern as described:

We have looked into the question of whether the oximeter used to determine BPD impacted the BPD and death/BPD outcomes by adding a covariate for the BPD oximeter (study or clinical) to the statistical models. We found that the effect of the BPD oximeter was significant; however, the interaction between BPD oximeter and treatment oximeter (low or high SpO2 target range) was not significant in any model, indicating that, if there was a BPD oximeter effect, it was not different in the two treatment groups. In addition, it should be noted that BPD oximeter is confounded with center (centers tended to be consistent in their use of the study or clinical oximeters to determine BPD). Therefore, by including center in the original models, we have already accounted for the effect of the BPD oximeter the center chose to use. Finally, because center and BPD oximeter are confounded, we cannot know whether the significant BPD oximeter effect is due to the BPD oximeters themselves or other characteristics that differ between centers.

---

From: Tyson, Jon E [mailto:Jon.E.Tyson@uth.tmc.edu]  
Sent: Tuesday, February 23, 2010 4:33 PM  
To: Higgins, Rosemary (NIH/NICHD) [E]; 'Cunningham, Meg'; [SCRN] Stoll,  
Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik;  
goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A;  
kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu;  
matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org;  
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vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; Wallace, Dennis;  
cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu;  
Luc.Brion@utsouthwestern.edu; bbatton@siumed.edu  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman,  
Jamie; lmoore@med.wayne.edu; pamela.neville@duke.edu; gonza025@mc.duke.edu;  
Smith, Nancy M; Brenda Vecchio; msumner@peds.uab.edu; Archer, Stephanie  
(NIH/NICHD) [E]  
Subject: RE: Steering Committee Call Tomorrow

While it may seem that I am fixated on an unimportant issue regarding a not quite significant difference, I think we undermine the credibility of Network studies if we are not completely forthright about problems in measuring what everyone would agree is an important secondary outcome. Not reporting that the assessment of BPD by oxygen administration could be biased by continued use of the study oximeters would seem to be in the category of not reporting protocol deviations and not something that is in the Network's best interest. Why not just put a footnote under the table describing the problem?

Jon E. Tyson, MD, MPH  
Center for Clinical Research & Evidence-Based Medicine  
UT Medical School at Houston  
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Houston, TX 77030  
voice 713-500-5651  
fax 713-500-0519

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
Sent: Tuesday, February 23, 2010 2:11 PM  
To: 'Cunningham, Meg'; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; Wallace, Dennis; cotte010@mc.duke.edu; Tyson, Jon E; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; bbatton@siumed.edu  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; lmoore@med.wayne.edu; pamela.neville@duke.edu; gonza025@mc.duke.edu; Smith, Nancy M; Brenda Vecchio; msumner@peds.uab.edu; Archer, Stephanie (NIH/NICHD) [E]  
Subject: RE: Steering Committee Call Tomorrow

If you joined the call already in progress, please send us an email so we can count your attendance.

Rose

From: Cunningham, Meg [mailto:mcunningham@rti.org]  
Sent: Monday, February 22, 2010 9:59 AM  
To: [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; Higgins, Rosemary (NIH/NICHD) [E]; ifrantz@tuftsmedicalcenter.org; Kathleen.A.Kennedy@uth.tmc.edu; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; Wallace, Dennis; cotte010@mc.duke.edu; jon.e.tyson@uth.tmc.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; bbatton@siumed.edu  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; lmoore@med.wayne.edu; pamela.neville@duke.edu; gonza025@mc.duke.edu; Nancy.M.Smith@uth.tmc.edu; Brenda Vecchio; msumner@peds.uab.edu; Archer, Stephanie (NIH/NICHD) [E]  
Subject: Steering Committee Call Tomorrow

Dear All -

The next standing Steering Committee call is scheduled for tomorrow, Tuesday, February 23rd at 3:00pm ET.

Please Dial:

Outside the USA 1-203-310 (b) (6)

or Within the USA 866-675 (b) (6)

Then, enter Participant Passcode: (b) (6)

Steering Committee Conference Call Agenda 02/23/2010

1. Early BP discussion (attached are a brief description of the time limited data collection proposal and a draft of the form which would be used.)
2. SUPPORT Manuscript discussion and update
3. New Business

Thanks,  
Meg

Meg Cunningham  
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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.

## **Higgins, Rosemary (NIH/NICHD) [E]**

---

**From:** Finer, Neil <nfiner@ucsd.edu>  
**Sent:** Tuesday, March 02, 2010 1:24 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** Re: \*\*\*\*\* Important -Follow Up ON BPD and Oximeters\*\*\*\*\*

I can join on my mobile  
Neil

Sent from my iPhone

On Mar 2, 2010, at 10:11 AM, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov<mailto:higginsr@mail.nih.gov>> wrote:

I would like to have a brief call this afternoon to discuss with the subcommittee.

Let me know if you could join a call sometime between 330-5 PM TODAY, let me know ASAP.

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Monday, March 01, 2010 11:00 AM  
**To:** 'Wally Carlo, M.D.'; 'Finer, Neil'; alaptook@WIHRI.org<mailto:alaptook@WIHRI.org>; Roger.Faix@hsc.utah.edu<mailto:Roger.Faix@hsc.utah.edu>; Bradley Yoder; kurt.schibler@cchmc.org<mailto:kurt.schibler@cchmc.org>; adas@rti.org<mailto:adas@rti.org>; nancy newman; Rich, Wade; Gantz, Marie; mcw3@case.edu<mailto:mcw3@case.edu>; Dennis Wallace  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin  
**Subject:** \*\*\*\*\* Important -Follow Up ON BPD and Oximeters\*\*\*\*\*  
**Importance:** High

To the SUPPORT Subcommittee

Given the email exchange, the subcommittee will need to ascertain whether or not to indicate in the SUPPORT papers whether or not a bias could have existed in reporting the secondary outcome of BPD based on oximeter. Previously the subcommittee had reviewed the oximeter use on a conference call and decided to defer this to a secondary paper. There has been discussion on the SC call and via email subsequently.

Therefore, please send me a yes/no vote to include this in the paper by March 2.

Thanks  
Rose

---

**From:** Tyson, Jon E [mailto:Jon.E.Tyson@uth.tmc.edu]  
**Sent:** Friday, February 26, 2010 6:28 PM  
**To:** Wallace, Dennis; Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara; alaptook@WIHRI.org<mailto:alaptook@WIHRI.org>; Bell, Edward; bpoindex@iupui.edu<mailto:bpoindex@iupui.edu>; Das, Abhik; goldb008@mc.duke.edu<mailto:goldb008@mc.duke.edu>; ifrantz@tuftsmedicalcenter.org<mailto:ifrantz@tuftsmedicalcenter.org>; Kennedy, Kathleen A; kurt.schibler@cchmc.org<mailto:kurt.schibler@cchmc.org>; kwatterberg@salud.unm.edu<mailto:kwatterberg@salud.unm.edu>;

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Luc.Brion@utsouthwestern.edu<mailto:Luc.Brion@utsouthwestern.edu>; Stevenson David (E-mail); Finer, Neil; Rich,  
Wade; Gantz, Marie  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]  
Subject: RE: Follow Up ON BPD and Oximeters

I don't understand your statement "Controlling for center adjusts for differences between centers including differences in the BPD oximeter used." To simplify the discussion, suppose every center always used the study oximeter in designating who had BPD by oxygen saturation. Because the true saturation that would prompt oxygen administration would differ in the two treatment groups, there would be systematic bias toward administering oxygen to more infants in the high sat group than in the low sat group. This is inherent in the study design. Whatever differences there were between centers, this bias would occur in every center and would not be eliminated by controlling for center. And if I understand the analysis, there would be no interaction between treatment oximeter and BPD oximeter because they would be the same in every baby in every center.

You indicate that 5 centers used the study oximeter in almost every baby. In saying "it's not possible to tease out the effect of the BPD oximeter from other between-center differences" (a statement that I certainly accept), aren't you saying that the effect of the study oximeter on the difference in the incidence of BPD by oxygen administration between high and low sat groups (i.e., the bias) can not be distinguished from the effect of the myriad of other factors in those centers that might affect that difference in incidence? If so, why would you expect to be able to discern that bias (the signal) from all the noise resulting from other factors? I understand from what you said that the same approach was used in virtually all infants in each center which makes the effective n to be based on the number of centers rather than the number of babies. As I understand the analysis, the power to assess an interaction would then be quite low.

The issue here is whether is simply whether to report somewhere in the paper (which could be noted under the table and wouldn't increase the word count for the text) a bias in evaluating a secondary outcome. This can be done with no delay in submitting the manuscript or waiting for Maria to return. If we had other real or potential sources of bias—say, a breaking of the blind for some infants, open label administration of a study drug to the control group, or differential loss to follow-up, we would certainly report it as a matter of course, whether or not there was a significant or near significant difference in the outcome and without testing and whether or not we assessed or found any interaction or other statistical evidence that this potential source of bias affected the results!

Jon E. Tyson, MD, MPH  
Center for Clinical Research & Evidence-Based Medicine UT Medical School at Houston  
6431 Fannin St., MSB 2.106  
Houston, TX 77030  
voice 713-500-5651  
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From: Wallace, Dennis [mailto:dwallace@rti.org]  
Sent: Friday, February 26, 2010 1:56 PM

To: Wallace, Dennis; Tyson, Jon E; Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara; alaptook@WIHRI.org<mailto:alaptook@WIHRI.org>; Bell, Edward; bpoindex@iupui.edu<mailto:bpoindex@iupui.edu>; Das, Abhik; goldb008@mc.duke.edu<mailto:goldb008@mc.duke.edu>; ifrantz@tuftsmedicalcenter.org<mailto:ifrantz@tuftsmedicalcenter.org>; Kennedy, Kathleen A; kurt.schibler@cchmc.org<mailto:kurt.schibler@cchmc.org>; kwatterberg@salud.unm.edu<mailto:kwatterberg@salud.unm.edu>; matthew.bizarro@yale.edu<mailto:matthew.bizarro@yale.edu>; mcw3@cwru.edu<mailto:mcw3@cwru.edu>; mcaplan@northshore.org<mailto:mcaplan@northshore.org>; Pablo.Sanchez@UTSouthwestern.edu<mailto:Pablo.Sanchez@UTSouthwestern.edu>; richard.ehrenkranz@yale.edu<mailto:richard.ehrenkranz@yale.edu>; Roger.Faix@hsc.utah.edu<mailto:Roger.Faix@hsc.utah.edu>; sshankar@med.wayne.edu<mailto:sshankar@med.wayne.edu>; vanmeurs@leland.stanford.edu<mailto:vanmeurs@leland.stanford.edu>; Wally Carlo, M.D.; cotte010@mc.duke.edu<mailto:cotte010@mc.duke.edu>; Bradley Yoder; rohls@salud.unm.edu<mailto:rohls@salud.unm.edu>; Luc.Brion@utsouthwestern.edu<mailto:Luc.Brion@utsouthwestern.edu>; Stevenson David (E-mail); Finer, Neil; Rich, Wade; Gantz, Marie  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]  
Subject: RE: Follow Up ON BPD and Oximeters

Hello all,

I accidentally hit the send button before finishing editing this response so ignore the earlier e-mail and see the response below.

Dennis

Dennis Wallace  
Senior Research Statistician  
Cox 241  
RTI International  
3040 Cornwallis Rd  
Research Triangle Park, NC 27709-2104  
Voice: 919-541-6271  
Fax: 919-541-6416

---

From: Wallace, Dennis  
Sent: Friday, February 26, 2010 2:53 PM  
To: 'Tyson, Jon E'; Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara; alaptook@WIHRI.org<mailto:alaptook@WIHRI.org>; Bell, Edward; bpoindex@iupui.edu<mailto:bpoindex@iupui.edu>; Das, Abhik; goldb008@mc.duke.edu<mailto:goldb008@mc.duke.edu>; ifrantz@tuftsmedicalcenter.org<mailto:ifrantz@tuftsmedicalcenter.org>; Kennedy, Kathleen A; kurt.schibler@cchmc.org<mailto:kurt.schibler@cchmc.org>; kwatterberg@salud.unm.edu<mailto:kwatterberg@salud.unm.edu>; matthew.bizarro@yale.edu<mailto:matthew.bizarro@yale.edu>; mcw3@cwru.edu<mailto:mcw3@cwru.edu>; mcaplan@northshore.org<mailto:mcaplan@northshore.org>; Pablo.Sanchez@UTSouthwestern.edu<mailto:Pablo.Sanchez@UTSouthwestern.edu>; richard.ehrenkranz@yale.edu<mailto:richard.ehrenkranz@yale.edu>; Roger.Faix@hsc.utah.edu<mailto:Roger.Faix@hsc.utah.edu>; sshankar@med.wayne.edu<mailto:sshankar@med.wayne.edu>; vanmeurs@leland.stanford.edu<mailto:vanmeurs@leland.stanford.edu>; Wally Carlo, M.D.; cotte010@mc.duke.edu<mailto:cotte010@mc.duke.edu>; Bradley Yoder; rohls@salud.unm.edu<mailto:rohls@salud.unm.edu>;

Luc.Brion@utsouthwestern.edu<mailto:Luc.Brion@utsouthwestern.edu>; 'Stevenson David (E-mail)'; 'Finer, Neil'; Rich, Wade; Gantz, Marie  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]  
Subject: RE: Follow Up ON BPD and Oximeters

Jon,

Marie flew out on a long-scheduled vacation after completing these analyses late Tuesday evening and has very limited e-mail and cell phone access. However, she has taken time to provide a preliminary response that I've outlined below with some added thoughts of my own in red font below. Based on these responses, I do believe that the critical concerns about bias have been addressed sufficiently for this initial manuscript, but if you think we need to have a more full discussion, we can talk after Marie returns next week. Because the programming for these outcome measures is relatively complicated, I'm hesitant to try to do any additional analyses prior to her return. However, as I indicated above, I don't think that we need to delay any submissions while trying to iron on the small details.

Dennis Wallace

Senior Research Statistician

Cox 241

RTI International

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Research Triangle Park, NC 27709-2104

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Fax: 919-541-6416

-----Original Message-----

From: Tyson, Jon E [mailto:Jon.E.Tyson@uth.tmc.edu]

Sent: Thursday, February 25, 2010 12:45 AM

To: Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara;  
alaptook@WIHRI.org<mailto:alaptook@WIHRI.org>; Bell, Edward; bpoindex@iupui.edu<mailto:bpoindex@iupui.edu>;  
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Wade; Gantz, Marie  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]  
Subject: RE: Follow Up ON BPD and Oximeters

Rose, before we can understand and interpret this information noted in the mail, we really need to know more about what was done and answers to questions like those below:

1. Which trial result was addressed – whether the evaluation of BPD was biased in the analyses of CPAP/limited ventilation vs. surfactant/conventional ventilation arm (not the analysis for which there is concern) or the analyses of the high vs. low oxygen saturation goal.

Although models were run for the different arms of the factorial design, the trial result that was addressed in the earlier e-mail was the impact of different oximeters on the comparison of the effects high vs. low oxygen saturation targets on BPD and BPD/death outcomes, which we believe is the question of interest.

2. Do we have reliable data to know whether individual infants were monitored on the study oximeter or on the clinical oximeter on the day the infant was 36 weeks and 0 and whether the oximeter was changed part way through that 24 hour period? What was done if the infant was switched on that day. As I understand it, the diagnosis of BPD was based on the entire 24 hours the day the infant was 36 weeks 0 days. Though the results of the survey weren't distributed, my impression from responses to my earlier e mails was that even the procedure usually followed in individual centers was not necessarily clear.

We can determine from form PHY02 what oximeter was used to determine the physiologic definition of BPD, but we do not have the detailed level of information that you described. However, based on the survey results, we do know that only 5 sites used the study oximeter for an oxygen-based definition, and only 3 used the study oximeter for challenge.

3. What variables in the model when the BPD oximeter was added? What variables were in the model when a BPD oximeter x study treatment group was added?

Variables in the model were treatment oximeter (low vs. high), center, GA group. Familial clustering was adjusted for as a random effect. I added BPD oximeter and also looked at the interaction between BPD oximeter and treatment

oximeter. These factors were identical to the factors used in the models for which secondary outcomes were reported in the manuscript.

4. Do I understand Maria and you to conclude that because centers tended to be consistent in their oximeter use, controlling for center would prevent a biased assessment of the effect on BPD by oxygen administration?

This comment makes me wonder if the analysis was done for the wrong comparison. This conclusion would be correct for analyses of the effect of CPAP/limited ventilation vs. surfactant/ conventional ventilation on BPD by oxygen delivery (because each treatment arm would contain equal numbers of infants in the high and low sat groups). However, this isn't the comparison in question. This conclusion would certainly not be correct in analyzing the effect of high vs low sat goals on BPD. In this analysis, centers that used the study oximeter would be systematically more likely to administer oxygen to the high sat group than to the low sat group. The problem wouldn't go away by controlling for center, and the more centers that used the study oximeter, the more biased the result would be. How many centers were there that used the study oximeter?

Controlling for center adjusts for differences between centers including differences in the BPD oximeter used. Thus, adding a covariate for BPD oximeter does not change the estimates for the treatment oximeter effect. We are not arguing that the BPD oximeter used did not have an impact. We did find that BPD oximeter was significant in the models, as was center. However, since center and BPD oximeter are strongly confounded (in fact we have almost complete aliasing of center and clinical/study oximeter), it's not possible to tease out the effect of the BPD oximeter from other between-center differences. In addition, the interaction between BPD oximeter and treatment oximeter was not significant. This indicates that the impact of treatment oximeter on the BPD outcomes was not significantly different in the centers that used the study oximeters to determine BPD and those that used the clinical oximeters.

5. What is the basis for believing that there would be anything near reasonable power to assess a oximeter x treatment group interaction?

Clearly, these analyses were conducted from a post-hoc perspective, and the study was never designed to have the power to determine that the interaction in our data set is statistically significant for a pre-specified interaction effect size. But, that is not a shortcoming unless the magnitude of the interaction effect is such that it represents an important scientific bias in study interpretation. Our preliminary analyses indicate that biases of such magnitude are not present in this data set. We can do more detailed analyses of the level of bias that might have been introduced after Marie returns from vacation, but nothing in the analyses conducted to date suggest that those magnitudes warrant delay of submission of this manuscript.

I know that everyone is anxious to get this paper submitted. While I have an external advisory committee tomorrow, I will try to respond tomorrow night if the information requested above is sent tomorrow during the day.

---

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]

Sent: Wednesday, February 24, 2010 7:53 AM

To: Tyson, Jon E; 'Cunningham, Meg'; [SCRN] Stoll, Barbara; alaptook@WIHRI.org<mailto:alaptook@WIHRI.org>; Bell, Edward; bpoindex@iupui.edu<mailto:bpoindex@iupui.edu>; Das, Abhik; goldb008@mc.duke.edu<mailto:goldb008@mc.duke.edu>; ifrantz@tuftsmedicalcenter.org<mailto:ifrantz@tuftsmedicalcenter.org>; Kennedy, Kathleen A; kurt.schibler@cchmc.org<mailto:kurt.schibler@cchmc.org>; kwatterberg@salud.unm.edu<mailto:kwatterberg@salud.unm.edu>; matthew.bizarro@yale.edu<mailto:matthew.bizarro@yale.edu>; mcw3@cwru.edu<mailto:mcw3@cwru.edu>; mcaplan@northshore.org<mailto:mcaplan@northshore.org>; Pablo.Sanchez@UTSouthwestern.edu<mailto:Pablo.Sanchez@UTSouthwestern.edu>; richard.ehrenkranz@yale.edu<mailto:richard.ehrenkranz@yale.edu>; Roger.Faix@hsc.utah.edu<mailto:Roger.Faix@hsc.utah.edu>; sshankar@med.wayne.edu<mailto:sshankar@med.wayne.edu>; vanmeurs@leland.stanford.edu<mailto:vanmeurs@leland.stanford.edu>; Wally Carlo, M.D.; Wallace, Dennis; cotte010@mc.duke.edu<mailto:cotte010@mc.duke.edu>; Bradley Yoder; rohls@salud.unm.edu<mailto:rohls@salud.unm.edu>; Luc.Brion@utsouthwestern.edu<mailto:Luc.Brion@utsouthwestern.edu>; 'Stevenson David (E-mail)'; 'Finer, Neil'; Rich, Wade; Gantz, Marie

Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]

Subject: Follow Up ON BPD and Oximeters

Hi all –

In Follow up to yesterday's discussion, Marie spent a great deal of time last evening running additional analyses to address (and now alleviate) Jon's concern as described:

We have looked into the question of whether the oximeter used to determine BPD impacted the BPD and death/BPD outcomes by adding a covariate for the BPD oximeter (study or clinical) to the statistical models. We found that the effect of the BPD oximeter was significant; however, the interaction between BPD oximeter and treatment oximeter (low or high SpO2 target range) was not significant in any model, indicating that, if there was a BPD oximeter effect, it was not different in the two treatment groups. In addition, it should be noted that BPD oximeter is confounded with center (centers tended to be consistent in their use of the study or clinical oximeters to determine BPD). Therefore, by



including center in the original models, we have already accounted for the effect of the BPD oximeter the center chose to use. Finally, because center and BPD oximeter are confounded, we cannot know whether the significant BPD oximeter effect is due to the BPD oximeters themselves or other characteristics that differ between centers.

---

From: Tyson, Jon E [mailto:Jon.E.Tyson@uth.tmc.edu]

Sent: Tuesday, February 23, 2010 4:33 PM

To: Higgins, Rosemary (NIH/NICHD) [E]; 'Cunningham, Meg'; [SCRN] Stoll, Barbara; alaptook@WIHRI.org<mailto:alaptook@WIHRI.org>; Bell, Edward; bpoindex@iupui.edu<mailto:bpoindex@iupui.edu>; Das, Abhik; goldb008@mc.duke.edu<mailto:goldb008@mc.duke.edu>; ifrantz@tuftsmedicalcenter.org<mailto:ifrantz@tuftsmedicalcenter.org>; Kennedy, Kathleen A; kurt.schibler@cchmc.org<mailto:kurt.schibler@cchmc.org>; kwatterberg@salud.unm.edu<mailto:kwatterberg@salud.unm.edu>; matthew.bizarro@yale.edu<mailto:matthew.bizarro@yale.edu>; mcw3@cwru.edu<mailto:mcw3@cwru.edu>; mcaplan@northshore.org<mailto:mcaplan@northshore.org>; Pablo.Sanchez@UTSouthwestern.edu<mailto:Pablo.Sanchez@UTSouthwestern.edu>; richard.ehrenkranz@yale.edu<mailto:richard.ehrenkranz@yale.edu>; Roger.Faix@hsc.utah.edu<mailto:Roger.Faix@hsc.utah.edu>; sshankar@med.wayne.edu<mailto:sshankar@med.wayne.edu>; vanmeurs@leland.stanford.edu<mailto:vanmeurs@leland.stanford.edu>; Wally Carlo, M.D.; Wallace, Dennis; cotte010@mc.duke.edu<mailto:cotte010@mc.duke.edu>; Bradley Yoder; rohls@salud.unm.edu<mailto:rohls@salud.unm.edu>; Luc.Brion@utsouthwestern.edu<mailto:Luc.Brion@utsouthwestern.edu>; <mailto:bbatton@siumed.edu> bbatton@siumed.edu<mailto:bbatton@siumed.edu>

Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; lmoore@med.wayne.edu<mailto:lmoore@med.wayne.edu>; pamelaneville@duke.edu<mailto:pamelaneville@duke.edu>; gonza025@mc.duke.edu<mailto:gonza025@mc.duke.edu>; Smith, Nancy M; Brenda Vecchio; msumner@peds.uab.edu<mailto:msumner@peds.uab.edu>; Archer, Stephanie (NIH/NICHD) [E]

Subject: RE: Steering Committee Call Tomorrow

While it may seem that I am fixated on an unimportant issue regarding a not quite significant difference, I think we undermine the credibility of Network studies if we are not completely forthright about problems in measuring what everyone would agree is an important secondary outcome. Not reporting that the assessment of BPD by oxygen administration could be biased by continued use of the study oximeters would seem to be in the category of not reporting protocol deviations and not something that is in the Network's best interest. Why not just put a footnote under the table describing the problem?

Jon E. Tyson, MD, MPH

Center for Clinical Research & Evidence-Based Medicine

UT Medical School at Houston

6431 Fannin St., MSB 2.106

Houston, TX 77030

voice 713-500-5651

fax 713-500-0519

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From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]

Sent: Tuesday, February 23, 2010 2:11 PM

To: 'Cunningham, Meg'; [SCRN] Stoll, Barbara; alaptook@WIHRI.org<mailto:alaptook@WIHRI.org>; Bell, Edward; bpoindex@iupui.edu<mailto:bpoindex@iupui.edu>; Das, Abhik; goldb008@mc.duke.edu<mailto:goldb008@mc.duke.edu>; ifrantz@tuftsmedicalcenter.org<mailto:ifrantz@tuftsmedicalcenter.org>; Kennedy, Kathleen A; kurt.schibler@cchmc.org<mailto:kurt.schibler@cchmc.org>; kwatterberg@salud.unm.edu<mailto:kwatterberg@salud.unm.edu>; matthew.bizzarro@yale.edu<mailto:matthew.bizzarro@yale.edu>; mcw3@cwru.edu<mailto:mcw3@cwru.edu>; mcaplan@northshore.org<mailto:mcaplan@northshore.org>; Pablo.Sanchez@UTSouthwestern.edu<mailto:Pablo.Sanchez@UTSouthwestern.edu>; richard.ehrenkranz@yale.edu<mailto:richard.ehrenkranz@yale.edu>; Roger.Faix@hsc.utah.edu<mailto:Roger.Faix@hsc.utah.edu>; sshankar@med.wayne.edu<mailto:sshankar@med.wayne.edu>; vanmeurs@leland.stanford.edu<mailto:vanmeurs@leland.stanford.edu>; Wally Carlo, M.D.; Wallace, Dennis; cotte010@mc.duke.edu<mailto:cotte010@mc.duke.edu>; Tyson, Jon E; Bradley Yoder; rohls@salud.unm.edu<mailto:rohls@salud.unm.edu>; Luc.Brion@utsouthwestern.edu<mailto:Luc.Brion@utsouthwestern.edu>; <mailto:bbatton@siumed.edu> bbatton@siumed.edu<mailto:bbatton@siumed.edu>

Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; lmoore@med.wayne.edu<mailto:lmoore@med.wayne.edu>; pamelaneville@duke.edu<mailto:pamelaneville@duke.edu>; gonza025@mc.duke.edu<mailto:gonza025@mc.duke.edu>; Smith, Nancy M; Brenda Vecchio; msumner@peds.uab.edu<mailto:msumner@peds.uab.edu>; Archer, Stephanie (NIH/NICHD) [E]

Subject: RE: Steering Committee Call Tomorrow

If you joined the call already in progress, please send us an email so we can count your attendance.

Rose

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From: Cunningham, Meg [mailto:mcunningham@rti.org]

Sent: Monday, February 22, 2010 9:59 AM

To: [SCRN] Stoll, Barbara; alaptook@WIHRI.org<mailto:alaptook@WIHRI.org>; Bell, Edward; bpoindex@iupui.edu<mailto:bpoindex@iupui.edu>; Das, Abhik; goldb008@mc.duke.edu<mailto:goldb008@mc.duke.edu>; Higgins, Rosemary (NIH/NICHD) [E]; ifrantz@tuftsmedicalcenter.org<mailto:ifrantz@tuftsmedicalcenter.org>; Kathleen.A.Kennedy@uth.tmc.edu<mailto:Kathleen.A.Kennedy@uth.tmc.edu>; kurt.schibler@cchmc.org<mailto:kurt.schibler@cchmc.org>; kwatterberg@salud.unm.edu<mailto:kwatterberg@salud.unm.edu>; matthew.bizarro@yale.edu<mailto:matthew.bizarro@yale.edu>; mcw3@cwru.edu<mailto:mcw3@cwru.edu>; mcaplan@northshore.org<mailto:mcaplan@northshore.org>; Pablo.Sanchez@UTSouthwestern.edu<mailto:Pablo.Sanchez@UTSouthwestern.edu>; richard.ehrenkranz@yale.edu<mailto:richard.ehrenkranz@yale.edu>; Roger.Faix@hsc.utah.edu<mailto:Roger.Faix@hsc.utah.edu>; sshankar@med.wayne.edu<mailto:sshankar@med.wayne.edu>; vanmeurs@leland.stanford.edu<mailto:vanmeurs@leland.stanford.edu>; Wally Carlo, M.D.; Wallace, Dennis; cotte010@mc.duke.edu<mailto:cotte010@mc.duke.edu>; jon.e.tyson@uth.tmc.edu<mailto:jon.e.tyson@uth.tmc.edu>; Bradley Yoder; rohls@salud.unm.edu<mailto:rohls@salud.unm.edu>; Luc.Brion@utsouthwestern.edu<mailto:Luc.Brion@utsouthwestern.edu>; <mailto:bbatton@siumed.edu> bbatton@siumed.edu<mailto:bbatton@siumed.edu>

Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; lmoore@med.wayne.edu<mailto:lmoore@med.wayne.edu>; pamela.neville@duke.edu<mailto:pamela.neville@duke.edu>; gonza025@mc.duke.edu<mailto:gonza025@mc.duke.edu>; Nancy.M.Smith@uth.tmc.edu<mailto:Nancy.M.Smith@uth.tmc.edu>; Brenda Vecchio; msumner@peds.uab.edu<mailto:msumner@peds.uab.edu>; Archer, Stephanie (NIH/NICHD) [E]

Subject: Steering Committee Call Tomorrow

Dear All -

The next standing Steering Committee call is scheduled for tomorrow, Tuesday, February 23rd at 3:00pm ET.

Please Dial:

Outside the USA 1-203-310-(b)

or Within the USA 866-675-(b)

Then, enter Participant Passcode: (b) (6)

Steering Committee Conference Call Agenda 02/23/2010

1. Early BP discussion (attached are a brief description of the time limited data collection proposal and a draft of the form which would be used.)
2. SUPPORT manuscript discussion and update
3. New Business

Thanks,

Meg

Meg Cunningham

RTI International

701 13th St. NW, Ste. 750

Washington, DC 20005

tel: 202-974-7837

fax: 202-728-2095

[www.rti.org](http://www.rti.org)<<http://www.rti.org>><<http://www.rti.org>>

**From:** Roger Faix  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: \*\*\*\*\* Important -Follow Up ON BPD and Oximeters\*\*\*\*\*  
**Date:** Tuesday, March 02, 2010 1:22:31 PM

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Hi Rose!

I have a presentation at another hospital from 1-2 Mountain time (3-4 Eastern time). I could join a call at 2:30 or later Mountain time (4:30 or later Eastern time).

Roger

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**From:** Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]  
**Sent:** Tuesday, March 02, 2010 11:08 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; 'Wally Carlo, M.D.'; 'Finer, Neil'; 'alaptook@WIHRI.org'; Roger Faix; Bradley Yoder; 'kurt.schibler@cchmc.org'; 'adas@rti.org'; 'nancy newman'; 'Rich, Wade'; 'Gantz, Marie'; 'mcw3@case.edu'; 'Dennis Wallace'  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; 'Zaterka-Baxter, Kristin'; Cunningham, Meg  
**Subject:** RE: \*\*\*\*\* Important -Follow Up ON BPD and Oximeters\*\*\*\*\*

**I would like to have a brief call this afternoon to discuss with the subcommittee.**

**Let me know if you could join a call sometime between 330-5 PM TODAY, let me know ASAP.**

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**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Monday, March 01, 2010 11:00 AM  
**To:** 'Wally Carlo, M.D.'; 'Finer, Neil'; alaptook@WIHRI.org; Roger.Faix@hsc.utah.edu; Bradley Yoder; kurt.schibler@cchmc.org; adas@rti.org; nancy newman; Rich, Wade; Gantz, Marie; mcw3@case.edu; Dennis Wallace  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin  
**Subject:** \*\*\*\*\* Important -Follow Up ON BPD and Oximeters\*\*\*\*\*  
**Importance:** High

To the SUPPORT Subcommittee

Given the email exchange, the subcommittee will need to ascertain whether or not to indicate in the SUPPORT papers whether or not a bias could have existed in reporting the secondary outcome of BPD based on oximeter. Previously the subcommittee had reviewed the oximeter use on a conference call and decided to defer this to a secondary paper. There has been discussion on the SC call and via email subsequently.

**Therefore, please send me a yes/no vote to include this in the paper by March 2.**

Thanks  
Rose

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**From:** Tyson, Jon E [mailto:Jon.E.Tyson@uth.tmc.edu]

**Sent:** Friday, February 26, 2010 6:28 PM

**To:** Wallace, Dennis; Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; Stevenson David (E-mail); Finer, Neil; Rich, Wade; Gantz, Marie

**Cc:** Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]

**Subject:** RE: Follow Up ON BPD and Oximeters

I don't understand your statement "Controlling for center adjusts for differences between centers including differences in the BPD oximeter used." To simplify the discussion, suppose every center always used the study oximeter in designating who had BPD by oxygen saturation. Because the true saturation that would prompt oxygen administration would differ in the two treatment groups, there would be systematic bias toward administering oxygen to more infants in the high sat group than in the low sat group. This is inherent in the study design. Whatever differences there were between centers, this bias would occur in every center and would not be eliminated by controlling for center. And if I understand the analysis, there would be no interaction between treatment oximeter and BPD oximeter because they would be the same in every baby in every center.

You indicate that 5 centers used the study oximeter in almost every baby. In saying "it's not possible to tease out the effect of the BPD oximeter from other between-center differences" (a statement that I certainly accept), aren't you saying that the effect of the study oximeter on the difference in the incidence of BPD by oxygen administration between high and low sat groups (i.e., the bias) can not be distinguished from the effect of the myriad of other factors in those centers that might affect that difference in incidence? If so, why would you expect to be able to discern that bias (the signal) from all the noise resulting from other factors? I understand from what you said that the same approach was used in virtually all infants in each center which makes the effective n to be based on the number of centers rather than the number of babies. As I understand the analysis, the power to assess an interaction would then be quite low.

The issue here is whether is simply whether to report somewhere in the paper (which could be noted under the table and wouldn't increase the word count for the text) a bias in evaluating a secondary outcome. This can be done with no delay in submitting the manuscript or waiting for Maria to return. *If we had other real or potential sources of bias—say, a breaking of the blind for some infants, open label administration of a study drug to the control group, or differential loss to follow-up, we would certainly report it as a matter of course, whether or not there was a significant or near significant difference in the outcome and without testing and whether or not we assessed or found any interaction or other statistical evidence that this potential source of bias affected the results!*

Jon E. Tyson, MD, MPH  
Center for Clinical Research & Evidence-Based Medicine  
UT Medical School at Houston  
6431 Fannin St., MSB 2.106  
Houston, TX 77030  
voice 713-500-5651  
fax 713-500-0519

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**From:** Wallace, Dennis [mailto:dwallace@rti.org]  
**Sent:** Friday, February 26, 2010 1:56 PM  
**To:** Wallace, Dennis; Tyson, Jon E; Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; Stevenson David (E-mail); Finer, Neil; Rich, Wade; Gantz, Marie  
**Cc:** Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: Follow Up ON BPD and Oximeters

Hello all,

I accidentally hit the send button before finishing editing this response so ignore the earlier e-mail and see the response below.

Dennis

Dennis Wallace  
Senior Research Statistician  
Cox 241  
RTI International  
3040 Cornwallis Rd  
Research Triangle Park, NC 27709-2104  
Voice: 919-541-6271  
Fax: 919-541-6416

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**From:** Wallace, Dennis  
**Sent:** Friday, February 26, 2010 2:53 PM  
**To:** 'Tyson, Jon E'; Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; 'Stevenson David (E-mail)'; 'Finer, Neil'; Rich, Wade; Gantz, Marie  
**Cc:** Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: Follow Up ON BPD and Oximeters

Jon,

Marie flew out on a long-scheduled vacation after completing these analyses late Tuesday evening and has very limited e-mail and cell phone access. However, she has taken time to provide a preliminary response that I've outlined below with some added thoughts of my own in red font below. Based on these responses, I do believe that the critical concerns about bias have been addressed sufficiently for this initial manuscript, but if you think we need to have a more full discussion, we can talk after Marie returns next week. Because the programming for these outcome measures is relatively complicated, I'm hesitant to try to do any additional analyses prior to her return. However, as I indicated above, I don't think that we need to delay any submissions while trying to iron on the small details.

Dennis Wallace  
Senior Research Statistician  
Cox 241  
RTI International  
3040 Cornwallis Rd  
Research Triangle Park, NC 27709-2104

Voice: 919-541-6271  
Fax: 919-541-6416

-----Original Message-----

From: Tyson, Jon E [mailto:Jon.E.Tyson@uth.tmc.edu]  
Sent: Thursday, February 25, 2010 12:45 AM  
To: Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; Wallace, Dennis; cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; 'Stevenson David (E-mail)'; 'Finer, Neil'; Rich, Wade; Gantz, Marie  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]  
Subject: RE: Follow Up ON BPD and Oximeters

Rose, before we can understand and interpret this information noted in the mail, we really need to know more about what was done and answers to questions like those below:

1. Which trial result was addressed - whether the evaluation of BPD was biased in the analyses of CPAP/limited ventilation vs. surfactant/conventional ventilation arm (not the analysis for which there is concern) or the analyses of the high vs. low oxygen saturation goal.

Although models were run for the different arms of the factorial design, the trial result that was addressed in the earlier e-mail was the impact of different oximeters on the comparison of the effects high vs. low oxygen saturation targets on BPD and BPD/death outcomes, which we believe is the question of interest.

2. Do we have reliable data to know whether individual infants were monitored on the study oximeter or on the clinical oximeter on the day the infant was 36 weeks and 0 and whether the oximeter was changed part way through that 24 hour period? What was done if the infant was switched on that day. As I understand it, the diagnosis of BPD was based on the entire 24 hours the day the infant was 36 weeks 0 days. Though the results of the survey weren't distributed, my impression from responses to my earlier e-mails was that even the procedure usually followed in individual centers was not necessarily clear.

We can determine from form PHY02 what oximeter was used to determine the physiologic definition of BPD, but we do not have the detailed level of information that you described. However, based on the survey results, we do know that only 5 sites used the study oximeter for an oxygen-based definition, and only 3 used the study oximeter for challenge.

3. What variables in the model when the BPD oximeter was added? What variables were in the model when a BPD oximeter x study treatment group was added?

Variables in the model were treatment oximeter (low vs. high), center, GA group. Familial clustering was adjusted for as a random effect. I added BPD oximeter and also looked at the interaction between BPD oximeter and treatment oximeter. These factors were identical to the factors used in the models for which secondary outcomes were reported in the manuscript.

4. Do I understand Maria and you to conclude that because centers tended to be consistent in their oximeter use, controlling for center would prevent a biased assessment of the effect on BPD by oxygen administration?

This comment makes me wonder if the analysis was done for the wrong comparison. This conclusion would be correct for analyses of the effect of CPAP/limited ventilation vs. surfactant/ conventional ventilation on BPD by



oxygen delivery (because each treatment arm would contain equal numbers of infants in the high and low sat groups). However, this isn't the comparison in question. This conclusion would certainly not be correct in analyzing the effect of high vs low sat goals on BPD. In this analysis, centers that used the study oximeter would be systematically more likely to administer oxygen to the high sat group than to the low sat group. The problem wouldn't go away by controlling for center, and the more centers that used the study oximeter, the more biased the result would be. How many centers were there that used the study oximeter?

Controlling for center adjusts for differences between centers including differences in the BPD oximeter used. Thus, adding a covariate for BPD oximeter does not change the estimates for the treatment oximeter effect. We are not arguing that the BPD oximeter used did not have an impact. We did find that BPD oximeter was significant in the models, as was center. However, since center and BPD oximeter are strongly confounded (in fact we have almost complete aliasing of center and clinical/study oximeter), it's not possible to tease out the effect of the BPD oximeter from other between-center differences. In addition, the interaction between BPD oximeter and treatment oximeter was not significant. This indicates that the impact of treatment oximeter on the BPD outcomes was not significantly different in the centers that used the study oximeters to determine BPD and those that used the clinical oximeters.

5. What is the basis for believing that there would be anything near reasonable power to assess a oximeter x treatment group interaction?

Clearly, these analyses were conducted from a post-hoc perspective, and the study was never designed to have the power to determine that the interaction in our data set is statistically significant for a pre-specified interaction effect size. But, that is not a shortcoming unless the magnitude of the interaction effect is such that it represents an important scientific bias in study interpretation. Our preliminary analyses indicate that biases of such magnitude are not present in this data set. We can do more detailed analyses of the level of bias that might have been introduced after Marie returns from vacation, but nothing in the analyses conducted to date suggest that those magnitudes warrant delay of submission of this manuscript.

I know that everyone is anxious to get this paper submitted. While I have an external advisory committee tomorrow, I will try to respond tomorrow night if the information requested above is sent tomorrow during the day.

---

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]  
Sent: Wednesday, February 24, 2010 7:53 AM  
To: Tyson, Jon E; 'Cunningham, Meg'; [SCRN] Stoll, Barbara;  
alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik;  
goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A;  
kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu;  
matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org;  
Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu;  
Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu;  
vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; Wallace, Dennis;  
cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu;  
Luc.Brion@utsouthwestern.edu; 'Stevenson David (E-mail)'; 'Finer, Neil';  
Rich, Wade; Gantz, Marie  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman,  
Jamie; Archer, Stephanie (NIH/NICHD) [E]  
Subject: Follow Up ON BPD and Oximeters

Hi all -

In Follow up to yesterday's discussion, Marie spent a great deal of time last evening running additional analyses to address (and now alleviate) Jon's concern as described:

We have looked into the question of whether the oximeter used to determine BPD impacted the BPD and death/BPD outcomes by adding a covariate for the BPD oximeter (study or clinical) to the statistical models. We found that the effect of the BPD oximeter was significant; however, the interaction between BPD oximeter and treatment oximeter (low or high SpO2 target range) was not significant in any model, indicating that, if there was a BPD oximeter effect, it was not different in the two treatment groups. In addition, it should be noted that BPD oximeter is confounded with center

(centers tended to be consistent in their use of the study or clinical oximeters to determine BPD). Therefore, by including center in the original models, we have already accounted for the effect of the BPD oximeter the center chose to use. Finally, because center and BPD oximeter are confounded, we cannot know whether the significant BPD oximeter effect is due to the BPD oximeters themselves or other characteristics that differ between centers.

From: Tyson, Jon E [mailto:Jon.E.Tyson@uth.tmc.edu]  
Sent: Tuesday, February 23, 2010 4:33 PM  
To: Higgins, Rosemary (NIH/NICHD) [E]; 'Cunningham, Meg'; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; Wallace, Dennis; cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; bbatton@siumed.edu  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; lmoore@med.wayne.edu; pamela.neville@duke.edu; gonza025@mc.duke.edu; Smith, Nancy M; Brenda Vecchio; msumner@peds.uab.edu; Archer, Stephanie (NIH/NICHD) [E]  
Subject: RE: Steering Committee Call Tomorrow

While it may seem that I am fixated on an unimportant issue regarding a not quite significant difference, I think we undermine the credibility of Network studies if we are not completely forthright about problems in measuring what everyone would agree is an important secondary outcome. Not reporting that the assessment of BPD by oxygen administration could be biased by continued use of the study oximeters would seem to be in the category of not reporting protocol deviations and not something that is in the Network's best interest. Why not just put a footnote under the table describing the problem?

Jon E. Tyson, MD, MPH  
Center for Clinical Research & Evidence-Based Medicine  
UT Medical School at Houston  
6431 Fannin St., MSB 2.106  
Houston, TX 77030  
voice 713-500-5651  
fax 713-500-0519

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
Sent: Tuesday, February 23, 2010 2:11 PM  
To: 'Cunningham, Meg'; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; Wallace, Dennis; cotte010@mc.duke.edu; Tyson, Jon E; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; bbatton@siumed.edu  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; lmoore@med.wayne.edu; pamela.neville@duke.edu; gonza025@mc.duke.edu; Smith, Nancy M; Brenda Vecchio; msumner@peds.uab.edu; Archer, Stephanie (NIH/NICHD) [E]  
Subject: RE: Steering Committee Call Tomorrow

If you joined the call already in progress, please send us an email so we can count your attendance.

Rose

From: Cunningham, Meg [mailto:mcunningham@rti.org]  
Sent: Monday, February 22, 2010 9:59 AM  
To: [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; Higgins, Rosemary (NIH/NICHD) [E]; ifrantz@tuftsmedicalcenter.org;

Kathleen.A.Kennedy@uth.tmc.edu; kurt.schibler@cchmc.org;  
kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu;  
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richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu;  
sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.;  
Wallace, Dennis; cotte010@mc.duke.edu; jon.e.tyson@uth.tmc.edu; Bradley  
Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; bbatton@siumed.edu  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman,  
Jamie; lmoore@med.wayne.edu; pamela.neville@duke.edu; gonza025@mc.duke.edu;  
Nancy.M.Smith@uth.tmc.edu; Brenda Vecchio; msumner@peds.uab.edu; Archer,  
Stephanie (NIH/NICHD) [E]  
Subject: Steering Committee Call Tomorrow

Dear All -

The next standing Steering Committee call is scheduled for tomorrow, Tuesday,  
February 23rd at 3:00pm ET.

Please Dial:

Outside the USA 1-203-310-(b)

or Within the USA 866-675-(b)

Then, enter Participant Passcode: (b) (6)

Steering Committee Conference Call Agenda 02/23/2010

1. Early BP discussion (attached are a brief description of the time limited data collection proposal and a draft of the form which would be used.)
2. SUPPORT manuscript discussion and update
3. New Business

Thanks,  
Meg

Meg Cunningham  
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701 13th St. NW, Ste. 750  
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fax: 202-728-2095  
[www.rti.org](http://www.rti.org)<<http://www.rti.org>>

## **Higgins, Rosemary (NIH/NICHD) [E]**

---

**From:** Finer, Neil <nfiner@ucsd.edu>  
**Sent:** Tuesday, March 02, 2010 12:14 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: SUPPORT SUBCOMMITTEE

I mean PT\_ I am speaking at the March of Dimes till 12:10 in Irvine California Si I could be available after that Is Marie available? - I had an idea for looking at the oximeters but tried to call Dennis yesterday and he did not reply.  
Neil

-----Original Message-----

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Tuesday, March 02, 2010 9:05 AM  
**To:** Finer, Neil  
**Subject:** RE: SUPPORT SUBCOMMITTEE

PT or ET?

Thanks  
Rose

-----Original Message-----

**From:** Finer, Neil [mailto:nfiner@ucsd.edu]  
**Sent:** Tuesday, March 02, 2010 12:03 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** Re: SUPPORT SUBCOMMITTEE

I can do a call after 12:30 today  
Neil

Sent from my iPhone

On Mar 2, 2010, at 8:18 AM, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov<mailto:higginsr@mail.nih.gov>> wrote:

Neil and Wally -  
For the question I sent to subcommittee yesterday -

7 no, 3 yes and 1 abstain

Should we try to schedule a short call today with the subcommittee? Not everyone is on the same page - let me know if you are available for a brief call

Rose  
Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network Pregnancy and Perinatology Branch Center for Developmental Biology and Perinatal Medicine Eunice Kennedy Shriver National Institute of Child Health and Human Development  
National Institutes of Health  
6100 Executive Blvd., Room 4B03

MSC 7510

Bethesda, MD 20892

For overnight delivery use Rockville, MD 20852

301-496-5575

301-496-3790 (FAX)

[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)<<mailto:higginsr@mail.nih.gov>>

**From:** Archer, Stephanie (NIH/NICHD) [E]  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: \*\*\*\*\* Important -Follow Up ON BPD and Oximeters\*\*\*\*\*  
**Date:** Tuesday, March 02, 2010 11:10:25 AM

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Right. I forgot to list that Marie still needs to vote too. From her previous statistics, she's most probably a no too.

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**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Tuesday, March 02, 2010 11:07 AM  
**To:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** FW: \*\*\*\*\* Important -Follow Up ON BPD and Oximeters\*\*\*\*\*

So is this 7 no, 3 yes and 1 abstain?

---

**From:** Laptook, Abbot [mailto:ALaptook@WIHRI.org]  
**Sent:** Tuesday, March 02, 2010 10:39 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** Re: \*\*\*\*\* Important -Follow Up ON BPD and Oximeters\*\*\*\*\*

I would defer to a secondary paper. I am concerned we have not sorted thru all the issues. Tx  
AL

Sent from my iPhone

On Mar 2, 2010, at 7:07 AM, "Higgins, Rosemary (NIH/NICHD) [E]"  
<higginsr@mail.nih.gov> wrote:

Abbot  
Can you send me your opinion??  
Thanks  
Rose

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Monday, March 01, 2010 11:00 AM  
**To:** 'Wally Carlo, M.D.'; 'Finer, Neil'; alaptook@WIHRI.org; Roger.Faix@hsc.utah.edu; Bradley Yoder; kurt.schibler@cchmc.org; adas@rti.org; nancy newman; Rich, Wade; Gantz, Marie; mcw3@case.edu; Dennis Wallace  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin  
**Subject:** \*\*\*\*\* Important -Follow Up ON BPD and Oximeters\*\*\*\*\*  
**Importance:** High

To the SUPPORT Subcommittee  
Given the email exchange, the subcommittee will need to ascertain whether or not to indicate in the SUPPORT papers whether or not a bias could have existed in reporting the secondary outcome of BPD based on oximeter. Previously the subcommittee had reviewed the oximeter use on a conference call and decided to defer this to a secondary paper. There has been discussion on the SC call and via email subsequently.

## Therefore, please send me a yes/no vote to include this in the paper by March 2.

Thanks  
Rose

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**From:** Tyson, Jon E [<mailto:Jon.E.Tyson@uth.tmc.edu>]  
**Sent:** Friday, February 26, 2010 6:28 PM  
**To:** Wallace, Dennis; Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara; [alaptook@WIHRI.org](mailto:alaptook@WIHRI.org); Bell, Edward; [bpindex@iupui.edu](mailto:bpindex@iupui.edu); Das, Abhik; [goldb008@mc.duke.edu](mailto:goldb008@mc.duke.edu); [ifrantz@tuftsmedicalcenter.org](mailto:ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; [kurt.schibler@cchmc.org](mailto:kurt.schibler@cchmc.org); [kwatterberg@salud.unm.edu](mailto:kwatterberg@salud.unm.edu); [matthew.bizzarro@yale.edu](mailto:matthew.bizzarro@yale.edu); [mcw3@cwru.edu](mailto:mcw3@cwru.edu); [mcaplan@northshore.org](mailto:mcaplan@northshore.org); [Pablo.Sanchez@UTSouthwestern.edu](mailto:Pablo.Sanchez@UTSouthwestern.edu); [richard.ehrenkranz@yale.edu](mailto:richard.ehrenkranz@yale.edu); [Roger.Faix@hsc.utah.edu](mailto:Roger.Faix@hsc.utah.edu); [sshankar@med.wayne.edu](mailto:sshankar@med.wayne.edu); [vanmeurs@leland.stanford.edu](mailto:vanmeurs@leland.stanford.edu); Wally Carlo, M.D.; [cotte010@mc.duke.edu](mailto:cotte010@mc.duke.edu); Bradley Yoder; [rohls@salud.unm.edu](mailto:rohls@salud.unm.edu); [Luc.Brion@utsouthwestern.edu](mailto:Luc.Brion@utsouthwestern.edu); Stevenson David (E-mail); Finer, Neil; Rich, Wade; Gantz, Marie  
**Cc:** Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: Follow Up ON BPD and Oximeters

I don't understand your statement "Controlling for center adjusts for differences between centers including differences in the BPD oximeter used." To simplify the discussion, suppose every center always used the study oximeter in designating who had BPD by oxygen saturation. Because the true saturation that would prompt oxygen administration would differ in the two treatment groups, there would be systematic bias toward administering oxygen to more infants in the high sat group than in the low sat group. This is inherent in the study design. Whatever differences there were between centers, this bias would occur in every center and would not be eliminated by controlling for center. And if I understand the analysis, there would be no interaction between treatment oximeter and BPD oximeter because they would be the same in every baby in every center.

You indicate that 5 centers used the study oximeter in almost every baby. In saying "it's not possible to tease out the effect of the BPD oximeter from other between-center differences" (a statement that I certainly accept), aren't you saying that the effect of the study oximeter on the difference in the incidence of BPD by oxygen administration between high and low sat groups (i.e., the bias) can not be distinguished from the effect of the myriad of other factors in those centers that might affect that difference in incidence? If so, why would you expect to be able to discern that bias (the signal) from all the noise resulting from other factors? I understand from what you said that the same approach was used in virtually all infants in each center which makes the effective  $n$  to be based on the number of centers rather than the number of babies. As I understand the analysis, the power to assess an interaction would then be quite low.

The issue here is whether is simply whether to report somewhere in the paper (which could be noted under the table and wouldn't increase the word count for the text) a bias in evaluating a secondary outcome. This can be done with no delay in submitting the manuscript or waiting for Maria to return. *If we had other real or potential sources of bias—say, a breaking of the blind for some infants, open label administration of a study drug to the control group, or differential loss to follow-up, we would certainly report it as a matter of course, whether or not there was a significant or near significant difference in the outcome and without testing and whether or not we assessed or found any interaction or other statistical evidence that this potential source of bias affected the results!*

Jon E. Tyson, MD, MPH  
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UT Medical School at Houston  
6431 Fannin St., MSB 2.106  
Houston, TX 77030  
voice 713-500-5651  
fax 713-500-0519

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**From:** Wallace, Dennis [<mailto:dwallace@rti.org>]  
**Sent:** Friday, February 26, 2010 1:56 PM  
**To:** Wallace, Dennis; Tyson, Jon E; Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara; [alaptook@WIHRI.org](mailto:alaptook@WIHRI.org); Bell, Edward; [bpoindex@iupui.edu](mailto:bpoindex@iupui.edu); Das, Abhik; [goldb008@mc.duke.edu](mailto:goldb008@mc.duke.edu); [ifrantz@tuftsmedicalcenter.org](mailto:ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; [kurt.schibler@cchmc.org](mailto:kurt.schibler@cchmc.org); [kwatterberg@salud.unm.edu](mailto:kwatterberg@salud.unm.edu); [matthew.bizzarro@yale.edu](mailto:matthew.bizzarro@yale.edu); [mcw3@cwru.edu](mailto:mcw3@cwru.edu); [mcaplan@northshore.org](mailto:mcaplan@northshore.org); [Pablo.Sanchez@UTSouthwestern.edu](mailto:Pablo.Sanchez@UTSouthwestern.edu); [richard.ehrenkranz@yale.edu](mailto:richard.ehrenkranz@yale.edu); [Roger.Faix@hsc.utah.edu](mailto:Roger.Faix@hsc.utah.edu); [sshankar@med.wayne.edu](mailto:sshankar@med.wayne.edu); [vanmeurs@leland.stanford.edu](mailto:vanmeurs@leland.stanford.edu); Wally Carlo, M.D.; [cotte010@mc.duke.edu](mailto:cotte010@mc.duke.edu); Bradley Yoder; [rohls@salud.unm.edu](mailto:rohls@salud.unm.edu); [Luc.Brion@utsouthwestern.edu](mailto:Luc.Brion@utsouthwestern.edu); Stevenson David (E-mail); Finer, Neil; Rich, Wade; Gantz, Marie  
**Cc:** Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: Follow Up ON BPD and Oximeters

Hello all,

I accidentally hit the send button before finishing editing this response so ignore the earlier e-mail and see the response below.

Dennis

Dennis Wallace  
Senior Research Statistician  
Cox 241  
RTI International  
3040 Cornwallis Rd  
Research Triangle Park, NC 27709-2104  
Voice: 919-541-6271  
Fax: 919-541-6416

---

**From:** Wallace, Dennis  
**Sent:** Friday, February 26, 2010 2:53 PM  
**To:** 'Tyson, Jon E'; Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara; [alaptook@WIHRI.org](mailto:alaptook@WIHRI.org); Bell, Edward; [bpoindex@iupui.edu](mailto:bpoindex@iupui.edu); Das, Abhik; [goldb008@mc.duke.edu](mailto:goldb008@mc.duke.edu); [ifrantz@tuftsmedicalcenter.org](mailto:ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; [kurt.schibler@cchmc.org](mailto:kurt.schibler@cchmc.org); [kwatterberg@salud.unm.edu](mailto:kwatterberg@salud.unm.edu); [matthew.bizzarro@yale.edu](mailto:matthew.bizzarro@yale.edu); [mcw3@cwru.edu](mailto:mcw3@cwru.edu); [mcaplan@northshore.org](mailto:mcaplan@northshore.org); [Pablo.Sanchez@UTSouthwestern.edu](mailto:Pablo.Sanchez@UTSouthwestern.edu); [richard.ehrenkranz@yale.edu](mailto:richard.ehrenkranz@yale.edu); [Roger.Faix@hsc.utah.edu](mailto:Roger.Faix@hsc.utah.edu); [sshankar@med.wayne.edu](mailto:sshankar@med.wayne.edu); [vanmeurs@leland.stanford.edu](mailto:vanmeurs@leland.stanford.edu); Wally Carlo, M.D.; [cotte010@mc.duke.edu](mailto:cotte010@mc.duke.edu); Bradley Yoder; [rohls@salud.unm.edu](mailto:rohls@salud.unm.edu); [Luc.Brion@utsouthwestern.edu](mailto:Luc.Brion@utsouthwestern.edu); 'Stevenson David (E-mail)'; 'Finer, Neil'; Rich, Wade; Gantz, Marie  
**Cc:** Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: Follow Up ON BPD and Oximeters

Jon,



Marie flew out on a long-scheduled vacation after completing these analyses late Tuesday evening and has very limited e-mail and cell phone access. However, she has taken time to provide a preliminary response that I've outlined below with some added thoughts of my own in red font below. Based on these responses, I do believe that the critical concerns about bias have been addressed sufficiently for this initial manuscript, but if you think we need to have a more full discussion, we can talk after Marie returns next week. Because the programming for these outcome measures is relatively complicated, I'm hesitant to try to do any additional analyses prior to her return. However, as I indicated above, I don't think that we need to delay any submissions while trying to iron on the small details.

Dennis Wallace

Senior Research Statistician

Cox 241

RTI International

3040 Cornwallis Rd

Research Triangle Park, NC 27709-2104

Voice: 919-541-6271

Fax: 919-541-6416

-----Original Message-----

From: Tyson, Jon E [mailto:Jon.E.Tyson@uth.tmc.edu]

Sent: Thursday, February 25, 2010 12:45 AM

To: Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN]

Stoll, Barbara; [alaptook@WIHRI.org](mailto:alaptook@WIHRI.org); Bell, Edward;

[bpointindex@iupui.edu](mailto:bpointindex@iupui.edu); Das, Abhik; [goldb008@mc.duke.edu](mailto:goldb008@mc.duke.edu);

[ifrantz@tuftsmedicalcenter.org](mailto:ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A;

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[Pablo.Sanchez@UTSouthwestern.edu](mailto:Pablo.Sanchez@UTSouthwestern.edu); [richard.ehrenkranz@yale.edu](mailto:richard.ehrenkranz@yale.edu);

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[Luc.Brion@utsouthwestern.edu](mailto:Luc.Brion@utsouthwestern.edu); 'Stevenson David (E-mail)'; 'Finer,

Neil'; Rich, Wade; Gantz, Marie

Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn

Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]

Subject: RE: Follow Up ON BPD and Oximeters

Rose, before we can understand and interpret this information noted in the mail, we really need to know more about what was done and answers to questions like those below:

1. Which trial result was addressed - whether the evaluation of BPD was biased in the analyses of CPAP/limited ventilation vs. surfactant/conventional ventilation arm (not the analysis for which there is concern) or the analyses of the high vs. low oxygen saturation goal.

Although models were run for the different arms of the factorial design, the trial result that was addressed in the earlier e-mail was the impact of different oximeters on the comparison of the effects high vs. low oxygen saturation targets on BPD and BPD/death outcomes, which we believe is the question of interest.

2. Do we have reliable data to know whether individual infants were monitored on the study oximeter or on the clinical oximeter on the day the infant was 36 weeks and 0 and whether the oximeter was changed part way through that 24 hour period? What was done if the infant was switched on that day. As I understand it, the diagnosis of BPD was based on the entire 24 hours the day the infant was 36 weeks 0 days. Though the results of the survey weren't distributed, my impression from responses to my earlier e-mails was that even the procedure usually followed in individual centers was not necessarily clear.

We can determine from form PHY02 what oximeter was used to determine the physiologic definition of BPD, but we do not have the detailed level of information that you described. However, based on the survey results, we do know that only 5 sites used the study oximeter for an oxygen-based definition, and only 3 used the study oximeter for challenge.

3. What variables in the model when the BPD oximeter was added? What variables were in the model when a BPD oximeter x study treatment group was added?

Variables in the model were treatment oximeter (low vs. high), center, GA group. Familial clustering was adjusted for as a random effect. I added BPD oximeter and also looked at the interaction between BPD oximeter and treatment oximeter. These factors were identical to the factors used in the models for which secondary outcomes were reported in the manuscript.

4. Do I understand Maria and you to conclude that because centers tended to be consistent in their oximeter use, controlling for center would prevent a biased assessment of the effect on BPD by oxygen administration?

This comment makes me wonder if the analysis was done for the wrong comparison. This conclusion would be correct for analyses of the effect of CPAP/limited ventilation vs. surfactant/ conventional ventilation on BPD by oxygen delivery (because each treatment arm would contain equal numbers of infants in the high and low sat

groups). However, this isn't the comparison in question. This conclusion would certainly not be correct in analyzing the effect of high vs low sat goals on BPD. In this analysis, centers that used the study oximeter would be systematically more likely to administer oxygen to the high sat group than to the low sat group. The problem wouldn't go away by controlling for center, and the more centers that used the study oximeter, the more biased the result would be. How many centers were there that used the study oximeter?

Controlling for center adjusts for differences between centers including differences in the BPD oximeter used. Thus, adding a covariate for BPD oximeter does not change the estimates for the treatment oximeter effect. We are not arguing that the BPD oximeter used did not have an impact. We did find that BPD oximeter was significant in the models, as was center. However, since center and BPD oximeter are strongly confounded (in fact we have almost complete aliasing of center and clinical/study oximeter), it's not possible to tease out the effect of the BPD oximeter from other between-center differences. In addition, the interaction between BPD oximeter and treatment oximeter was not significant. This indicates that the impact of treatment oximeter on the BPD outcomes was not significantly different in the centers that used the study oximeters to determine BPD and those that used the clinical oximeters.

5. What is the basis for believing that there would be anything near reasonable power to assess a oximeter x treatment group interaction?

Clearly, these analyses were conducted from a post-hoc perspective, and the study was never designed to have the power to determine that the interaction in our data set is statistically significant for a pre-specified interaction effect size. But, that is not a shortcoming unless the magnitude of the interaction effect is such that it represents an important scientific bias in study interpretation. Our preliminary analyses indicate that biases of such magnitude are not present in this data set. We can do more detailed analyses of the level of bias that might have been introduced after Marie returns from vacation, but nothing in the analyses conducted to date suggest that those magnitudes warrant delay of submission of this manuscript.

I know that everyone is anxious to get this paper submitted. While I have an external advisory committee tomorrow, I will try to respond tomorrow night if the information requested above is sent tomorrow during the day.

---

From: Higgins, Rosemary (NIH/NICHD) [E] [[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)]

Sent: Wednesday, February 24, 2010 7:53 AM

To: Tyson, Jon E; 'Cunningham, Meg'; [SCRN] Stoll, Barbara; [alaprook@WIHRI.org](mailto:alaprook@WIHRI.org); Bell, Edward; [bpoindex@iupui.edu](mailto:bpoindex@iupui.edu); Das, Abhik;

goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; [kurt.schibler@cchmc.org](mailto:kurt.schibler@cchmc.org); [kwatterberg@salud.unm.edu](mailto:kwatterberg@salud.unm.edu); [matthew.bizzarro@yale.edu](mailto:matthew.bizzarro@yale.edu); [mcw3@cwru.edu](mailto:mcw3@cwru.edu); [mcaplan@northshore.org](mailto:mcaplan@northshore.org); [Pablo.Sanchez@UTSouthwestern.edu](mailto:Pablo.Sanchez@UTSouthwestern.edu); [richard.ehrenkranz@yale.edu](mailto:richard.ehrenkranz@yale.edu); [Roger.Faix@hsc.utah.edu](mailto:Roger.Faix@hsc.utah.edu); [sshankar@med.wayne.edu](mailto:sshankar@med.wayne.edu); [vanmeurs@leland.stanford.edu](mailto:vanmeurs@leland.stanford.edu); Wally Carlo, M.D.; Wallace, Dennis; [cotte010@mc.duke.edu](mailto:cotte010@mc.duke.edu); Bradley Yoder; [rohls@salud.unm.edu](mailto:rohls@salud.unm.edu); [Luc.Brion@utsouthwestern.edu](mailto:Luc.Brion@utsouthwestern.edu); 'Stevenson David (E-mail)'; 'Finer, Neil'; Rich, Wade; Gantz, Marie

Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]

Subject: Follow Up ON BPD and Oximeters

Hi all -

In Follow up to yesterday's discussion, Marie spent a great deal of time last evening running additional analyses to address (and now alleviate) Jon's concern as described:

We have looked into the question of whether the oximeter used to determine BPD impacted the BPD and death/BPD outcomes by adding a covariate for the BPD oximeter (study or clinical) to the statistical models. We found that the effect of the BPD oximeter was significant; however, the interaction between BPD oximeter and treatment oximeter (low or high SpO2 target range) was not significant in any model, indicating that, if there was a BPD oximeter effect, it was not different in the two treatment groups. In addition, it should be noted that BPD oximeter is confounded with center (centers tended to be consistent in their use of the study or clinical oximeters to determine BPD). Therefore, by including center in the original models, we have already accounted for the effect of the BPD oximeter the center chose to use. Finally, because center and BPD oximeter are confounded, we cannot know whether the significant BPD oximeter effect is due to the BPD oximeters themselves or other characteristics that differ between centers.

---

From: Tyson, Jon E [<mailto:Jon.E.Tyson@uth.tmc.edu>]

Sent: Tuesday, February 23, 2010 4:33 PM

To: Higgins, Rosemary (NIH/NICHD) [E]; 'Cunningham, Meg'; [SCRN] Stoll, Barbara; [alaptook@WIHRI.org](mailto:alaptook@WIHRI.org); Bell, Edward; [bpoindex@iupui.edu](mailto:bpoindex@iupui.edu); Das, Abhik; [goldb008@mc.duke.edu](mailto:goldb008@mc.duke.edu); [ifrantz@tuftsmedicalcenter.org](mailto:ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; [kurt.schibler@cchmc.org](mailto:kurt.schibler@cchmc.org); [kwatterberg@salud.unm.edu](mailto:kwatterberg@salud.unm.edu); [matthew.bizzarro@yale.edu](mailto:matthew.bizzarro@yale.edu); [mcw3@cwru.edu](mailto:mcw3@cwru.edu); [mcaplan@northshore.org](mailto:mcaplan@northshore.org); [Pablo.Sanchez@UTSouthwestern.edu](mailto:Pablo.Sanchez@UTSouthwestern.edu); [richard.ehrenkranz@yale.edu](mailto:richard.ehrenkranz@yale.edu); [Roger.Faix@hsc.utah.edu](mailto:Roger.Faix@hsc.utah.edu); [sshankar@med.wayne.edu](mailto:sshankar@med.wayne.edu); [vanmeurs@leland.stanford.edu](mailto:vanmeurs@leland.stanford.edu); Wally Carlo, M.D.; Wallace, Dennis; [cotte010@mc.duke.edu](mailto:cotte010@mc.duke.edu); Bradley Yoder; [rohls@salud.unm.edu](mailto:rohls@salud.unm.edu); [Luc.Brion@utsouthwestern.edu](mailto:Luc.Brion@utsouthwestern.edu); [bbatton@siumed.edu](mailto:bbatton@siumed.edu)

Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; [lmoore@med.wayne.edu](mailto:lmoore@med.wayne.edu); [pamela.neville@duke.edu](mailto:pamela.neville@duke.edu); [gonza025@mc.duke.edu](mailto:gonza025@mc.duke.edu); Smith, Nancy M; Brenda Vecchio; [msumner@peds.uab.edu](mailto:msumner@peds.uab.edu); Archer, Stephanie (NIH/NICHD) [E]

Subject: RE: Steering Committee Call Tomorrow

While it may seem that I am fixated on an unimportant issue regarding a not quite significant difference, I think we undermine the credibility of Network studies if we are not completely forthright about problems in measuring what everyone would agree is an important secondary outcome. Not reporting that the assessment of BPD by oxygen administration could be biased by continued use of the study oximeters would seem to be in the category of not reporting protocol deviations and not something that is in the Network's best interest. Why not just put a footnote under the table describing the problem?

Jon E. Tyson, MD, MPH

Center for Clinical Research & Evidence-Based Medicine

UT Medical School at Houston

6431 Fannin St., MSB 2.106

Houston, TX 77030

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From: Higgins, Rosemary (NIH/NICHD) [E]  
[mailto:higginsr@mail.nih.gov]

Sent: Tuesday, February 23, 2010 2:11 PM

To: 'Cunningham, Meg'; [SCRN] Stoll, Barbara; [alaptook@WIHRI.org](mailto:alaptook@WIHRI.org); Bell, Edward; [bpoindex@iupui.edu](mailto:bpoindex@iupui.edu); Das, Abhik; [goldb008@mc.duke.edu](mailto:goldb008@mc.duke.edu); [ifrantz@tuftsmedicalcenter.org](mailto:ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; [kurt.schibler@cchmc.org](mailto:kurt.schibler@cchmc.org); [kwatterberg@salud.unm.edu](mailto:kwatterberg@salud.unm.edu); [matthew.bizzarro@yale.edu](mailto:matthew.bizzarro@yale.edu); [mcw3@cwru.edu](mailto:mcw3@cwru.edu); [mcaplan@northshore.org](mailto:mcaplan@northshore.org); [Pablo.Sanchez@UTSouthwestern.edu](mailto:Pablo.Sanchez@UTSouthwestern.edu); [richard.ehrenkranz@yale.edu](mailto:richard.ehrenkranz@yale.edu); [Roger.Faix@hsc.utah.edu](mailto:Roger.Faix@hsc.utah.edu); [sshankar@med.wayne.edu](mailto:sshankar@med.wayne.edu); [vanmeurs@leland.stanford.edu](mailto:vanmeurs@leland.stanford.edu); Wally Carlo, M.D.; Wallace, Dennis; [cotte010@mc.duke.edu](mailto:cotte010@mc.duke.edu); Tyson, Jon E; Bradley Yoder; [rohls@salud.unm.edu](mailto:rohls@salud.unm.edu); [Luc.Brion@utsouthwestern.edu](mailto:Luc.Brion@utsouthwestern.edu); [bbatton@siumed.edu](mailto:bbatton@siumed.edu)

Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; [lmoore@med.wayne.edu](mailto:lmoore@med.wayne.edu); [pamela.neville@duke.edu](mailto:pamela.neville@duke.edu); [gonza025@mc.duke.edu](mailto:gonza025@mc.duke.edu); Smith, Nancy M; Brenda Vecchio; [msummer@peds.uab.edu](mailto:msummer@peds.uab.edu); Archer, Stephanie (NIH/NICHD) [E]

Subject: RE: Steering Committee Call Tomorrow

If you joined the call already in progress, please send us an email so we can count your attendance.

Rose

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From: Cunningham, Meg [mailto:mcunningham@rti.org]

Sent: Monday, February 22, 2010 9:59 AM

To: [SCRN] Stoll, Barbara; [alaptook@WIHRI.org](mailto:alaptook@WIHRI.org); Bell, Edward; [bpoindex@iupui.edu](mailto:bpoindex@iupui.edu); Das, Abhik; [goldb008@mc.duke.edu](mailto:goldb008@mc.duke.edu); Higgins, Rosemary (NIH/NICHD) [E]; [ifrantz@tuftsmedicalcenter.org](mailto:ifrantz@tuftsmedicalcenter.org); [Kathleen.A.Kennedy@uth.tmc.edu](mailto:Kathleen.A.Kennedy@uth.tmc.edu); [kurt.schibler@cchmc.org](mailto:kurt.schibler@cchmc.org); [kwatterberg@salud.unm.edu](mailto:kwatterberg@salud.unm.edu); [matthew.bizzarro@yale.edu](mailto:matthew.bizzarro@yale.edu); [mcw3@cwru.edu](mailto:mcw3@cwru.edu); [mcaplan@northshore.org](mailto:mcaplan@northshore.org); [Pablo.Sanchez@UTSouthwestern.edu](mailto:Pablo.Sanchez@UTSouthwestern.edu); [richard.ehrenkranz@yale.edu](mailto:richard.ehrenkranz@yale.edu); [Roger.Faix@hsc.utah.edu](mailto:Roger.Faix@hsc.utah.edu); [sshankar@med.wayne.edu](mailto:sshankar@med.wayne.edu); [vanmeurs@leland.stanford.edu](mailto:vanmeurs@leland.stanford.edu); Wally Carlo, M.D.; Wallace, Dennis; [cotte010@mc.duke.edu](mailto:cotte010@mc.duke.edu); [jon.e.tyson@uth.tmc.edu](mailto:jon.e.tyson@uth.tmc.edu); Bradley Yoder; [rohls@salud.unm.edu](mailto:rohls@salud.unm.edu); [Luc.Brion@utsouthwestern.edu](mailto:Luc.Brion@utsouthwestern.edu); [bbatton@siumed.edu](mailto:bbatton@siumed.edu)

Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; [lmoore@med.wayne.edu](mailto:lmoore@med.wayne.edu); [pamela.neville@duke.edu](mailto:pamela.neville@duke.edu); [gonza025@mc.duke.edu](mailto:gonza025@mc.duke.edu); [Nancy.M.Smith@uth.tmc.edu](mailto:Nancy.M.Smith@uth.tmc.edu); Brenda Vecchio; [msummer@peds.uab.edu](mailto:msummer@peds.uab.edu); Archer, Stephanie (NIH/NICHD) [E]

Subject: Steering Committee Call Tomorrow

Dear All -

The next standing Steering Committee call is scheduled for tomorrow, Tuesday, February 23rd at 3:00pm ET.

Please Dial:

Outside the USA 1-203-310-(b) (6)

or Within the USA 866-675-(b) (6)

Then, enter Participant Passcode: (b) (6)

Steering Committee Conference Call Agenda 02/23/2010

1. Early BP discussion (attached are a brief description of the time limited data collection proposal and a draft of the form which would be used.)
2. SUPPORT manuscript discussion and update
3. New Business

Thanks,

Meg

Meg Cunningham

RTI International

701 13th St. NW, Ste. 750

Washington, DC 20005

tel: 202-974-7837

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[www.rti.org](http://www.rti.org)<<http://www.rti.org>>

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**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: Vote | Stephens, SUPPORT Pulmonary Outcomes request for 6 and 12 months data  
**Date:** Tuesday, March 02, 2010 9:58:00 AM

I will need to send another vote to clarify – there was quite a bit of negative sentiment about this

Rose

**From:** Archer, Stephanie (NIH/NICHD) [E]  
**Sent:** Tuesday, March 02, 2010 9:57 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Vote | Stephens, SUPPORT Pulmonary Outcomes request for 6 and 12 months data

The second comment is from Neil, who doesn't get a Steering Committee vote any more.

The 4<sup>th</sup> comment is from Wally saying that some unanalyzed unmasked data would be OK. Many of the remaining comments are from people agreeing with Wally.

UNM	To be used for study design? then yes
UCSD	I would not give the data to Tim as his outcomes are all at 18-22 months. There would be no rational in seeing these as we are still collecting the data. I could not see any outcomes that were before this window. Does he want blinded data?? Perhaps I have missed the point of his question. Can you further clarify what he wants to do with the data??
NICHD	Tim had sent the following as a basis for his request: One of the criticisms of the School Age Breathing Outcomes Proposal is the lack of preliminary data from Breathing Outcomes that supports longer term follow up. To address this concern Richard and I thought it would be helpful to have preliminary analyses of a few questions from Breathing Outcomes. The concept was approved by the steering committee and the protocol has been reviewed by protocol review subcommittee with a request for revisions. The data requested is to provide support for longer term FU (at school age). I hope this clarifies the subject.
Alabama	I would think that some unmasked data evaluation not analyzed by treatment group may be ok. Any analysis by treatment group should wait until the data collection are completed.
Indiana	I agree with Wally – if he needs data analyzed by treatment group (which it sounds like he would) then I think the answer should be no until all data collection is complete.
Iowa	If I understand correctly, that the request is just for internal Network use of the data, Iowa votes YES.
NICHD	This is for the protocol revision and possible application for funds from another institute
Iowa	If it's to go outside the Network, Wally has a point - the premature unblinding of outcome data may be inappropriate. So probably no, but I'll follow the unfolding discussion.
Cincinnati	I think it is premature to give out this information. I vote no.
Utah	The concerns raised by Neil et al are quite legitimate in my opinion. Any analysis that requires unmasking should be deferred.
Emory	Upon reflection-- could we give him 6 mo data now and wait until all have had their 12 month assessments

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Tuesday, March 02, 2010 9:51 AM  
**To:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: Vote | Stephens, SUPPORT Pulmonary Outcomes request for 6 and 12 months data

I am very confused. (b) (5)

**From:** Archer, Stephanie (NIH/NICHD) [E]  
**Sent:** Tuesday, March 02, 2010 9:47 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Vote | Stephens, SUPPORT Pulmonary Outcomes request for 6 and 12 months data

Sorry, should have read "not unblinded". Spell check strikes again!

Here are the comments:

To be used for study design? then yes
I would not give the data to Tim as his outcomes are all at 18-22 months. There would be no rational in seeing these as we are still collecting the data. I could not see any outcomes that were before this window. Does he want blinded data?? Perhaps I have missed the point of his question. Can you further clarify what he wants to do with the data??
Tim had sent the following as a basis for his request: One of the criticisms of the School Age Breathing Outcomes Proposal is the lack of preliminary data from Breathing Outcomes that supports longer term follow up. To address this concern Richard and I thought it would be helpful to have preliminary analyses of a few questions from Breathing Outcomes. The concept was approved by the steering committee and the protocol has been reviewed by protocol review subcommittee with a request for revisions. The data requested is to provide support for longer term FU (at school age). I hope this clarifies the subject.
I would think that some unmasked data evaluation not analyzed by treatment group may be ok. Any analysis by treatment group should wait until the data collection are completed.
I agree with Wally – if he needs data analyzed by treatment group (which it sounds like he would) then I think the answer should be no until all data collection is complete.



If I understand correctly, that the request is just for internal Network use of the data, Iowa votes YES.
This is for the protocol revision and possible application for funds from another institute
If it's to go outside the Network, Wally has a point - the premature unblinding of outcome data may be inappropriate. So probably no, but I'll follow the unfolding discussion.
I think it is premature to give out this information. I vote no.
The concerns raised by Neil et al are quite legitimate in my opinion. Any analysis that requires unmasking should be deferred.
Upon reflection-- could we give him 6 mo data now and wait until all have had their 12 month assessments

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Tuesday, March 02, 2010 9:39 AM  
**To:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: Vote | Stephens, SUPPORT Pulmonary Outcomes request for 6 and 12 months data

What does not unblended mean?? I thought there was more negative sentiment for this one?

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**From:** Archer, Stephanie (NIH/NICHD) [E]  
**Sent:** Tuesday, March 02, 2010 9:16 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** Vote | Stephens, SUPPORT Pulmonary Outcomes request for 6 and 12 months data

So far we have:

Yes = 3  
Yes, but not unblended = 8  
No = 1

Missing:  
Dallas  
Yale  
Stanford  
Tufts  
RTI  
NICHD

**From:** Kurt Schibler  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](mailto:Higgins.Rosemary@NIH.NICHD)  
**Subject:** Re: \*\*\*\*\* Important -Follow Up ON BPD and Oximeters\*\*\*\*\*  
**Date:** Tuesday, March 02, 2010 9:44:31 AM  
**Importance:** High

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Hi Rose,

I vote yes to report this potential for bias. I think Jon's argument has clarified the point to me and I favor adding it as a note to the table as suggested. In my view it does not materially change the outcome or importance of the paper, but it does limit the possibility that the Network could be criticized later for not reporting concern raised about a potential bias. Let me know if we need further discussion.

Kurt

On 3/1/10 10:59 AM, "Higgins, Rosemary (NIH/NICHD) [E]" <[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)> wrote:

To the SUPPORT Subcommittee

Given the email exchange, the subcommittee will need to ascertain whether or not to indicate in the SUPPORT papers whether or not a bias could have existed in reporting the secondary outcome of BPD based on oximeter. Previously the subcommittee had reviewed the oximeter use on a conference call and decided to defer this to a secondary paper. There has been discussion on the SC call and via email subsequently.

**Therefore, please send me a yes/no vote to include this in the paper by March 2.**

Thanks  
Rose

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**From:** Tyson, Jon E [<mailto:Jon.E.Tyson@uth.tmc.edu>]  
**Sent:** Friday, February 26, 2010 6:28 PM  
**To:** Wallace, Dennis; Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara; [alaptook@WIHRI.org](mailto:alaptook@WIHRI.org); Bell, Edward; [bpointindex@iupui.edu](mailto:bpointindex@iupui.edu); Das, Abhik; [goldb008@mc.duke.edu](mailto:goldb008@mc.duke.edu); [ifrantz@tuftsmedicalcenter.org](mailto:ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; [kurt.schibler@cchmc.org](mailto:kurt.schibler@cchmc.org); [kwatterberg@salud.unm.edu](mailto:kwatterberg@salud.unm.edu); [matthew.bizzarro@yale.edu](mailto:matthew.bizzarro@yale.edu); [mcw3@cwru.edu](mailto:mcw3@cwru.edu); [mcaplan@northshore.org](mailto:mcaplan@northshore.org); [Pablo.Sanchez@UTSouthwestern.edu](mailto:Pablo.Sanchez@UTSouthwestern.edu); [richard.ehrenkranz@yale.edu](mailto:richard.ehrenkranz@yale.edu); [Roger.Faix@hsc.utah.edu](mailto:Roger.Faix@hsc.utah.edu); [sshankar@med.wayne.edu](mailto:sshankar@med.wayne.edu); [vanmeurs@leland.stanford.edu](mailto:vanmeurs@leland.stanford.edu); Wally Carlo, M.D.; [cotte010@mc.duke.edu](mailto:cotte010@mc.duke.edu); Bradley Yoder; [rohls@salud.unm.edu](mailto:rohls@salud.unm.edu); [Luc.Brion@utsouthwestern.edu](mailto:Luc.Brion@utsouthwestern.edu); Stevenson David (E-mail); Finer, Neil; Rich, Wade; Gantz, Marie  
**Cc:** Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: Follow Up ON BPD and Oximeters

I don't understand your statement "Controlling for center adjusts for differences between centers including differences in the BPD oximeter used." To simplify the discussion, suppose every center

always used the study oximeter in designating who had BPD by oxygen saturation. Because the true saturation that would prompt oxygen administration would differ in the two treatment groups, there would be systematic bias toward administering oxygen to more infants in the high sat group than in the low sat group. This is inherent in the study design. Whatever differences there were between centers, this bias would occur in every center and would not be eliminated by controlling for center. And if I understand the analysis, there would be no interaction between treatment oximeter and BPD oximeter because they would be the same in every baby in every center.

You indicate that 5 centers used the study oximeter in almost every baby. In saying "it's not possible to tease out the effect of the BPD oximeter from other between-center differences" (a statement that I certainly accept), aren't you saying that the effect of the study oximeter on the difference in the incidence of BPD by oxygen administration between high and low sat groups (i.e., the bias) can not be distinguished from the effect of the myriad of other factors in those centers that might affect that difference in incidence? If so, why would you expect to be able to discern that bias (the signal) from all the noise resulting from other factors? I understand from what you said that the same approach was used in virtually all infants in each center which makes the effective n to be based on the number of centers rather than the number of babies. As I understand the analysis, the power to assess an interaction would then be quite low.

The issue here is whether is simply whether to report somewhere in the paper (which could be noted under the table and wouldn't increase the word count for the text) a bias in evaluating a secondary outcome. This can be done with no delay in submitting the manuscript or waiting for Maria to return. *If we had other real or potential sources of bias—say, a breaking of the blind for some infants, open label administration of a study drug to the control group, or differential loss to follow-up, we would certainly report it as a matter of course, whether or not there was a significant or near significant difference in the outcome and without testing and whether or not we assessed or found any interaction or other statistical evidence that this potential source of bias affected the results!*

Jon E. Tyson, MD, MPH  
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UT Medical School at Houston  
6431 Fannin St., MSB 2.106  
Houston, TX 77030  
voice 713-500-5651  
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**From:** Wallace, Dennis [<mailto:dwallace@rti.org>]

**Sent:** Friday, February 26, 2010 1:56 PM

**To:** Wallace, Dennis; Tyson, Jon E; Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara; [alaptook@WIHRI.org](mailto:alaptook@WIHRI.org); Bell, Edward; [bpoindex@iupui.edu](mailto:bpoindex@iupui.edu); Das, Abhik; [goldb008@mc.duke.edu](mailto:goldb008@mc.duke.edu); [ifrantz@tuftsmedicalcenter.org](mailto:ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; [kurt.schibler@cchmc.org](mailto:kurt.schibler@cchmc.org); [kwatterberg@salud.unm.edu](mailto:kwatterberg@salud.unm.edu); [matthew.bizzarro@yale.edu](mailto:matthew.bizzarro@yale.edu); [mcw3@cwru.edu](mailto:mcw3@cwru.edu); [mcaplan@northshore.org](mailto:mcaplan@northshore.org); [Pablo.Sanchez@UTSouthwestern.edu](mailto:Pablo.Sanchez@UTSouthwestern.edu); [richard.ehrenkranz@yale.edu](mailto:richard.ehrenkranz@yale.edu); [Roger.Faix@hsc.utah.edu](mailto:Roger.Faix@hsc.utah.edu); [sshankar@med.wayne.edu](mailto:sshankar@med.wayne.edu); [vanmeurs@leland.stanford.edu](mailto:vanmeurs@leland.stanford.edu); Wally Carlo, M.D.; [cotte010@mc.duke.edu](mailto:cotte010@mc.duke.edu); Bradley Yoder; [rohls@salud.unm.edu](mailto:rohls@salud.unm.edu); [Luc.Brion@utsouthwestern.edu](mailto:Luc.Brion@utsouthwestern.edu); Stevenson David (E-mail); Finer, Neil; Rich, Wade; Gantz, Marie

**Cc:** Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]

**Subject:** RE: Follow Up ON BPD and Oximeters

Hello all,

I accidentally hit the send button before finishing editing this response so ignore the earlier e-mail and see the response below.

Dennis

Dennis Wallace  
Senior Research Statistician  
Cox 241  
RTI International  
3040 Cornwallis Rd  
Research Triangle Park, NC 27709-2104  
Voice: 919-541-6271  
Fax: 919-541-6416

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**From:** Wallace, Dennis  
**Sent:** Friday, February 26, 2010 2:53 PM  
**To:** 'Tyson, Jon E'; Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara; [alaptook@WIHRI.org](mailto:alaptook@WIHRI.org); Bell, Edward; [bpindex@iupui.edu](mailto:bpindex@iupui.edu); Das, Abhik; [goldb008@mc.duke.edu](mailto:goldb008@mc.duke.edu); [ifrantz@tuftsmedicalcenter.org](mailto:ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; [kurt.schibler@cchmc.org](mailto:kurt.schibler@cchmc.org); [kwatterberg@salud.unm.edu](mailto:kwatterberg@salud.unm.edu); [matthew.bizzarro@yale.edu](mailto:matthew.bizzarro@yale.edu); [mcw3@cwru.edu](mailto:mcw3@cwru.edu); [mcaplan@northshore.org](mailto:mcaplan@northshore.org); [Pablo.Sanchez@UTSouthwestern.edu](mailto:Pablo.Sanchez@UTSouthwestern.edu); [richard.ehrenkranz@yale.edu](mailto:richard.ehrenkranz@yale.edu); [Roger.Faix@hsc.utah.edu](mailto:Roger.Faix@hsc.utah.edu); [sshankar@med.wayne.edu](mailto:sshankar@med.wayne.edu); [vanmeurs@leland.stanford.edu](mailto:vanmeurs@leland.stanford.edu); Wally Carlo, M.D.; [cotte010@mc.duke.edu](mailto:cotte010@mc.duke.edu); Bradley Yoder; [rohls@salud.unm.edu](mailto:rohls@salud.unm.edu); [Luc.Brion@utsouthwestern.edu](mailto:Luc.Brion@utsouthwestern.edu); 'Stevenson David (E-mail)'; 'Finer, Neil'; Rich, Wade; Gantz, Marie  
**Cc:** Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: Follow Up ON BPD and Oximeters

Jon,

Marie flew out on a long-scheduled vacation after completing these analyses late Tuesday evening and has very limited e-mail and cell phone access. However, she has taken time to provide a preliminary response that I've outlined below with some added thoughts of my own in red font below. Based on these responses, I do believe that the critical concerns about bias have been addressed sufficiently for this initial manuscript, but if you think we need to have a more full discussion, we can talk after Marie returns next week. Because the programming for these outcome measures is relatively complicated, I'm hesitant to try to do any additional analyses prior to her return. However, as I indicated above, I don't think that we need to delay any submissions while trying to iron on the small details.

Dennis Wallace  
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RTI International  
3040 Cornwallis Rd  
Research Triangle Park, NC 27709-2104  
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Fax: 919-541-6416

-----Original Message-----

From: Tyson, Jon E [<mailto:Jon.E.Tyson@uth.tmc.edu>]  
Sent: Thursday, February 25, 2010 12:45 AM  
To: Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara; [alaptook@WIHRI.org](mailto:alaptook@WIHRI.org); Bell, Edward;

bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu;  
ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A;  
kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu;  
matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org;  
Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu;  
Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu;  
vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; Wallace, Dennis;  
cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu;  
Luc.Brion@utsouthwestern.edu; 'Stevenson David (E-mail)'; 'Finer,  
Neil'; Rich, Wade; Gantz, Marie  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn  
Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]  
Subject: RE: Follow Up ON BPD and Oximeters

Rose, before we can understand and interpret this information noted in the mail, we really need to know more about what was done and answers to questions like those below:

1. Which trial result was addressed - whether the evaluation of BPD was biased in the analyses of CPAP/limited ventilation vs. surfactant/conventional ventilation arm (not the analysis for which there is concern) or the analyses of the high vs. low oxygen saturation goal.

Although models were run for the different arms of the factorial design, the trial result that was addressed in the earlier e-mail was the impact of different oximeters on the comparison of the effects high vs. low oxygen saturation targets on BPD and BPD/death outcomes, which we believe is the question of interest.

2. Do we have reliable data to know whether individual infants were monitored on the study oximeter or on the clinical oximeter on the day the infant was 36 weeks and 0 and whether the oximeter was changed part way through that 24 hour period? What was done if the infant was switched on that day. As I understand it, the diagnosis of BPD was based on the entire 24 hours the day the infant was 36 weeks 0 days. Though the results of the survey weren't distributed, my impression from responses to my earlier e-mails was that even the procedure usually followed in individual centers was not necessarily clear.

We can determine from form PHY02 what oximeter was used to determine the physiologic definition of BPD, but we do not have the detailed level of information that you described. However, based on the survey results, we do know that only 5 sites used the study oximeter for an oxygen-based definition, and only 3 used the study oximeter for challenge.

3. What variables in the model when the BPD oximeter was added? What variables were in the model when a BPD oximeter x study treatment group was added?

Variables in the model were treatment oximeter (low vs. high), center, GA group. Familial clustering was adjusted for as a random effect. I added BPD oximeter and also looked at the interaction between BPD oximeter and treatment oximeter. These factors were identical to the factors used in the models for which secondary outcomes were reported in the manuscript.

4. Do I understand Maria and you to conclude that because centers tended to be consistent in their oximeter use, controlling for center would prevent a biased assessment of the effect on BPD by oxygen administration?

This comment makes me wonder if the analysis was done for the wrong comparison. This conclusion would be correct for analyses of the effect of CPAP/limited ventilation vs. surfactant/conventional ventilation on BPD by oxygen delivery (because each treatment arm would contain equal numbers of infants in the high and low saturation groups). However, this isn't the comparison in question. This

conclusion would certainly not be correct in analyzing the effect of high vs low sat goals on BPD. In this analysis, centers that used the study oximeter would be systematically more likely to administer oxygen to the high sat group than to the low sat group. The problem wouldn't go away by controlling for center, and the more centers that used the study oximeter, the more biased the result would be. How many centers were there that used the study oximeter?

Controlling for center adjusts for differences between centers including differences in the BPD oximeter used. Thus, adding a covariate for BPD oximeter does not change the estimates for the treatment oximeter effect. We are not arguing that the BPD oximeter used did not have an impact. We did find that BPD oximeter was significant in the models, as was center. However, since center and BPD oximeter are strongly confounded (in fact we have almost complete aliasing of center and clinical/study oximeter), it's not possible to tease out the effect of the BPD oximeter from other between-center differences. In addition, the interaction between BPD oximeter and treatment oximeter was not significant. This indicates that the impact of treatment oximeter on the BPD outcomes was not significantly different in the centers that used the study oximeters to determine BPD and those that used the clinical oximeters.

5. What is the basis for believing that there would be anything near reasonable power to assess a oximeter x treatment group interaction?

Clearly, these analyses were conducted from a post-hoc perspective, and the study was never designed to have the power to determine that the interaction in our data set is statistically significant for a pre-specified interaction effect size. But, that is not a shortcoming unless the magnitude of the interaction effect is such that it represents an important scientific bias in study interpretation. Our preliminary analyses indicate that biases of such magnitude are not present in this data set. We can do more detailed analyses of the level of bias that might have been introduced after Marie returns from vacation, but nothing in the analyses conducted to date suggest that those magnitudes warrant delay of submission of this manuscript.

I know that everyone is anxious to get this paper submitted. While I have an external advisory committee tomorrow, I will try to respond tomorrow night if the information requested above is sent tomorrow during the day.

---

From: Higgins, Rosemary (NIH/NICHD) [E] [[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)]  
Sent: Wednesday, February 24, 2010 7:53 AM  
To: Tyson, Jon E; 'Cunningham, Meg'; [SCRN] Stoll, Barbara; [alaptook@WIHRI.org](mailto:alaptook@WIHRI.org); Bell, Edward; [bpoindex@iupui.edu](mailto:bpoindex@iupui.edu); Das, Abhik; [goldb008@mc.duke.edu](mailto:goldb008@mc.duke.edu); [ifrantz@tuftsmedicalcenter.org](mailto:ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; [kurt.schibler@cchmc.org](mailto:kurt.schibler@cchmc.org); [kwatterberg@salud.unm.edu](mailto:kwatterberg@salud.unm.edu); [matthew.bizzarro@yale.edu](mailto:matthew.bizzarro@yale.edu); [mcw3@cwru.edu](mailto:mcw3@cwru.edu); [mcaplan@northshore.org](mailto:mcaplan@northshore.org); [Pablo.Sanchez@UTSouthwestern.edu](mailto:Pablo.Sanchez@UTSouthwestern.edu); [richard.ehrenkranz@yale.edu](mailto:richard.ehrenkranz@yale.edu); [Roger.Faix@hsc.utah.edu](mailto:Roger.Faix@hsc.utah.edu); [sshankar@med.wayne.edu](mailto:sshankar@med.wayne.edu); [vanmeurs@leland.stanford.edu](mailto:vanmeurs@leland.stanford.edu); Wally Carlo, M.D.; Wallace, Dennis; [cotte010@mc.duke.edu](mailto:cotte010@mc.duke.edu); Bradley Yoder; [rohls@salud.unm.edu](mailto:rohls@salud.unm.edu); [Luc.Brion@utsouthwestern.edu](mailto:Luc.Brion@utsouthwestern.edu); 'Stevenson David (E-mail)'; 'Finer, Neil'; Rich, Wade; Gantz, Marie  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn; Petrie, Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]  
Subject: Follow Up ON BPD and Oximeters

Hi all -

In Follow up to yesterday's discussion, Marie spent a great deal of time last evening running additional analyses to address (and now alleviate) Jon's concern as described:

We have looked into the question of whether the oximeter used to determine BPD impacted the BPD and death/BPD outcomes by adding a covariate for the BPD oximeter (study or clinical) to the

statistical models. We found that the effect of the BPD oximeter was significant; however, the interaction between BPD oximeter and treatment oximeter (low or high SpO2 target range) was not significant in any model, indicating that, if there was a BPD oximeter effect, it was not different in the two treatment groups. In addition, it should be noted that BPD oximeter is confounded with center (centers tended to be consistent in their use of the study or clinical oximeters to determine BPD). Therefore, by including center in the original models, we have already accounted for the effect of the BPD oximeter the center chose to use. Finally, because center and BPD oximeter are confounded, we cannot know whether the significant BPD oximeter effect is due to the BPD oximeters themselves or other characteristics that differ between centers.

From: Tyson, Jon E [mailto:Jon.E.Tyson@uth.tmc.edu]  
Sent: Tuesday, February 23, 2010 4:33 PM  
To: Higgins, Rosemary (NIH/NICHD) [E]; 'Cunningham, Meg'; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; Wallace, Dennis; cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; bbatton@siumed.edu  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; lmoore@med.wayne.edu; pamela.neville@duke.edu; gonza025@mc.duke.edu; Smith, Nancy M; Brenda Vecchio; msumner@peds.uab.edu; Archer, Stephanie (NIH/NICHD) [E]  
Subject: RE: Steering Committee Call Tomorrow

While it may seem that I am fixated on an unimportant issue regarding a not quite significant difference, I think we undermine the credibility of Network studies if we are not completely forthright about problems in measuring what everyone would agree is an important secondary outcome. Not reporting that the assessment of BPD by oxygen administration could be biased by continued use of the study oximeters would seem to be in the category of not reporting protocol deviations and not something that is in the Network's best interest. Why not just put a footnote under the table describing the problem?

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fax 713-500-0519

From: Higgins, Rosemary (NIH/NICHD) [E]  
[mailto:higginsr@mail.nih.gov]  
Sent: Tuesday, February 23, 2010 2:11 PM  
To: 'Cunningham, Meg'; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; Wallace, Dennis; cotte010@mc.duke.edu; Tyson, Jon E; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; bbatton@siumed.edu  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; lmoore@med.wayne.edu; pamela.neville@duke.edu; gonza025@mc.duke.edu; Smith, Nancy M; Brenda Vecchio; msumner@peds.uab.edu; Archer, Stephanie (NIH/NICHD) [E]

Subject: RE: Steering Committee Call Tomorrow

If you joined the call already in progress, please send us an email so we can count your attendance.

Rose

From: Cunningham, Meg [<mailto:mcunningham@rti.org>]  
Sent: Monday, February 22, 2010 9:59 AM  
To: [SCRN] Stoll, Barbara; [alaptook@WIHRI.org](mailto:alaptook@WIHRI.org); Bell, Edward; [bpointex@iupui.edu](mailto:bpointex@iupui.edu); Das, Abhik; [goldb008@mc.duke.edu](mailto:goldb008@mc.duke.edu); Higgins, Rosemary (NIH/NICHD) [E]; [ifrantz@tuftsmedicalcenter.org](mailto:ifrantz@tuftsmedicalcenter.org); [Kathleen.AKennedy@uth.tmc.edu](mailto:Kathleen.AKennedy@uth.tmc.edu); [kurt.schibler@cchmc.org](mailto:kurt.schibler@cchmc.org); [kwatterberg@salud.unm.edu](mailto:kwatterberg@salud.unm.edu); [matthew.bizzarro@yale.edu](mailto:matthew.bizzarro@yale.edu); [mcw3@cwru.edu](mailto:mcw3@cwru.edu); [mcaplan@northshore.org](mailto:mcaplan@northshore.org); [Pablo.Sanchez@UTSouthwestern.edu](mailto:Pablo.Sanchez@UTSouthwestern.edu); [richard.ehrenkranz@yale.edu](mailto:richard.ehrenkranz@yale.edu); [Roger.Faix@hsc.utah.edu](mailto:Roger.Faix@hsc.utah.edu); [sshankar@med.wayne.edu](mailto:sshankar@med.wayne.edu); [vanmeurs@leland.stanford.edu](mailto:vanmeurs@leland.stanford.edu); Wally Carlo, M.D.; Wallace, Dennis; [cotte010@mc.duke.edu](mailto:cotte010@mc.duke.edu); [jon.e.tyson@uth.tmc.edu](mailto:jon.e.tyson@uth.tmc.edu); Bradley Yoder; [rohls@salud.unm.edu](mailto:rohls@salud.unm.edu); [Luc.Brion@utsouthwestern.edu](mailto:Luc.Brion@utsouthwestern.edu); [bbatton@siumed.edu](mailto:bbatton@siumed.edu)  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; [lmoore@med.wayne.edu](mailto:lmoore@med.wayne.edu); [pamela.neville@duke.edu](mailto:pamela.neville@duke.edu); [gonza025@mc.duke.edu](mailto:gonza025@mc.duke.edu); [Nancy.M.Smith@uth.tmc.edu](mailto:Nancy.M.Smith@uth.tmc.edu); Brenda Vecchio; [msummer@peds.uab.edu](mailto:msummer@peds.uab.edu); Archer, Stephanie (NIH/NICHD) [E]  
Subject: Steering Committee Call Tomorrow

Dear All -

The next standing Steering Committee call is scheduled for tomorrow, Tuesday, February 23rd at 3:00pm ET.

Please Dial:

Outside the USA 1-203-310-(b)

or Within the USA 866-675-(b)

Then, enter Participant Passcode: (b) (6)

Steering Committee Conference Call Agenda 02/23/2010

1. Early BP discussion (attached are a brief description of the time limited data collection proposal and a draft of the form which would be used.)
2. SUPPORT manuscript discussion and update
3. New Business

Thanks,  
Meg

Meg Cunningham  
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Washington, DC 20005  
tel: 202-974-7837  
fax: 202-728-2095  
[www.rti.org](http://www.rti.org)<<http://www.rti.org>>



**From:** Archer, Stephanie (NIH/NICHD) [E]  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: \*\*\*\*\* Important -Follow Up ON BPD and Oximeters\*\*\*\*\*  
**Date:** Tuesday, March 02, 2010 9:13:14 AM

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So far we have:

Yes = 2  
No = 6  
Abstain = 1

Missing:  
Abbot  
Kurt

-----Original Message-----

From: Higgins, Rosemary (NIH/NICHD) [E]  
Sent: Tuesday, March 02, 2010 6:19 AM  
To: Archer, Stephanie (NIH/NICHD) [E]  
Subject: Fw: \*\*\*\*\* Important -Follow Up ON BPD and Oximeters\*\*\*\*\*

----- Original Message -----

From: Das, Abhik <adas@rti.org>  
To: Higgins, Rosemary (NIH/NICHD) [E]  
Cc: Wallace, Dennis <dwallace@rti.org>; Gantz, Marie <mgantz@rti.org>  
Sent: Tue Mar 02 06:12:15 2010  
Subject: RE: \*\*\*\*\* Important -Follow Up ON BPD and Oximeters\*\*\*\*\*

No

Abhik Das  
Senior Research Statistician  
RTI International

-----Original Message-----

From: Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]  
Sent: Monday, March 01, 2010 10:59 AM Eastern Standard Time  
To: 'Wally Carlo, M.D.'; 'Finer, Neil'; alaptook@WIHRI.org; Roger.Faix@hsc.utah.edu; Bradley Yoder; kurt.schibler@cchmc.org; Das, Abhik; nancy newman; Rich, Wade; Gantz, Marie; mcw3@case.edu; Wallace, Dennis  
Cc: Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin  
Subject: \*\*\*\*\* Important -Follow Up ON BPD and Oximeters\*\*\*\*\*

To the SUPPORT Subcommittee

Given the email exchange, the subcommittee will need to ascertain whether or not to indicate in the SUPPORT papers whether or not a bias could have existed in reporting the secondary outcome of BPD based on oximeter. Previously the subcommittee had reviewed the oximeter use on a conference call and decided to defer this to a secondary paper. There has been discussion on the SC call and via email subsequently.

Therefore, please send me a yes/no vote to include this in the paper by March 2.

Thanks  
Rose

---

From: Tyson, Jon E [mailto:Jon.E.Tyson@uth.tmc.edu]

Sent: Friday, February 26, 2010 6:28 PM

To: Wallace, Dennis; Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; Stevenson David (E-mail); Finer, Neil; Rich, Wade; Gantz, Marie

Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]

Subject: RE: Follow Up ON BPD and Oximeters

I don't understand your statement "Controlling for center adjusts for differences between centers including differences in the BPD oximeter used." To simplify the discussion, suppose every center always used the study oximeter in designating who had BPD by oxygen saturation. Because the true saturation that would prompt oxygen administration would differ in the two treatment groups, there would be systematic bias toward administering oxygen to more infants in the high sat group than in the low sat group. This is inherent in the study design. Whatever differences there were between centers, this bias would occur in every center and would not be eliminated by controlling for center. And if I understand the analysis, there would be no interaction between treatment oximeter and BPD oximeter because they would be the same in every baby in every center.

You indicate that 5 centers used the study oximeter in almost every baby. In saying "it's not possible to tease out the effect of the BPD oximeter from other between-center differences" (a statement that I certainly accept), aren't you saying that the effect of the study oximeter on the difference in the incidence of BPD by oxygen administration between high and low sat groups (i.e., the bias) can not be distinguished from the effect of the myriad of other factors in those centers that might affect that difference in incidence? If so, why would you expect to be able to discern that bias (the signal) from all the noise resulting from other factors? I understand from what you said that the same approach was used in virtually all infants in each center which makes the effective n to be based on the number of centers rather than the number of babies. As I understand the analysis, the power to assess an interaction would then be quite low.

The issue here is whether is simply whether to report somewhere in the paper (which could be noted under the table and wouldn't increase the word count for the text) a bias in evaluating a secondary outcome. This can be done with no delay in submitting the manuscript or waiting for Maria to return. If we had other real or potential sources of bias-say, a breaking of the blind for some infants, open label administration of a study drug to the control group, or differential loss to follow-up, we would certainly report it as a matter of course, whether or not there was a significant or near significant difference in the outcome and without testing and whether or not we assessed or found any interaction or other statistical evidence that this potential source of bias affected the results!

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From: Wallace, Dennis [mailto:dwallace@rti.org]

Sent: Friday, February 26, 2010 1:56 PM

To: Wallace, Dennis; Tyson, Jon E; Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu;

ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; Stevenson David (E-mail); Finer, Neil; Rich, Wade; Gantz, Marie

Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]

Subject: RE: Follow Up ON BPD and Oximeters

Hello all,

I accidentally hit the send button before finishing editing this response so ignore the earlier e-mail and see the response below.

Dennis

Dennis Wallace  
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Cox 241  
RTI International  
3040 Cornwallis Rd  
Research Triangle Park, NC 27709-2104  
Voice: 919-541-6271  
Fax: 919-541-6416

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From: Wallace, Dennis

Sent: Friday, February 26, 2010 2:53 PM

To: 'Tyson, Jon E'; Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; 'Stevenson David (E-mail)'; 'Finer, Neil'; Rich, Wade; Gantz, Marie

Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]

Subject: RE: Follow Up ON BPD and Oximeters

Jon,

Marie flew out on a long-scheduled vacation after completing these analyses late Tuesday evening and has very limited e-mail and cell phone access. However, she has taken time to provide a preliminary response that I've outlined below with some added thoughts of my own in red font below. Based on these responses, I do believe that the critical concerns about bias have been addressed sufficiently for this initial manuscript, but if you think we need to have a more full discussion, we can talk after Marie returns next week. Because the programming for these outcome measures is relatively complicated, I'm hesitant to try to do any additional analyses prior to her return. However, as I indicated above, I don't think that we need to delay any submissions while trying to iron on the small details.

Dennis Wallace

Senior Research Statistician

Cox 241

RTI International

3040 Cornwallis Rd

Research Triangle Park, NC 27709-2104

Voice: 919-541-6271

Fax: 919-541-6416

-----Original Message-----

From: Tyson, Jon E [<mailto:Jon.E.Tyson@uth.tmc.edu>]

Sent: Thursday, February 25, 2010 12:45 AM

To: Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara; [alaptook@WIHRI.org](mailto:alaptook@WIHRI.org); Bell, Edward; [bpoindex@iupui.edu](mailto:bpoindex@iupui.edu); Das, Abhik; [goldb008@mc.duke.edu](mailto:goldb008@mc.duke.edu); [ifrantz@tuftsmedicalcenter.org](mailto:ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; [kurt.schibler@cchmc.org](mailto:kurt.schibler@cchmc.org); [kwatterberg@salud.unm.edu](mailto:kwatterberg@salud.unm.edu); [matthew.bizzarro@yale.edu](mailto:matthew.bizzarro@yale.edu); [mcw3@cwru.edu](mailto:mcw3@cwru.edu); [mcaplan@northshore.org](mailto:mcaplan@northshore.org); [Pablo.Sanchez@UTSouthwestern.edu](mailto:Pablo.Sanchez@UTSouthwestern.edu); [richard.ehrenkranz@yale.edu](mailto:richard.ehrenkranz@yale.edu); [Roger.Faix@hsc.utah.edu](mailto:Roger.Faix@hsc.utah.edu); [sshankar@med.wayne.edu](mailto:sshankar@med.wayne.edu); [vanmeurs@leland.stanford.edu](mailto:vanmeurs@leland.stanford.edu); Wally Carlo, M.D.; Wallace, Dennis; [cotte010@mc.duke.edu](mailto:cotte010@mc.duke.edu); Bradley Yoder; [rohls@salud.unm.edu](mailto:rohls@salud.unm.edu); [Luc.Brion@utsouthwestern.edu](mailto:Luc.Brion@utsouthwestern.edu); 'Stevenson David (E-mail)'; 'Finer, Neil'; Rich, Wade; Gantz, Marie

Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]

Subject: RE: Follow Up ON BPD and Oximeters

Rose, before we can understand and interpret this information noted in the mail, we really need to know more about what was done and answers to questions like those below:

1. Which trial result was addressed - whether the evaluation of BPD was biased in the analyses of CPAP/limited ventilation vs. surfactant/conventional ventilation arm (not the analysis for which there is concern) or the analyses of the high vs. low oxygen saturation goal.

Although models were run for the different arms of the factorial design, the trial result that was addressed in the earlier e-mail was the impact of different oximeters on the comparison of the effects high vs. low oxygen saturation targets on BPD and BPD/death outcomes, which we believe is the question of interest.

2. Do we have reliable data to know whether individual infants were monitored on the study oximeter or on the clinical oximeter on the day the infant was 36 weeks and 0 and whether the oximeter was changed part way through that 24 hour period? What was done if the infant was switched on that day. As I understand it, the diagnosis of BPD was based on the entire 24 hours the day the infant was 36 weeks 0 days. Though the results of the survey weren't distributed, my impression from responses to my earlier e mails was that even the procedure usually followed in individual centers was not necessarily clear.

We can determine from form PHY02 what oximeter was used to determine the physiologic definition of BPD, but we do not have the detailed level of information that you described. However, based on the survey results, we do know that only 5 sites used the study oximeter for an oxygen-based definition, and only 3 used the study oximeter for challenge.

3. What variables in the model when the BPD oximeter was added? What variables were in the model when a BPD oximeter x study treatment group was added?

Variables in the model were treatment oximeter (low vs. high), center, GA group. Familial clustering was adjusted for as a random effect. I added BPD oximeter and also looked at the interaction between BPD oximeter and treatment oximeter. These factors were identical to the factors used in the models for which secondary outcomes were reported in the manuscript.

4. Do I understand Maria and you to conclude that because centers tended to be consistent in their oximeter use, controlling for center would prevent a biased assessment of the effect on BPD by oxygen administration?

This comment makes me wonder if the analysis was done for the wrong comparison. This conclusion would be correct for analyses of the effect of CPAP/limited ventilation vs. surfactant/ conventional ventilation on BPD by oxygen delivery (because each treatment arm would contain equal numbers of infants in the high and low sat groups). However, this isn't the comparison in question. This conclusion would certainly not be correct in analyzing the effect of high vs low sat goals on BPD. In this analysis, centers that used the study oximeter would be systematically more likely to administer oxygen to the high sat group than to the low sat group. The problem wouldn't go away by controlling for center, and the more centers that used the study oximeter, the more biased the result would be. How many centers were there that used the study oximeter?

Controlling for center adjusts for differences between centers including differences in the BPD oximeter used. Thus, adding a covariate for BPD oximeter does not change the estimates for the treatment oximeter effect. We are not arguing that the BPD oximeter used did not have an impact. We did find that BPD oximeter was significant in the models, as was center. However, since center and BPD oximeter are strongly confounded (in fact we have almost complete aliasing of center and clinical/study oximeter), it's not possible to tease out the effect of the BPD oximeter from other between-center differences. In addition, the interaction between BPD oximeter and treatment oximeter was not significant. This indicates that the impact of treatment oximeter on the BPD outcomes was not significantly different in the centers that used the study oximeters to determine BPD and those that used the clinical oximeters.

5. What is the basis for believing that there would be anything near reasonable power to assess a oximeter x treatment group interaction?

Clearly, these analyses were conducted from a post-hoc perspective, and the study was never designed to have the power to determine that the interaction in our data set is statistically significant for a pre-specified interaction effect size. But, that is not a shortcoming unless the magnitude of the interaction effect is such that it represents an important scientific bias in study interpretation. Our preliminary analyses indicate that biases of such magnitude are not present in this data set. We can do more detailed analyses of the level of bias that might have been introduced after Marie returns from vacation, but nothing in the analyses conducted to date suggest that those magnitudes warrant delay of submission of this manuscript.

I know that everyone is anxious to get this paper submitted. While I have an external advisory committee tomorrow, I will try to respond tomorrow night if the information requested above is sent tomorrow during the day.

---

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]

Sent: Wednesday, February 24, 2010 7:53 AM

To: Tyson, Jon E; 'Cunningham, Meg'; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; Wallace, Dennis; cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; 'Stevenson David (E-mail)'; 'Finer, Neil'; Rich, Wade; Gantz, Marie

Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]

Subject: Follow Up ON BPD and Oximeters

Hi all -

In Follow up to yesterday's discussion, Marie spent a great deal of time last evening running additional analyses to address (and now alleviate) Jon's concern as described:

We have looked into the question of whether the oximeter used to determine BPD impacted the BPD and death/BPD outcomes by adding a covariate for the BPD oximeter (study or clinical) to the statistical models. We found that the effect of the BPD oximeter was significant; however, the interaction between BPD oximeter and treatment oximeter (low or high SpO2 target range) was not significant in any model, indicating that, if there was a BPD oximeter effect, it was not different in the two treatment groups. In addition, it should be noted that BPD oximeter is confounded with center (centers tended to be consistent in their use of the study or clinical oximeters to determine BPD). Therefore, by including center in the original models, we have already accounted for the effect of the BPD oximeter the center chose to use. Finally, because center and BPD oximeter are confounded, we cannot know whether the significant BPD oximeter effect is due to the BPD oximeters themselves or other characteristics that

differ between centers.

---

From: Tyson, Jon E [<mailto:Jon.E.Tyson@uth.tmc.edu>]

Sent: Tuesday, February 23, 2010 4:33 PM

To: Higgins, Rosemary (NIH/NICHD) [E]; 'Cunningham, Meg'; [SCRN] Stoll, Barbara; [alaptook@WIHRI.org](mailto:alaptook@WIHRI.org); Bell, Edward; [bpoindex@iupui.edu](mailto:bpoindex@iupui.edu); Das, Abhik; [goldb008@mc.duke.edu](mailto:goldb008@mc.duke.edu); [ifrantz@tuftsmedicalcenter.org](mailto:ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; [kurt.schibler@cchmc.org](mailto:kurt.schibler@cchmc.org); [kwatterberg@salud.unm.edu](mailto:kwatterberg@salud.unm.edu); [matthew.bizzarro@yale.edu](mailto:matthew.bizzarro@yale.edu); [mcw3@cwru.edu](mailto:mcw3@cwru.edu); [mcaplan@northshore.org](mailto:mcaplan@northshore.org); [Pablo.Sanchez@UTSouthwestern.edu](mailto:Pablo.Sanchez@UTSouthwestern.edu); [richard.ehrenkranz@yale.edu](mailto:richard.ehrenkranz@yale.edu); [Roger.Faix@hsc.utah.edu](mailto:Roger.Faix@hsc.utah.edu); [sshankar@med.wayne.edu](mailto:sshankar@med.wayne.edu); [vanmeurs@leland.stanford.edu](mailto:vanmeurs@leland.stanford.edu); Wally Carlo, M.D.; Wallace, Dennis; [cotte010@mc.duke.edu](mailto:cotte010@mc.duke.edu); Bradley Yoder; [rohls@salud.unm.edu](mailto:rohls@salud.unm.edu); [Luc.Brion@utsouthwestern.edu](mailto:Luc.Brion@utsouthwestern.edu); [bbatton@siumed.edu](mailto:bbatton@siumed.edu)

Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; [lmoore@med.wayne.edu](mailto:lmoore@med.wayne.edu); [pamela.neville@duke.edu](mailto:pamela.neville@duke.edu); [gonza025@mc.duke.edu](mailto:gonza025@mc.duke.edu); Smith, Nancy M; Brenda Vecchio; [msumner@peds.uab.edu](mailto:msumner@peds.uab.edu); Archer, Stephanie (NIH/NICHD) [E]

Subject: RE: Steering Committee Call Tomorrow

While it may seem that I am fixated on an unimportant issue regarding a not quite significant difference, I think we undermine the credibility of Network studies if we are not completely forthright about problems in measuring what everyone would agree is an important secondary outcome. Not reporting that the assessment of BPD by oxygen administration could be biased by continued use of the study oximeters would seem to be in the category of not reporting protocol deviations and not something that is in the Network's best interest. Why not just put a footnote under the table describing the problem?

Jon E. Tyson, MD, MPH

Center for Clinical Research & Evidence-Based Medicine

UT Medical School at Houston

6431 Fannin St., MSB 2.106

Houston, TX 77030

voice 713-500-5651

fax 713-500-0519

---

From: Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]

Sent: Tuesday, February 23, 2010 2:11 PM

To: 'Cunningham, Meg'; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; Wallace, Dennis; cotte010@mc.duke.edu; Tyson, Jon E; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; bbatton@siumed.edu

Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; lmoore@med.wayne.edu; pamelaneville@duke.edu; gonza025@mc.duke.edu; Smith, Nancy M; Brenda Vecchio; msumner@peds.uab.edu; Archer, Stephanie (NIH/NICHD) [E]

Subject: RE: Steering Committee Call Tomorrow

If you joined the call already in progress, please send us an email so we can count your attendance.

Rose

---

From: Cunningham, Meg [mailto:mcunningham@rti.org]

Sent: Monday, February 22, 2010 9:59 AM

To: [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; Higgins, Rosemary (NIH/NICHD) [E]; ifrantz@tuftsmedicalcenter.org; Kathleen.A.Kennedy@uth.tmc.edu; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; Wallace, Dennis; cotte010@mc.duke.edu; jon.e.tyson@uth.tmc.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; bbatton@siumed.edu

Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; lmoore@med.wayne.edu; pamelaneville@duke.edu; gonza025@mc.duke.edu; Nancy.M.Smith@uth.tmc.edu; Brenda Vecchio; msumner@peds.uab.edu; Archer, Stephanie (NIH/NICHD) [E]

Subject: Steering Committee Call Tomorrow

Dear All -

The next standing Steering Committee call is scheduled for tomorrow, Tuesday, February 23rd at 3:00pm ET.

Please Dial:



Outside the USA 1-203-310-(b)

or Within the USA 866-675-(b)

Then, enter Participant Passcode: (b) (6)

Steering Committee Conference Call Agenda 02/23/2010

1. Early BP discussion (attached are a brief description of the time limited data collection proposal and a draft of the form which would be used.)
2. SUPPORT manuscript discussion and update
3. New Business

Thanks,

Meg

Meg Cunningham

RTI International

701 13th St. NW, Ste. 750

Washington, DC 20005

tel: 202-974-7837

fax: 202-728-2095

www.rti.org<<http://www.rti.org>>

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Michele.Walsh@UHhospitals.org"  
**Subject:** Re: \*\*\*\*\* Important -Follow Up ON BPD and Oximeters\*\*\*\*\*  
**Date:** Monday, March 01, 2010 6:54:22 PM

---

For several of the subcommittees, since there is a coordinator or two investigators from the same site, given expertise, YES!

---

**From:** Walsh, Michele <Michele.Walsh@UHhospitals.org>  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Mon Mar 01 18:52:19 2010  
**Subject:** RE: \*\*\*\*\* Important -Follow Up ON BPD and Oximeters\*\*\*\*\*

Can one site have 2 votes?

Michele Walsh  
beeper (b) (6)  
Ph 216 844 3759

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Monday, March 01, 2010 6:49 PM  
**To:** Walsh, Michele  
**Subject:** Re: \*\*\*\*\* Important -Follow Up ON BPD and Oximeters\*\*\*\*\*

Yes, she is on the subcommittee

---

**From:** Walsh, Michele <Michele.Walsh@UHhospitals.org>  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Mon Mar 01 18:45:10 2010  
**Subject:** RE: \*\*\*\*\* Important -Follow Up ON BPD and Oximeters\*\*\*\*\*

Nancy Newman?

Michele Walsh  
beeper (b) (6)  
Ph 216 844 3759

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Monday, March 01, 2010 6:36 PM  
**To:** Walsh, Michele  
**Subject:** Re: \*\*\*\*\* Important -Follow Up ON BPD and Oximeters\*\*\*\*\*

As an fyi, Nancy sent me an "abstain" vote

---

**From:** Walsh, Michele <Michele.Walsh@UHhospitals.org>  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Mon Mar 01 17:33:58 2010  
**Subject:** RE: \*\*\*\*\* Important -Follow Up ON BPD and Oximeters\*\*\*\*\*

I vote NO. I am convinced that the analyses

Are fair and not biased.

Michele Walsh  
beeper (b) (6)  
Ph 216 844 3759

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Monday, March 01, 2010 11:00 AM  
**To:** 'Wally Carlo, M.D.'; 'Finer, Neil'; alaptook@WIHRI.org; Roger.Faix@hsc.utah.edu; Bradley Yoder; kurt.schibler@cchmc.org; adas@rti.org; nancy.newman; Rich, Wade; Gantz, Marie; mcw3@case.edu; Dennis Wallace  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin  
**Subject:** \*\*\*\*\* Important -Follow Up ON BPD and Oximeters\*\*\*\*\*  
**Importance:** High

To the SUPPORT Subcommittee

Given the email exchange, the subcommittee will need to ascertain whether or not to indicate in the SUPPORT papers whether or not a bias could have existed in reporting the secondary outcome of BPD based on oximeter. Previously the subcommittee had reviewed the oximeter use on a conference call and decided to defer this to a secondary paper. There has been discussion on the SC call and via email subsequently.

**Therefore, please send me a yes/no vote to include this in the paper by March 2.**

Thanks  
Rose

---

**From:** Tyson, Jon E [mailto:Jon.E.Tyson@uth.tmc.edu]  
**Sent:** Friday, February 26, 2010 6:28 PM  
**To:** Wallace, Dennis; Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; Stevenson David (E-mail); Finer, Neil; Rich, Wade; Gantz, Marie  
**Cc:** Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: Follow Up ON BPD and Oximeters

I don't understand your statement "Controlling for center adjusts for differences between centers including differences in the BPD oximeter used." To simplify the discussion, suppose every center always used the study oximeter in designating who had BPD by oxygen saturation. Because the true saturation that would prompt oxygen administration would differ in the two treatment groups, there would be systematic bias toward administering oxygen to more infants in the high sat group than in the low sat group. This is inherent in the study design. Whatever differences there were between centers, this bias would occur in every center and would not be eliminated by controlling for center. And if I understand the analysis, there would be no interaction between treatment oximeter and BPD oximeter because they

would be the same in every baby in every center.

You indicate that 5 centers used the study oximeter in almost every baby. In saying "it's not possible to tease out the effect of the BPD oximeter from other between-center differences" (a statement that I certainly accept), aren't you saying that the effect of the study oximeter on the difference in the incidence of BPD by oxygen administration between high and low sat groups (i.e., the bias) can not be distinguished from the effect of the myriad of other factors in those centers that might affect that difference in incidence? If so, why would you expect to be able to discern that bias (the signal) from all the noise resulting from other factors? I understand from what you said that the same approach was used in virtually all infants in each center which makes the effective  $n$  to be based on the number of centers rather than the number of babies. As I understand the analysis, the power to assess an interaction would then be quite low.

The issue here is whether is simply whether to report somewhere in the paper (which could be noted under the table and wouldn't increase the word count for the text) a bias in evaluating a secondary outcome. This can be done with no delay in submitting the manuscript or waiting for Maria to return. *If we had other real or potential sources of bias—say, a breaking of the blind for some infants, open label administration of a study drug to the control group, or differential loss to follow-up, we would certainly report it as a matter of course, whether or not there was a significant or near significant difference in the outcome and without testing and whether or not we assessed or found any interaction or other statistical evidence that this potential source of bias affected the results!*

Jon E. Tyson, MD, MPH  
Center for Clinical Research & Evidence-Based Medicine  
UT Medical School at Houston  
6431 Fannin St., MSB 2.106  
Houston, TX 77030  
voice 713-500-5651  
fax 713-500-0519

---

**From:** Wallace, Dennis [mailto:dwallace@rti.org]  
**Sent:** Friday, February 26, 2010 1:56 PM  
**To:** Wallace, Dennis; Tyson, Jon E; Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; Stevenson David (E-mail); Finer, Neil; Rich, Wade; Gantz, Marie  
**Cc:** Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: Follow Up ON BPD and Oximeters

Hello all,

I accidentally hit the send button before finishing editing this response so ignore the earlier e-mail and see the response below.

Dennis

Dennis Wallace  
Senior Research Statistician  
Cox 241  
RTI International  
3040 Cornwallis Rd  
Research Triangle Park, NC 27709-2104  
Voice: 919-541-6271

Fax: 919-541-6416

---

**From:** Wallace, Dennis

**Sent:** Friday, February 26, 2010 2:53 PM

**To:** 'Tyson, Jon E'; Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; 'Stevenson David (E-mail)'; 'Finer, Neil'; Rich, Wade; Gantz, Marie

**Cc:** Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]

**Subject:** RE: Follow Up ON BPD and Oximeters

Jon,

Marie flew out on a long-scheduled vacation after completing these analyses late Tuesday evening and has very limited e-mail and cell phone access. However, she has taken time to provide a preliminary response that I've outlined below with some added thoughts of my own in red font below. Based on these responses, I do believe that the critical concerns about bias have been addressed sufficiently for this initial manuscript, but if you think we need to have a more full discussion, we can talk after Marie returns next week. Because the programming for these outcome measures is relatively complicated, I'm hesitant to try to do any additional analyses prior to her return. However, as I indicated above, I don't think that we need to delay any submissions while trying to iron on the small details.

Dennis Wallace  
Senior Research Statistician  
Cox 241  
RTI International  
3040 Cornwallis Rd  
Research Triangle Park, NC 27709-2104  
Voice: 919-541-6271  
Fax: 919-541-6416

-----Original Message-----

**From:** Tyson, Jon E [mailto:Jon.E.Tyson@uth.tmc.edu]

**Sent:** Thursday, February 25, 2010 12:45 AM

**To:** Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; Wallace, Dennis; cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; 'Stevenson David (E-mail)'; 'Finer, Neil'; Rich, Wade; Gantz, Marie

**Cc:** Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]

**Subject:** RE: Follow Up ON BPD and Oximeters

Rose, before we can understand and interpret this information noted in the mail, we really need to know more about what was done and answers to questions like those below:

1. Which trial result was addressed - whether the evaluation of BPD was biased in the analyses of CPAP/limited ventilation vs. surfactant/conventional ventilation arm (not the analysis for which there is concern) or the analyses of the high vs. low oxygen saturation goal.

Although models were run for the different arms of the factorial design, the trial result that was addressed in the earlier e-mail was the impact of different oximeters on the comparison of the effects high vs. low oxygen

saturation targets on BPD and BPD/death outcomes, which we believe is the question of interest.

2. Do we have reliable data to know whether individual infants were monitored on the study oximeter or on the clinical oximeter on the day the infant was 36 weeks and 0 and whether the oximeter was changed part way through that 24 hour period? What was done if the infant was switched on that day. As I understand it, the diagnosis of BPD was based on the entire 24 hours the day the infant was 36 weeks 0 days. Though the results of the survey weren't distributed, my impression from responses to my earlier e mails was that even the procedure usually followed in individual centers was not necessarily clear.

We can determine from form PHY02 what oximeter was used to determine the physiologic definition of BPD, but we do not have the detailed level of information that you described. However, based on the survey results, we do know that only 5 sites used the study oximeter for an oxygen-based definition, and only 3 used the study oximeter for challenge.

3. What variables in the model when the BPD oximeter was added? What variables were in the model when a BPD oximeter x study treatment group was added?

Variables in the model were treatment oximeter (low vs. high), center, GA group. Familial clustering was adjusted for as a random effect. I added BPD oximeter and also looked at the interaction between BPD oximeter and treatment oximeter. These factors were identical to the factors used in the models for which secondary outcomes were reported in the manuscript.

4. Do I understand Maria and you to conclude that because centers tended to be consistent in their oximeter use, controlling for center would prevent a biased assessment of the effect on BPD by oxygen administration?

This comment makes me wonder if the analysis was done for the wrong comparison. This conclusion would be correct for analyses of the effect of CPAP/limited ventilation vs. surfactant/ conventional ventilation on BPD by oxygen delivery (because each treatment arm would contain equal numbers of infants in the high and low sat groups). However, this isn't the comparison in question. This conclusion would certainly not be correct in analyzing the effect of high vs low sat goals on BPD. In this analysis, centers that used the study oximeter would be systematically more likely to administer oxygen to the high sat group than to the low sat group. The problem wouldn't go away by controlling for center, and the more centers that used the study oximeter, the more biased the result would be. How many centers were there that used the study oximeter?

Controlling for center adjusts for differences between centers including differences in the BPD oximeter used. Thus, adding a covariate for BPD oximeter does not change the estimates for the treatment oximeter effect. We are not arguing that the BPD oximeter used did not have an impact. We did find that BPD oximeter was significant in the models, as was center. However, since center and BPD oximeter are strongly confounded (in fact we have almost complete aliasing of center and clinical/study oximeter), it's not possible to tease out the effect of the BPD oximeter from other between-center differences. In addition, the interaction between BPD oximeter and treatment oximeter was not significant. This indicates that the impact of treatment oximeter on the BPD outcomes was not significantly different in the centers that used the study oximeters to determine BPD and those that used the clinical oximeters.

5. What is the basis for believing that there would be anything near reasonable power to assess a oximeter x treatment group interaction?

Clearly, these analyses were conducted from a post-hoc perspective, and the study was never designed to have the power to determine that the interaction in our data set is statistically significant for a pre-specified interaction effect size. But, that is not a shortcoming unless the magnitude of the interaction effect is such that it represents an important scientific bias in study interpretation. Our preliminary analyses indicate that biases of

such magnitude are not present in this data set. We can do more detailed analyses of the level of bias that might have been introduced after Marie returns from vacation, but nothing in the analyses conducted to date suggest that those magnitudes warrant delay of submission of this manuscript.

I know that everyone is anxious to get this paper submitted. While I have an external advisory committee tomorrow, I will try to respond tomorrow night if the information requested above is sent tomorrow during the day.

---

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]  
Sent: Wednesday, February 24, 2010 7:53 AM  
To: Tyson, Jon E; 'Cunningham, Meg'; [SCRN] Stoll, Barbara;  
alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik;  
goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A;  
kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu;  
matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org;  
Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu;  
Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu;  
vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; Wallace, Dennis;  
cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu;  
Luc.Brion@utsouthwestern.edu; 'Stevenson David (E-mail)'; 'Finer, Neil';  
Rich, Wade; Gantz, Marie  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman,  
Jamie; Archer, Stephanie (NIH/NICHD) [E]  
Subject: Follow Up ON BPD and Oximeters

Hi all -

In Follow up to yesterday's discussion, Marie spent a great deal of time last evening running additional analyses to address (and now alleviate) Jon's concern as described:

We have looked into the question of whether the oximeter used to determine BPD impacted the BPD and death/BPD outcomes by adding a covariate for the BPD oximeter (study or clinical) to the statistical models. We found that the effect of the BPD oximeter was significant; however, the interaction between BPD oximeter and treatment oximeter (low or high SpO2 target range) was not significant in any model, indicating that, if there was a BPD oximeter effect, it was not different in the two treatment groups. In addition, it should be noted that BPD oximeter is confounded with center (centers tended to be consistent in their use of the study or clinical oximeters to determine BPD). Therefore, by including center in the original models, we have already accounted for the effect of the BPD oximeter the center chose to use. Finally, because center and BPD oximeter are confounded, we cannot know whether the significant BPD oximeter effect is due to the BPD oximeters themselves or other characteristics that differ between centers.

---

From: Tyson, Jon E [mailto:Jon.E.Tyson@uth.tmc.edu]  
Sent: Tuesday, February 23, 2010 4:33 PM  
To: Higgins, Rosemary (NIH/NICHD) [E]; 'Cunningham, Meg'; [SCRN] Stoll,  
Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik;  
goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A;  
kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu;  
matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org;  
Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu;  
Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu;  
vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; Wallace, Dennis;  
cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu;  
Luc.Brion@utsouthwestern.edu; bbatton@siumed.edu  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman,  
Jamie; lmoore@med.wayne.edu; pamela.neville@duke.edu; gonza025@mc.duke.edu;  
Smith, Nancy M; Brenda Vecchio; msumner@peds.uab.edu; Archer, Stephanie  
(NIH/NICHD) [E]  
Subject: RE: Steering Committee Call Tomorrow

While it may seem that I am fixated on an unimportant issue regarding a not quite significant difference, I think we undermine the credibility of Network studies if we are not completely forthright about problems in measuring what everyone would agree is an important secondary outcome. Not reporting that the assessment of BPD by oxygen administration could be biased by continued use of the study oximeters would seem to be in the category of not reporting protocol deviations and not something that is in

the Network's best interest. Why not just put a footnote under the table describing the problem?

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Houston, TX 77030  
voice 713-500-5651  
fax 713-500-0519

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
Sent: Tuesday, February 23, 2010 2:11 PM  
To: 'Cunningham, Meg'; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; Wallace, Dennis; cotte010@mc.duke.edu; Tyson, Jon E; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; bbatton@siumed.edu  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; lmoore@med.wayne.edu; pamela.neville@duke.edu; gonza025@mc.duke.edu; Smith, Nancy M; Brenda Vecchio; msumner@peds.uab.edu; Archer, Stephanie (NIH/NICHD) [E]  
Subject: RE: Steering Committee Call Tomorrow

If you joined the call already in progress, please send us an email so we can count your attendance.

Rose

From: Cunningham, Meg [mailto:mcunningham@rti.org]  
Sent: Monday, February 22, 2010 9:59 AM  
To: [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; Higgins, Rosemary (NIH/NICHD) [E]; ifrantz@tuftsmedicalcenter.org; Kathleen.A.Kennedy@uth.tmc.edu; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; Wallace, Dennis; cotte010@mc.duke.edu; jon.e.tyson@uth.tmc.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; bbatton@siumed.edu  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; lmoore@med.wayne.edu; pamela.neville@duke.edu; gonza025@mc.duke.edu; Nancy.M.Smith@uth.tmc.edu; Brenda Vecchio; msumner@peds.uab.edu; Archer, Stephanie (NIH/NICHD) [E]  
Subject: Steering Committee Call Tomorrow

Dear All -

The next standing Steering Committee call is scheduled for tomorrow, Tuesday, February 23rd at 3:00pm ET.

Please Dial:

Outside the USA 1-203-310 (b) (6)  
or Within the USA 866-675 (b) (6)

Then, enter Participant Passcode: (b) (6)

Steering Committee Conference Call Agenda 02/23/2010

1. Early BP discussion (attached are a brief description of the time limited data collection proposal and a draft of the form which would be used.)
2. SUPPORT manuscript discussion and update
3. New Business

Thanks,  
Meg



Meg Cunningham  
RTI International  
701 13th St. NW, Ste. 750  
Washington, DC 20005  
tel: 202-974-7837  
fax: 202-728-2095  
www.rti.org<<http://www.rti.org>>

Visit us at [www.UHhospitals.org](http://www.UHhospitals.org).

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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.

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**From:** Nancy Newman  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** Re: \*\*\*\*\* Important -Follow Up ON BPD and Oximeters\*\*\*\*\*  
**Date:** Monday, March 01, 2010 1:50:15 PM

---

yes.

On Mon, Mar 1, 2010 at 1:45 PM, Higgins, Rosemary (NIH/NICHD) [E]  
<[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)> wrote:

SO is this an abstain??

---

**From:** Nancy Newman [mailto:[nxs5@case.edu](mailto:nxs5@case.edu)]  
**Sent:** Monday, March 01, 2010 1:43 PM

**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** Re: \*\*\*\*\* Important -Follow Up ON BPD and Oximeters\*\*\*\*\*

HI Rose- i do not feel this issue is for me to vote on. i read all the comments- a touch issue for sure! thanks. ....Nancy

On Mon, Mar 1, 2010 at 10:59 AM, Higgins, Rosemary (NIH/NICHD) [E]  
<[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)> wrote:

To the SUPPORT Subcommittee

Given the email exchange, the subcommittee will need to ascertain whether or not to indicate in the SUPPORT papers whether or not a bias could have existed in reporting the secondary outcome of BPD based on oximeter. Previously the subcommittee had reviewed the oximeter use on a conference call and decided to defer this to a secondary paper. There has been discussion on the SC call and via email subsequently.

**Therefore, please send me a yes/no vote to include this in the paper by March 2.**

Thanks

Rose

---

**From:** Tyson, Jon E [mailto:Jon.E.Tyson@uth.tmc.edu]  
**Sent:** Friday, February 26, 2010 6:28 PM  
**To:** Wallace, Dennis; Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; Stevenson David (E-mail); Finer, Neil; Rich, Wade; Gantz, Marie  
**Cc:** Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: Follow Up ON BPD and Oximeters

I don't understand your statement "Controlling for center adjusts for differences between centers including differences in the BPD oximeter used." To simplify the discussion, suppose every center always used the study oximeter in designating who had BPD by oxygen saturation. Because the true saturation that would prompt oxygen administration would differ in the two treatment groups, there would be systematic bias toward administering oxygen to more infants in the high sat group than in the low sat group. This is inherent in the study design. Whatever differences there were between centers, this bias would occur in every center and would not be eliminated by controlling for center. And if I understand the analysis, there would be no interaction between treatment oximeter and BPD oximeter because they would be the same in every baby in every center.

You indicate that 5 centers used the study oximeter in almost every baby. In saying "it's not possible to tease out the effect of the BPD oximeter from other between-center differences" (a statement that I certainly accept), aren't you saying that the effect of the study oximeter on the difference in the incidence of BPD by oxygen administration between high and low sat groups (i.e., the bias) can not be distinguished from the effect of the myriad of other factors in those centers that might affect that difference in incidence? If so, why would you expect to be able to discern that bias (the signal) from all the noise resulting from other factors? I understand from what you said that the same approach was used in virtually all infants in each center which makes the effective n to be based on the number of centers rather than the number of babies. As I understand the analysis, the power to assess an interaction would then be quite low.

The issue here is whether is simply whether to report somewhere in the paper (which could be noted under the table and wouldn't increase the word count for the text) a bias in evaluating a secondary outcome. This can be done with no delay in submitting the manuscript or waiting for Maria to return. *If we had other real or potential sources of bias—say, a breaking of the blind for some infants, open label administration of a study drug to the control group, or differential loss to follow-up, we would certainly report it as a matter of course, whether or not there was a significant or near significant difference in the outcome and without testing and whether or not we assessed or found any interaction or other statistical evidence that this potential source of bias affected the results!*

Jon E. Tyson, MD, MPH

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Houston, TX 77030

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---

**From:** Wallace, Dennis [mailto:[dwallace@rti.org](mailto:dwallace@rti.org)]

**Sent:** Friday, February 26, 2010 1:56 PM

**To:** Wallace, Dennis; Tyson, Jon E; Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara; [alaptook@WIHRI.org](mailto:alaptook@WIHRI.org); Bell, Edward; [bpointex@iupui.edu](mailto:bpointex@iupui.edu); Das, Abhik; [goldb008@mc.duke.edu](mailto:goldb008@mc.duke.edu); [ifrantz@tuftsmedicalcenter.org](mailto:ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; [kurt.schibler@cchmc.org](mailto:kurt.schibler@cchmc.org); [kwatterberg@salud.unm.edu](mailto:kwatterberg@salud.unm.edu); [matthew.bizzarro@yale.edu](mailto:matthew.bizzarro@yale.edu); [mcw3@cwru.edu](mailto:mcw3@cwru.edu); [mcaplan@northshore.org](mailto:mcaplan@northshore.org); Pablo.Sanchez@UTSouthwestern.edu; [richard.ehrenkranz@yale.edu](mailto:richard.ehrenkranz@yale.edu); [Roger.Faix@hsc.utah.edu](mailto:Roger.Faix@hsc.utah.edu); [sshankar@med.wayne.edu](mailto:sshankar@med.wayne.edu); [vanmeurs@leland.stanford.edu](mailto:vanmeurs@leland.stanford.edu); Wally Carlo, M.D.; [cotte010@mc.duke.edu](mailto:cotte010@mc.duke.edu); Bradley Yoder; [rohls@salud.unm.edu](mailto:rohls@salud.unm.edu); [Luc.Brion@utsouthwestern.edu](mailto:Luc.Brion@utsouthwestern.edu); Stevenson David (E-mail); Finer, Neil; Rich, Wade; Gantz, Marie

**Cc:** Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]

**Subject:** RE: Follow Up ON BPD and Oximeters

Hello all,

I accidentally hit the send button before finishing editing this response so ignore the earlier e-mail and see the response below.

Dennis

Dennis Wallace

Senior Research Statistician

Cox 241

RTI International

3040 Cornwallis Rd

Research Triangle Park, NC 27709-2104

Voice: 919-541-6271

Fax: 919-541-6416

---

**From:** Wallace, Dennis  
**Sent:** Friday, February 26, 2010 2:53 PM  
**To:** 'Tyson, Jon E'; Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; [bpoindex@iupui.edu](mailto:bpoindex@iupui.edu); Das, Abhik; [goldb008@mc.duke.edu](mailto:goldb008@mc.duke.edu); [ifrantz@tuftsmedicalcenter.org](mailto:ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; [kurt.schibler@cchmc.org](mailto:kurt.schibler@cchmc.org); [kwatterberg@salud.unm.edu](mailto:kwatterberg@salud.unm.edu); [matthew.bizzarro@yale.edu](mailto:matthew.bizzarro@yale.edu); [mcw3@cwru.edu](mailto:mcw3@cwru.edu); [mcaplan@northshore.org](mailto:mcaplan@northshore.org); Pablo.Sanchez@UTSouthwestern.edu; [richard.ehrenkranz@yale.edu](mailto:richard.ehrenkranz@yale.edu); [Roger.Faix@hsc.utah.edu](mailto:Roger.Faix@hsc.utah.edu); [sshankar@med.wayne.edu](mailto:sshankar@med.wayne.edu); [vanmeurs@leland.stanford.edu](mailto:vanmeurs@leland.stanford.edu); Wally Carlo, M.D.; [cotte010@mc.duke.edu](mailto:cotte010@mc.duke.edu); Bradley Yoder; [rohls@salud.unm.edu](mailto:rohls@salud.unm.edu); [Luc.Brion@utsouthwestern.edu](mailto:Luc.Brion@utsouthwestern.edu); 'Stevenson David (E-mail)'; 'Finer, Neil'; Rich, Wade; Gantz, Marie  
**Cc:** Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: Follow Up ON BPD and Oximeters

Jon,

Marie flew out on a long-scheduled vacation after completing these analyses late Tuesday evening and has very limited e-mail and cell phone access. However, she has taken time to provide a preliminary response that I've outlined below with some added thoughts of my own in red font below. Based on these responses, I do believe that the critical concerns about bias have been addressed sufficiently for this initial manuscript, but if you think we need to have a more full discussion, we can talk after Marie returns next week. Because the programming for these outcome measures is relatively complicated, I'm hesitant to try to do any additional analyses prior to her return. However, as I indicated above, I don't think that we need to delay any submissions while trying to iron on the small details.

Dennis Wallace

Senior Research Statistician

Cox 241

RTI International

3040 Cornwallis Rd

Research Triangle Park, NC 27709-2104

Voice: 919-541-6271

Fax: 919-541-6416

-----Original Message-----

From: Tyson, Jon E [<mailto:Jon.E.Tyson@uth.tmc.edu>]  
Sent: Thursday, February 25, 2010 12:45 AM  
To: Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; [bpoindex@iupui.edu](mailto:bpoindex@iupui.edu); Das, Abhik; [goldb008@mc.duke.edu](mailto:goldb008@mc.duke.edu); [ifrantz@tuftsmedicalcenter.org](mailto:ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; [kurt.schibler@cchmc.org](mailto:kurt.schibler@cchmc.org); [kwatterberg@salud.unm.edu](mailto:kwatterberg@salud.unm.edu); [matthew.bizzarro@yale.edu](mailto:matthew.bizzarro@yale.edu); [mcw3@cwru.edu](mailto:mcw3@cwru.edu); [mcaplan@northshore.org](mailto:mcaplan@northshore.org);

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Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu;  
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cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu;  
Luc.Brion@utsouthwestern.edu; 'Stevenson David (E-mail)'; 'Finer, Neil';  
Rich, Wade; Gantz, Marie  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman,  
Jamie; Archer, Stephanie (NIH/NICHD) [E]  
Subject: RE: Follow Up ON BPD and Oximeters

Rose, before we can understand and interpret this information noted in the mail, we really need to know more about what was done and answers to questions like those below:

1. Which trial result was addressed - whether the evaluation of BPD was biased in the analyses of CPAP/limited ventilation vs. surfactant/conventional ventilation arm (not the analysis for which there is concern) or the analyses of the high vs. low oxygen saturation goal.

Although models were run for the different arms of the factorial design, the trial result that was addressed in the earlier e-mail was the impact of different oximeters on the comparison of the effects high vs. low oxygen saturation targets on BPD and BPD/death outcomes, which we believe is the question of interest.

2. Do we have reliable data to know whether individual infants were monitored on the study oximeter or on the clinical oximeter on the day the infant was 36 weeks and 0 and whether the oximeter was changed part way through that 24 hour period? What was done if the infant was switched on that day. As I understand it, the diagnosis of BPD was based on the entire 24 hours the day the infant was 36 weeks 0 days. Though the results of the survey weren't distributed, my impression from responses to my earlier e-mails was that even the procedure usually followed in individual centers was not necessarily clear.

We can determine from form PHY02 what oximeter was used to determine the physiologic definition of BPD, but we do not have the detailed level of information that you described. However, based on the survey results, we do know that only 5 sites used the study oximeter for an oxygen-based definition, and only 3 used the study oximeter for challenge.

3. What variables in the model when the BPD oximeter was added? What variables were in the model when a BPD oximeter x study treatment group was added?

Variables in the model were treatment oximeter (low vs. high), center, GA group. Familial clustering was adjusted for as a random effect. I added BPD oximeter and also looked at the interaction between BPD oximeter and

treatment oximeter. These factors were identical to the factors used in the models for which secondary outcomes were reported in the manuscript.

4. Do I understand Maria and you to conclude that because centers tended to be consistent in their oximeter use, controlling for center would prevent a biased assessment of the effect on BPD by oxygen administration?

This comment makes me wonder if the analysis was done for the wrong comparison. This conclusion would be correct for analyses of the effect of CPAP/limited ventilation vs. surfactant/ conventional ventilation on BPD by oxygen delivery (because each treatment arm would contain equal numbers of infants in the high and low sat groups). However, this isn't the comparison in question. This conclusion would certainly not be correct in analyzing the effect of high vs low sat goals on BPD. In this analysis, centers that used the study oximeter would be systematically more likely to administer oxygen to the high sat group than to the low sat group. The problem wouldn't go away by controlling for center, and the more centers that used the study oximeter, the more biased the result would be. How many centers were there that used the study oximeter?

Controlling for center adjusts for differences between centers including differences in the BPD oximeter used. Thus, adding a covariate for BPD oximeter does not change the estimates for the treatment oximeter effect. We are not arguing that the BPD oximeter used did not have an impact. We did find that BPD oximeter was significant in the models, as was center. However, since center and BPD oximeter are strongly confounded (in fact we have almost complete aliasing of center and clinical/study oximeter), it's not possible to tease out the effect of the BPD oximeter from other between-center differences. In addition, the interaction between BPD oximeter and treatment oximeter was not significant. This indicates that the impact of treatment oximeter on the BPD outcomes was not significantly different in the centers that used the study oximeters to determine BPD and those that used the clinical oximeters.

5. What is the basis for believing that there would be anything near reasonable power to assess a oximeter x treatment group interaction?

Clearly, these analyses were conducted from a post-hoc perspective, and the study was never designed to have the power to determine that the interaction in our data set is statistically significant for a pre-specified interaction effect size. But, that is not a shortcoming unless the magnitude of the interaction effect is such that it represents an important scientific bias in study interpretation. Our preliminary analyses indicate that biases of such magnitude are not present in this data set. We can do more detailed analyses of the level of bias that might have been introduced after Marie returns from vacation, but nothing in the analyses conducted to date suggest that those magnitudes warrant delay of submission of this manuscript.

I know that everyone is anxious to get this paper submitted. While I have an external advisory committee tomorrow, I will try to respond tomorrow night if the information requested above is sent tomorrow during the day.

---

From: Higgins, Rosemary (NIH/NICHD) [E] [[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)]

Sent: Wednesday, February 24, 2010 7:53 AM

To: Tyson, Jon E; 'Cunningham, Meg'; [SCRN] Stoll, Barbara; [alaptook@WIHRI.org](mailto:alaptook@WIHRI.org); Bell, Edward; [bpoindex@iupui.edu](mailto:bpoindex@iupui.edu); Das, Abhik; [goldb008@mc.duke.edu](mailto:goldb008@mc.duke.edu); [ifrantz@tuftsmedicalcenter.org](mailto:ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; [kurt.schibler@cchmc.org](mailto:kurt.schibler@cchmc.org); [kwatterberg@salud.unm.edu](mailto:kwatterberg@salud.unm.edu); [matthew.bizzarro@yale.edu](mailto:matthew.bizzarro@yale.edu); [mcw3@cwru.edu](mailto:mcw3@cwru.edu); [mcaplan@northshore.org](mailto:mcaplan@northshore.org); Pablo.Sanchez@UTSouthwestern.edu; [richard.ehrenkranz@yale.edu](mailto:richard.ehrenkranz@yale.edu); [Roger.Faix@hsc.utah.edu](mailto:Roger.Faix@hsc.utah.edu); [sshankar@med.wayne.edu](mailto:sshankar@med.wayne.edu); [vanmeurs@leland.stanford.edu](mailto:vanmeurs@leland.stanford.edu); Wally Carlo, M.D.; Wallace, Dennis; [cotte010@mc.duke.edu](mailto:cotte010@mc.duke.edu); Bradley Yoder; [rohls@salud.unm.edu](mailto:rohls@salud.unm.edu); [Luc.Brion@utsouthwestern.edu](mailto:Luc.Brion@utsouthwestern.edu); 'Stevenson David (E-mail)'; 'Finer, Neil'; Rich, Wade; Gantz, Marie

Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]

Subject: Follow Up ON BPD and Oximeters

Hi all -

In Follow up to yesterday's discussion, Marie spent a great deal of time last evening running additional analyses to address (and now alleviate) Jon's concern as described:

We have looked into the question of whether the oximeter used to determine BPD impacted the BPD and death/BPD outcomes by adding a covariate for the BPD oximeter (study or clinical) to the statistical models. We found that the effect of the BPD oximeter was significant; however, the interaction between BPD oximeter and treatment oximeter (low or high SpO2 target range) was not significant in any model, indicating that, if there was a BPD oximeter effect, it was not different in the two treatment groups. In addition, it should be noted that BPD oximeter is confounded with center (centers tended to be consistent in their use of the study or clinical oximeters to determine BPD). Therefore, by including center in the original models, we have already accounted for the effect of the BPD oximeter the center chose to use. Finally, because center and BPD oximeter are confounded, we cannot know whether the significant BPD oximeter effect is due to the BPD oximeters themselves or other characteristics that differ between centers.

---

From: Tyson, Jon E [<mailto:Jon.E.Tyson@uth.tmc.edu>]

Sent: Tuesday, February 23, 2010 4:33 PM



To: Higgins, Rosemary (NIH/NICHD) [E]; 'Cunningham, Meg'; [SCRN] Stoll, Barbara; [alaptook@WIHRI.org](mailto:alaptook@WIHRI.org); Bell, Edward; [bpoindex@iupui.edu](mailto:bpoindex@iupui.edu); Das, Abhik; [goldb008@mc.duke.edu](mailto:goldb008@mc.duke.edu); [ifrantz@tuftsmedicalcenter.org](mailto:ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; [kurt.schibler@cchmc.org](mailto:kurt.schibler@cchmc.org); [kwatterberg@salud.unm.edu](mailto:kwatterberg@salud.unm.edu); [matthew.bizzarro@yale.edu](mailto:matthew.bizzarro@yale.edu); [mcw3@cwru.edu](mailto:mcw3@cwru.edu); [mcaplan@northshore.org](mailto:mcaplan@northshore.org); Pablo.Sanchez@UTSouthwestern.edu; [richard.ehrenkranz@yale.edu](mailto:richard.ehrenkranz@yale.edu); [Roger.Faix@hsc.utah.edu](mailto:Roger.Faix@hsc.utah.edu); [sshankar@med.wayne.edu](mailto:sshankar@med.wayne.edu); [vanmeurs@leland.stanford.edu](mailto:vanmeurs@leland.stanford.edu); Wally Carlo, M.D.; Wallace, Dennis; [cotte010@mc.duke.edu](mailto:cotte010@mc.duke.edu); Bradley Yoder; [rohls@salud.unm.edu](mailto:rohls@salud.unm.edu); [Luc.Brion@utsouthwestern.edu](mailto:Luc.Brion@utsouthwestern.edu); [bbatton@siumed.edu](mailto:bbatton@siumed.edu)

Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; [lmoore@med.wayne.edu](mailto:lmoore@med.wayne.edu); [pamela.neville@duke.edu](mailto:pamela.neville@duke.edu); [gonza025@mc.duke.edu](mailto:gonza025@mc.duke.edu); Smith, Nancy M; Brenda Vecchio; [msummer@peds.uab.edu](mailto:msummer@peds.uab.edu); Archer, Stephanie (NIH/NICHD) [E]

Subject: RE: Steering Committee Call Tomorrow

While it may seem that I am fixated on an unimportant issue regarding a not quite significant difference, I think we undermine the credibility of Network studies if we are not completely forthright about problems in measuring what everyone would agree is an important secondary outcome. Not reporting that the assessment of BPD by oxygen administration could be biased by continued use of the study oximeters would seem to be in the category of not reporting protocol deviations and not something that is in the Network's best interest. Why not just put a footnote under the table describing the problem?

Jon E. Tyson, MD, MPH

Center for Clinical Research & Evidence-Based Medicine

UT Medical School at Houston

6431 Fannin St., MSB 2.106

Houston, TX 77030

voice 713-500-5651

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From: Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]

Sent: Tuesday, February 23, 2010 2:11 PM

To: 'Cunningham, Meg'; [SCRN] Stoll, Barbara; [alaptook@WIHRI.org](mailto:alaptook@WIHRI.org); Bell, Edward; [bpoindex@iupui.edu](mailto:bpoindex@iupui.edu); Das, Abhik; [goldb008@mc.duke.edu](mailto:goldb008@mc.duke.edu); [ifrantz@tuftsmedicalcenter.org](mailto:ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; [kurt.schibler@cchmc.org](mailto:kurt.schibler@cchmc.org); [kwatterberg@salud.unm.edu](mailto:kwatterberg@salud.unm.edu); [matthew.bizzarro@yale.edu](mailto:matthew.bizzarro@yale.edu); [mcw3@cwru.edu](mailto:mcw3@cwru.edu); [mcaplan@northshore.org](mailto:mcaplan@northshore.org); Pablo.Sanchez@UTSouthwestern.edu; [richard.ehrenkranz@yale.edu](mailto:richard.ehrenkranz@yale.edu); [Roger.Faix@hsc.utah.edu](mailto:Roger.Faix@hsc.utah.edu); [sshankar@med.wayne.edu](mailto:sshankar@med.wayne.edu); [vanmeurs@leland.stanford.edu](mailto:vanmeurs@leland.stanford.edu); Wally Carlo, M.D.; Wallace, Dennis; [cotte010@mc.duke.edu](mailto:cotte010@mc.duke.edu); Tyson, Jon E; Bradley Yoder; [rohls@salud.unm.edu](mailto:rohls@salud.unm.edu); [Luc.Brion@utsouthwestern.edu](mailto:Luc.Brion@utsouthwestern.edu); [bbatton@siumed.edu](mailto:bbatton@siumed.edu)

Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; [lmoore@med.wayne.edu](mailto:lmoore@med.wayne.edu); [pamela.neville@duke.edu](mailto:pamela.neville@duke.edu); [gonza025@mc.duke.edu](mailto:gonza025@mc.duke.edu);

Smith, Nancy M; Brenda Vecchio; [msumner@peds.uab.edu](mailto:msumner@peds.uab.edu); Archer, Stephanie (NIH/NICHD) [E]

Subject: RE: Steering Committee Call Tomorrow

If you joined the call already in progress, please send us an email so we can count your attendance.

Rose

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From: Cunningham, Meg [mailto:[mcunningham@rti.org](mailto:mcunningham@rti.org)]

Sent: Monday, February 22, 2010 9:59 AM

To: [SCRN] Stoll, Barbara; [alaptook@WIHRI.org](mailto:alaptook@WIHRI.org); Bell, Edward; [bpoindex@iupui.edu](mailto:bpoindex@iupui.edu); Das, Abhik; [goldb008@mc.duke.edu](mailto:goldb008@mc.duke.edu); Higgins, Rosemary (NIH/NICHD) [E]; [ifrantz@tuftsmedicalcenter.org](mailto:ifrantz@tuftsmedicalcenter.org); [Kathleen.A.Kennedy@uth.tmc.edu](mailto:Kathleen.A.Kennedy@uth.tmc.edu); [kurt.schibler@cchmc.org](mailto:kurt.schibler@cchmc.org); [kwatterberg@salud.unm.edu](mailto:kwatterberg@salud.unm.edu); [matthew.bizzarro@yale.edu](mailto:matthew.bizzarro@yale.edu); [mcw3@cwru.edu](mailto:mcw3@cwru.edu); [mcaplan@northshore.org](mailto:mcaplan@northshore.org); Pablo.Sanchez@UTSouthwestern.edu; [richard.ehrenkranz@yale.edu](mailto:richard.ehrenkranz@yale.edu); [Roger.Faix@hsc.utah.edu](mailto:Roger.Faix@hsc.utah.edu); [sshankar@med.wayne.edu](mailto:sshankar@med.wayne.edu); [vanmeurs@leland.stanford.edu](mailto:vanmeurs@leland.stanford.edu); Wally Carlo, M.D.; Wallace, Dennis; [cotte010@mc.duke.edu](mailto:cotte010@mc.duke.edu); [jon.e.tyson@uth.tmc.edu](mailto:jon.e.tyson@uth.tmc.edu); Bradley Yoder; [rohls@salud.unm.edu](mailto:rohls@salud.unm.edu); [Luc.Brion@utsouthwestern.edu](mailto:Luc.Brion@utsouthwestern.edu); [bbatton@siumed.edu](mailto:bbatton@siumed.edu)

Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; [lmoore@med.wayne.edu](mailto:lmoore@med.wayne.edu); [pamela.neville@duke.edu](mailto:pamela.neville@duke.edu); [gonza025@mc.duke.edu](mailto:gonza025@mc.duke.edu); [Nancy.M.Smith@uth.tmc.edu](mailto:Nancy.M.Smith@uth.tmc.edu); Brenda Vecchio; [msumner@peds.uab.edu](mailto:msumner@peds.uab.edu); Archer, Stephanie (NIH/NICHD) [E]

Subject: Steering Committee Call Tomorrow

Dear All -

The next standing Steering Committee call is scheduled for tomorrow, Tuesday, February 23rd at 3:00pm ET.

Please Dial:

Outside the USA 1-203-310-(b) (6)

or Within the USA 866-675-(b) (6)

Then, enter Participant Passcode: [REDACTED] ( )

Steering Committee Conference Call Agenda 02/23/2010

1. Early BP discussion (attached are a brief description of the time limited data collection proposal and a draft of the form which would be used.)
2. SUPPORT manuscript discussion and update
3. New Business

Thanks,

Meg

Meg Cunningham

RTI International

701 13th St. NW, Ste. 750

Washington, DC 20005

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fax: 202-728-2095

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**Blansfield, Earl (NIH/NICHD) [E]**

---

**From:** onbehalfof+editorial+nejm.org@manuscriptcentral.com on behalf of editorial@nejm.org  
**Sent:** Monday, March 01, 2010 12:32 PM  
**To:** nfiner@ucsd.edu; wcarlo@peds.uab.edu; michele.walsh@cwru.edu; wrich@ucsd.edu; mgantz@rti.org; alaptook@wihri.org; Bradley.yoder@hsc.utah.edu; roger.faix@has.utah.edu; adas@rti.org; poo@rti.org; nambalavanan@peds.uab.edu; (b) (6); edward.donovan@cchmc.org; vivek.narendran@cchmc.org; nxs5@cwru.edu; ifrantz@tuftsmedicalcenter.org; Pablo.Sanchez@UTSouthwestern.edu; susie.buchter@oz.ped.emory.edu; (b) (6); nirupama\_laroia@urmc.rochester.edu; bpoindex@iupui.edu; cotte010@mc.duke.edu; vanmeurs@leland.stanford.edu; bsood@med.wayne.edu; sduara@med.miami.edu; moshea@wfubmc.edu; edward.bell@uiowa.edu; vineet.bhandari@yale.edu; kwatterberg@salud.unm.edu; Higgins, Rosemary (NIH/NICHD) [E]; (b) (6)  
**Subject:** New England Journal of Medicine - 09-11783.R3

Dear Dr. Finer and co-authors,

Thank you for submitting your revision, of "Early CPAP versus Surfactant in Extremely Preterm Infants: The SUPPORT Trial" to the New England Journal of Medicine.

Your submission will be forwarded to the editor, and may be sent out for review as necessary.

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

New England Journal of Medicine  
10 Shattuck Street  
Boston, MA 02115  
(617) 734-9800  
Fax: (617) 739-9864  
<http://www.nejm.org>

**From:** Archer, Stephanie (NIH/NICHD) [E]  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** FW: \*\*\*\*\* Important -Follow Up ON BPD and Oximeters\*\*\*\*\*  
**Date:** Monday, March 01, 2010 12:02:36 PM

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Do Roger and Brad get separate votes, or only one for Utah?

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**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Monday, March 01, 2010 11:51 AM  
**To:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** FW: \*\*\*\*\* Important -Follow Up ON BPD and Oximeters\*\*\*\*\*

---

**From:** Roger Faix [mailto:Roger.Faix@hsc.utah.edu]  
**Sent:** Monday, March 01, 2010 11:50 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: \*\*\*\*\* Important -Follow Up ON BPD and Oximeters\*\*\*\*\*

Having read all of the comments and given our current inability to quantitate the impact of the non-standardized use of oximeters to determine the presence/absence of BPD, I believe we should include a statement acknowledging the potential for bias.

This can be clarified/modified in later manuscripts if quantitation of the impact or non-impact of this non-standardized oximeter use becomes possible.

Roger

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**From:** Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]  
**Sent:** Monday, March 01, 2010 8:59 AM  
**To:** 'Wally Carlo, M.D.'; 'Finer, Neil'; alaptook@WIHRI.org; Roger Faix; Bradley Yoder; kurt.schibler@cchmc.org; adas@rti.org; nancy.newman; Rich, Wade; Gantz, Marie; mcw3@case.edu; Dennis Wallace  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin  
**Subject:** \*\*\*\*\* Important -Follow Up ON BPD and Oximeters\*\*\*\*\*

To the SUPPORT Subcommittee

Given the email exchange, the subcommittee will need to ascertain whether or not to indicate in the SUPPORT papers whether or not a bias could have existed in reporting the secondary outcome of BPD based on oximeter. Previously the subcommittee had reviewed the oximeter use on a conference call and decided to defer this to a secondary paper. There has been discussion on the SC call and via email subsequently.

**Therefore, please send me a yes/no vote to include this in the paper by March 2.**

Thanks  
Rose

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**From:** Tyson, Jon E [mailto:Jon.E.Tyson@uth.tmc.edu]  
**Sent:** Friday, February 26, 2010 6:28 PM  
**To:** Wallace, Dennis; Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; Stevenson David (E-mail); Finer, Neil; Rich, Wade; Gantz, Marie  
**Cc:** Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: Follow Up ON BPD and Oximeters

I don't understand your statement "Controlling for center adjusts for differences between centers including differences in the BPD oximeter used." To simplify the discussion, suppose every center always used the study oximeter in designating who had BPD by oxygen saturation. Because the true saturation that would prompt oxygen administration would differ in the two treatment groups, there would be systematic bias toward administering oxygen to more infants in the high sat group than in the low sat group. This is inherent in the study design. Whatever differences there were between centers, this bias would occur in every center and would not be eliminated by controlling for center. And if I understand the analysis, there would be no interaction between treatment oximeter and BPD oximeter because they would be the same in every baby in every center.

You indicate that 5 centers used the study oximeter in almost every baby. In saying "it's not possible to tease out the effect of the BPD oximeter from other between-center differences" (a statement that I certainly accept), aren't you saying that the effect of the study oximeter on the difference in the incidence of BPD by oxygen administration between high and low sat groups (i.e., the bias) can not be distinguished from the effect of the myriad of other factors in those centers that might affect that difference in incidence? If so, why would you expect to be able to discern that bias (the signal) from all the noise resulting from other factors? I understand from what you said that the same approach was used in virtually all infants in each center which makes the effective n to be based on the number of centers rather than the number of babies. As I understand the analysis, the power to assess an interaction would then be quite low.

The issue here is whether is simply whether to report somewhere in the paper (which could be noted under the table and wouldn't increase the word count for the text) a bias in evaluating a secondary outcome. This can be done with no delay in submitting the manuscript or waiting for Maria to return. *If we had other real or potential sources of bias—say, a breaking of the blind for some infants, open label administration of a study drug to the control group, or differential loss to follow-up, we would certainly report it as a matter of course, whether or not there was a significant or near significant difference in the outcome and without testing and whether or not we assessed or found any interaction or other statistical evidence that this potential source of bias affected the results!*

Jon E. Tyson, MD, MPH  
Center for Clinical Research & Evidence-Based Medicine  
UT Medical School at Houston  
6431 Fannin St., MSB 2.106  
Houston, TX 77030  
voice 713-500-5651  
fax 713-500-0519

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**From:** Wallace, Dennis [mailto:dwallace@rti.org]  
**Sent:** Friday, February 26, 2010 1:56 PM

**To:** Wallace, Dennis; Tyson, Jon E; Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; Stevenson David (E-mail); Finer, Neil; Rich, Wade; Gantz, Marie  
**Cc:** Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: Follow Up ON BPD and Oximeters

Hello all,

I accidentally hit the send button before finishing editing this response so ignore the earlier e-mail and see the response below.  
Dennis

Dennis Wallace  
Senior Research Statistician  
Cox 241  
RTI International  
3040 Cornwallis Rd  
Research Triangle Park, NC 27709-2104  
Voice: 919-541-6271  
Fax: 919-541-6416

---

**From:** Wallace, Dennis  
**Sent:** Friday, February 26, 2010 2:53 PM  
**To:** 'Tyson, Jon E'; Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; 'Stevenson David (E-mail)'; 'Finer, Neil'; Rich, Wade; Gantz, Marie  
**Cc:** Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: Follow Up ON BPD and Oximeters

Jon,

Marie flew out on a long-scheduled vacation after completing these analyses late Tuesday evening and has very limited e-mail and cell phone access. However, she has taken time to provide a preliminary response that I've outlined below with some added thoughts of my own in red font below. Based on these responses, I do believe that the critical concerns about bias have been addressed sufficiently for this initial manuscript, but if you think we need to have a more full discussion, we can talk after Marie returns next week. Because the programming for these outcome measures is relatively complicated, I'm hesitant to try to do any additional analyses prior to her return. However, as I indicated above, I don't think that we need to delay any submissions while trying to iron on the small details.

Dennis Wallace  
Senior Research Statistician  
Cox 241  
RTI International  
3040 Cornwallis Rd  
Research Triangle Park, NC 27709-2104  
Voice: 919-541-6271  
Fax: 919-541-6416

-----Original Message-----

From: Tyson, Jon E [mailto:Jon.E.Tyson@uth.tmc.edu]  
Sent: Thursday, February 25, 2010 12:45 AM  
To: Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; Wallace, Dennis; cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; 'Stevenson David (E-mail)'; 'Finer, Neil'; Rich, Wade; Gantz, Marie  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]  
Subject: RE: Follow Up ON BPD and Oximeters

Rose, before we can understand and interpret this information noted in the mail, we really need to know more about what was done and answers to questions like those below:

1. Which trial result was addressed - whether the evaluation of BPD was biased in the analyses of CPAP/limited ventilation vs. surfactant/conventional ventilation arm (not the analysis for which there is concern) or the analyses of the high vs. low oxygen saturation goal.

Although models were run for the different arms of the factorial design, the trial result that was addressed in the earlier e-mail was the impact of different oximeters on the comparison of the effects high vs. low oxygen saturation targets on BPD and BPD/death outcomes, which we believe is the question of interest.

2. Do we have reliable data to know whether individual infants were monitored on the study oximeter or on the clinical oximeter on the day the infant was 36 weeks and 0 and whether the oximeter was changed part way through that 24 hour period? What was done if the infant was switched on that day. As I understand it, the diagnosis of BPD was based on the entire 24 hours the day the infant was 36 weeks 0 days. Though the results of the survey weren't distributed, my impression from responses to my earlier e mails was that even the procedure usually followed in individual centers was not necessarily clear.

We can determine from form PHY02 what oximeter was used to determine the physiologic definition of BPD, but we do not have the detailed level of information that you described. However, based on the survey results, we do know that only 5 sites used the study oximeter for an oxygen-based definition, and only 3 used the study oximeter for challenge.

3. What variables in the model when the BPD oximeter was added? What variables were in the model when a BPD oximeter x study treatment group was added?

Variables in the model were treatment oximeter (low vs. high), center, GA group. Familial clustering was adjusted for as a random effect. I added BPD oximeter and also looked at the interaction between BPD oximeter and treatment oximeter. These factors were identical to the factors used in the models for which secondary outcomes were reported in the manuscript.

4. Do I understand Maria and you to conclude that because centers tended to be consistent in their oximeter use, controlling for center would prevent a biased assessment of the effect on BPD by oxygen administration?

This comment makes me wonder if the analysis was done for the wrong comparison. This conclusion would be correct for analyses of the effect of CPAP/limited ventilation vs. surfactant/conventional ventilation on BPD by oxygen delivery (because each treatment arm would contain equal numbers of infants in the high and low sat groups). However, this isn't the comparison in question. This conclusion would certainly not be correct in analyzing the



effect of high vs low sat goals on BPD. In this analysis, centers that used the study oximeter would be systematically more likely to administer oxygen to the high sat group than to the low sat group. The problem wouldn't go away by controlling for center, and the more centers that used the study oximeter, the more biased the result would be. How many centers were there that used the study oximeter?

Controlling for center adjusts for differences between centers including differences in the BPD oximeter used. Thus, adding a covariate for BPD oximeter does not change the estimates for the treatment oximeter effect. We are not arguing that the BPD oximeter used did not have an impact. We did find that BPD oximeter was significant in the models, as was center. However, since center and BPD oximeter are strongly confounded (in fact we have almost complete aliasing of center and clinical/study oximeter), it's not possible to tease out the effect of the BPD oximeter from other between-center differences. In addition, the interaction between BPD oximeter and treatment oximeter was not significant. This indicates that the impact of treatment oximeter on the BPD outcomes was not significantly different in the centers that used the study oximeters to determine BPD and those that used the clinical oximeters.

5. What is the basis for believing that there would be anything near reasonable power to assess a oximeter x treatment group interaction?

Clearly, these analyses were conducted from a post-hoc perspective, and the study was never designed to have the power to determine that the interaction in our data set is statistically significant for a pre-specified interaction effect size. But, that is not a shortcoming unless the magnitude of the interaction effect is such that it represents an important scientific bias in study interpretation. Our preliminary analyses indicate that biases of such magnitude are not present in this data set. We can do more detailed analyses of the level of bias that might have been introduced after Marie returns from vacation, but nothing in the analyses conducted to date suggest that those magnitudes warrant delay of submission of this manuscript.

I know that everyone is anxious to get this paper submitted. While I have an external advisory committee tomorrow, I will try to respond tomorrow night if the information requested above is sent tomorrow during the day.

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From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]  
Sent: Wednesday, February 24, 2010 7:53 AM  
To: Tyson, Jon E; 'Cunningham, Meg'; [SCRN] Stoll, Barbara;  
alaptok@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik;  
goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A;  
kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu;  
matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org;  
Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu;  
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vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; Wallace, Dennis;  
cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu;  
Luc.Brion@utsouthwestern.edu; 'Stevenson David (E-mail)'; 'Finer, Neil';  
Rich, Wade; Gantz, Marie  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman,  
Jamie; Archer, Stephanie (NIH/NICHD) [E]  
Subject: Follow Up ON BPD and Oximeters

Hi all -

In Follow up to yesterday's discussion, Marie spent a great deal of time last evening running additional analyses to address (and now alleviate) Jon's concern as described:

We have looked into the question of whether the oximeter used to determine BPD impacted the BPD and death/BPD outcomes by adding a covariate for the BPD oximeter (study or clinical) to the statistical models. We found that the effect of the BPD oximeter was significant; however, the interaction between BPD oximeter and treatment oximeter (low or high SpO2 target range) was not significant in any model, indicating that, if there was a BPD oximeter effect, it was not different in the two treatment groups. In addition, it should be noted that BPD oximeter is confounded with center (centers tended to be consistent in their use of the study or clinical oximeters to determine BPD). Therefore, by including center in the original models, we have already accounted for the effect of the BPD oximeter the

center chose to use. Finally, because center and BPD oximeter are confounded, we cannot know whether the significant BPD oximeter effect is due to the BPD oximeters themselves or other characteristics that differ between centers.

---

From: Tyson, Jon E [mailto:Jon.E.Tyson@uth.tmc.edu]  
Sent: Tuesday, February 23, 2010 4:33 PM  
To: Higgins, Rosemary (NIH/NICHD) [E]; 'Cunningham, Meg'; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; Wallace, Dennis; cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; bbatton@siumed.edu  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; lmoore@med.wayne.edu; pamela.neville@duke.edu; gonza025@mc.duke.edu; Smith, Nancy M; Brenda Vecchio; msumner@peds.uab.edu; Archer, Stephanie (NIH/NICHD) [E]  
Subject: RE: Steering Committee Call Tomorrow

While it may seem that I am fixated on an unimportant issue regarding a not quite significant difference, I think we undermine the credibility of Network studies if we are not completely forthright about problems in measuring what everyone would agree is an important secondary outcome. Not reporting that the assessment of BPD by oxygen administration could be biased by continued use of the study oximeters would seem to be in the category of not reporting protocol deviations and not something that is in the Network's best interest. Why not just put a footnote under the table describing the problem?

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Center for Clinical Research & Evidence-Based Medicine  
UT Medical School at Houston  
6431 Fannin St., MSB 2.106  
Houston, TX 77030  
voice 713-500-5651  
fax 713-500-0519

---

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
Sent: Tuesday, February 23, 2010 2:11 PM  
To: 'Cunningham, Meg'; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; Wallace, Dennis; cotte010@mc.duke.edu; Tyson, Jon E; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; bbatton@siumed.edu  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; lmoore@med.wayne.edu; pamela.neville@duke.edu; gonza025@mc.duke.edu; Smith, Nancy M; Brenda Vecchio; msumner@peds.uab.edu; Archer, Stephanie (NIH/NICHD) [E]  
Subject: RE: Steering Committee Call Tomorrow

If you joined the call already in progress, please send us an email so we can count your attendance.

Rose

---

From: Cunningham, Meg [mailto:mcunningham@rti.org]  
Sent: Monday, February 22, 2010 9:59 AM  
To: [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; Higgins, Rosemary (NIH/NICHD) [E]; ifrantz@tuftsmedicalcenter.org; Kathleen.A.Kennedy@uth.tmc.edu; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu;

richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu;  
sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.;  
Wallace, Dennis; cotte010@mc.duke.edu; jon.e.tyson@uth.tmc.edu; Bradley  
Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; bbatton@siumed.edu  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman,  
Jamie; lmoore@med.wayne.edu; pamela.neville@duke.edu; gonza025@mc.duke.edu;  
Nancy.M.Smith@uth.tmc.edu; Brenda Vecchio; msumner@peds.uab.edu; Archer,  
Stephanie (NIH/NICHD) [E]  
Subject: Steering Committee Call Tomorrow

Dear All -

The next standing Steering Committee call is scheduled for tomorrow, Tuesday,  
February 23rd at 3:00pm ET.

Please Dial:

Outside the USA 1-203-310-(b)

or Within the USA 866-675-(b)

Then, enter Participant Passcode: (b) (6)

Steering Committee Conference Call Agenda 02/23/2010

1. Early BP discussion (attached are a brief description of the time limited data collection proposal and a draft of the form which would be used.)
2. SUPPORT manuscript discussion and update
3. New Business

Thanks,  
Meg

Meg Cunningham  
RTI International  
701 13th St. NW, Ste. 750  
Washington, DC 20005  
tel: 202-974-7837  
fax: 202-728-2095  
www.rti.org<<http://www.rti.org>>

## Higgins, Rosemary (NIH/NICHD) [E]

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**From:** Finer, Neil <nfiner@ucsd.edu>  
**Sent:** Monday, March 01, 2010 11:49 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: \*\*\*\*\* Important -Follow Up ON BPD and Oximeters\*\*\*\*\*

I vote No  
Neil

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Monday, March 01, 2010 8:00 AM  
**To:** 'Wally Carlo, M.D.'; Finer, Neil; alaptook@WIHRI.org; Roger.Faix@hsc.utah.edu; Bradley Yoder; kurt.schibler@cchmc.org; adas@rti.org; nancy newman; Rich, Wade; Gantz, Marie; mcw3@case.edu; Dennis Wallace  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin  
**Subject:** \*\*\*\*\* Important -Follow Up ON BPD and Oximeters\*\*\*\*\*  
**Importance:** High

To the SUPPORT Subcommittee

Given the email exchange, the subcommittee will need to ascertain whether or not to indicate in the SUPPORT papers whether or not a bias could have existed in reporting the secondary outcome of BPD based on oximeter. Previously the subcommittee had reviewed the oximeter use on a conference call and decided to defer this to a secondary paper. There has been discussion on the SC call and via email subsequently.

**Therefore, please send me a yes/no vote to include this in the paper by March 2.**

Thanks  
Rose

---

**From:** Tyson, Jon E [mailto:Jon.E.Tyson@uth.tmc.edu]  
**Sent:** Friday, February 26, 2010 6:28 PM  
**To:** Wallace, Dennis; Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpointex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; Stevenson David (E-mail); Finer, Neil; Rich, Wade; Gantz, Marie  
**Cc:** Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: Follow Up ON BPD and Oximeters

I don't understand your statement "Controlling for center adjusts for differences between centers including differences in the BPD oximeter used." To simplify the discussion, suppose every center always used the study oximeter in designating who had BPD by oxygen saturation. Because the true saturation that would prompt oxygen administration would differ in the two treatment groups, there would be systematic bias toward administering oxygen to more infants in the high sat group than in the low sat group. This is inherent

in the study design. Whatever differences there were between centers, this bias would occur in every center and would not be eliminated by controlling for center. And if I understand the analysis, there would be no interaction between treatment oximeter and BPD oximeter because they would be the same in every baby in every center.

You indicate that 5 centers used the study oximeter in almost every baby. In saying "it's not possible to tease out the effect of the BPD oximeter from other between-center differences" (a statement that I certainly accept), aren't you saying that the effect of the study oximeter on the difference in the incidence of BPD by oxygen administration between high and low sat groups (i.e., the bias) can not be distinguished from the effect of the myriad of other factors in those centers that might affect that difference in incidence? If so, why would you expect to be able to discern that bias (the signal) from all the noise resulting from other factors? I understand from what you said that the same approach was used in virtually all infants in each center which makes the effective n to be based on the number of centers rather than the number of babies. As I understand the analysis, the power to assess an interaction would then be quite low.

The issue here is whether is simply whether to report somewhere in the paper (which could be noted under the table and wouldn't increase the word count for the text) a bias in evaluating a secondary outcome. This can be done with no delay in submitting the manuscript or waiting for Maria to return. *If we had other real or potential sources of bias—say, a breaking of the blind for some infants, open label administration of a study drug to the control group, or differential loss to follow-up, we would certainly report it as a matter of course, whether or not there was a significant or near significant difference in the outcome and without testing and whether or not we assessed or found any interaction or other statistical evidence that this potential source of bias affected the results!*

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UT Medical School at Houston  
6431 Fannin St., MSB 2.106  
Houston, TX 77030  
voice 713-500-5651  
fax 713-500-0519

---

**From:** Wallace, Dennis [mailto:dwallace@rti.org]

**Sent:** Friday, February 26, 2010 1:56 PM

**To:** Wallace, Dennis; Tyson, Jon E; Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; Stevenson David (E-mail); Finer, Neil; Rich, Wade; Gantz, Marie

**Cc:** Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]

**Subject:** RE: Follow Up ON BPD and Oximeters

Hello all,

I accidentally hit the send button before finishing editing this response so ignore the earlier e-mail and see the response below.

Dennis

Dennis Wallace  
Senior Research Statistician  
Cox 241  
RTI International

3040 Cornwallis Rd  
Research Triangle Park, NC 27709-2104  
Voice: 919-541-6271  
Fax: 919-541-6416

---

**From:** Wallace, Dennis  
**Sent:** Friday, February 26, 2010 2:53 PM  
**To:** 'Tyson, Jon E'; Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; 'Stevenson David (E-mail)'; 'Finer, Neil'; Rich, Wade; Gantz, Marie  
**Cc:** Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: Follow Up ON BPD and Oximeters

Jon,

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Senior Research Statistician  
Cox 241  
RTI International  
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Research Triangle Park, NC 27709-2104  
Voice: 919-541-6271  
Fax: 919-541-6416

-----Original Message-----

**From:** Tyson, Jon E [mailto:Jon.E.Tyson@uth.tmc.edu]  
**Sent:** Thursday, February 25, 2010 12:45 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; Wallace, Dennis; cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; 'Stevenson David (E-mail)'; 'Finer, Neil'; Rich, Wade; Gantz, Marie  
**Cc:** Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: Follow Up ON BPD and Oximeters

Rose, before we can understand and interpret this information noted in the mail, we really need to know more about what was done and answers to questions like those below:

1. Which trial result was addressed - whether the evaluation of BPD was biased in the analyses of CPAP/limited ventilation vs. surfactant/conventional ventilation arm (not the analysis for which there is concern) or the analyses of the high vs. low oxygen saturation goal.

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2. Do we have reliable data to know whether individual infants were monitored on the study oximeter or on the clinical oximeter on the day the infant was 36 weeks and 0 and whether the oximeter was changed part way through that 24 hour period? What was done if the infant was switched on that day. As I understand it, the diagnosis of BPD was based on the entire 24 hours the day the infant was 36 weeks 0 days. Though the results of the survey weren't distributed, my impression from responses to my earlier e mails was that even the procedure usually followed in individual centers was not necessarily clear.

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3. What variables in the model when the BPD oximeter was added? What variables were in the model when a BPD oximeter x study treatment group was added?

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4. Do I understand Maria and you to conclude that because centers tended to be consistent in their oximeter use, controlling for center would prevent a biased assessment of the effect on BPD by oxygen administration?

This comment makes me wonder if the analysis was done for the wrong comparison, This conclusion would be correct for analyses of the effect of CPAP/limited ventilation vs. surfactant/ conventional ventilation on BPD by oxygen delivery (because each treatment arm would contain equal numbers of infants in the high and low sat groups). However, this isn't the comparison in question. This conclusion would certainly not be correct in analyzing the effect of high vs low sat goals on BPD. In this analysis, centers that used the study oximeter would be systematically more likely to administer oxygen to the high sat group than to the low sat group. The problem wouldn't go away by controlling for center, and the more centers that used the study oximeter, the more biased the result would be. How many centers were there that used the study oximeter?

Controlling for center adjusts for differences between centers including differences in the BPD oximeter used. Thus, adding a covariate for BPD oximeter does not change the estimates for the treatment oximeter effect. We are not arguing that the BPD oximeter used did not have an impact. We did find that BPD oximeter was significant in the models, as was center. However, since center and BPD oximeter are strongly confounded (in fact we have almost complete aliasing of center and clinical/study oximeter), it's not possible to tease out the effect of the BPD oximeter from other between-center differences. In addition, the interaction between BPD oximeter and treatment oximeter was not significant. This indicates that the impact of treatment oximeter on the BPD outcomes was

not significantly different in the centers that used the study oximeters to determine BPD and those that used the clinical oximeters.

5. What is the basis for believing that there would be anything near reasonable power to assess a oximeter x treatment group interaction?

Clearly, these analyses were conducted from a post-hoc perspective, and the study was never designed to have the power to determine that the interaction in our data set is statistically significant for a pre-specified interaction effect size. But, that is not a shortcoming unless the magnitude of the interaction effect is such that it represents an important scientific bias in study interpretation. Our preliminary analyses indicate that biases of such magnitude are not present in this data set. We can do more detailed analyses of the level of bias that might have been introduced after Marie returns from vacation, but nothing in the analyses conducted to date suggest that those magnitudes warrant delay of submission of this manuscript.

I know that everyone is anxious to get this paper submitted. While I have an external advisory committee tomorrow, I will try to respond tomorrow night if the information requested above is sent tomorrow during the day.

---

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]  
Sent: Wednesday, February 24, 2010 7:53 AM  
To: Tyson, Jon E; 'Cunningham, Meg'; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; Wallace, Dennis; cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; 'Stevenson David (E-mail)'; 'Finer, Neil'; Rich, Wade; Gantz, Marie  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]  
Subject: Follow Up ON BPD and Oximeters

Hi all -

In Follow up to yesterday's discussion, Marie spent a great deal of time last evening running additional analyses to address (and now alleviate) Jon's concern as described:

We have looked into the question of whether the oximeter used to determine BPD impacted the BPD and death/BPD outcomes by adding a covariate for the BPD oximeter (study or clinical) to the statistical models. We found that the effect of the BPD oximeter was significant; however, the interaction between BPD oximeter and treatment oximeter (low or high SpO2 target range) was not significant in any model, indicating that, if there was a BPD oximeter effect, it was not different in the two treatment groups. In addition, it should be noted that BPD oximeter is confounded with center (centers tended to be consistent in their use of the study or clinical oximeters to determine BPD). Therefore, by including center in the original models, we have already accounted for the effect of the BPD oximeter the center chose to use. Finally, because center and BPD oximeter are confounded, we cannot know whether the significant BPD oximeter effect is due to the BPD oximeters themselves or other characteristics that differ between centers.

---

From: Tyson, Jon E [mailto:Jon.E.Tyson@uth.tmc.edu]  
Sent: Tuesday, February 23, 2010 4:33 PM  
To: Higgins, Rosemary (NIH/NICHD) [E]; 'Cunningham, Meg'; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu;



mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; Wallace, Dennis; cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; bbatton@siumed.edu  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; lmoore@med.wayne.edu; pamela.neville@duke.edu; gonza025@mc.duke.edu; Smith, Nancy M; Brenda Vecchio; msumner@peds.uab.edu; Archer, Stephanie (NIH/NICHD) [E]  
Subject: RE: Steering Committee Call Tomorrow

While it may seem that I am fixated on an unimportant issue regarding a not quite significant difference, I think we undermine the credibility of Network studies if we are not completely forthright about problems in measuring what everyone would agree is an important secondary outcome. Not reporting that the assessment of BPD by oxygen administration could be biased by continued use of the study oximeters would seem to be in the category of not reporting protocol deviations and not something that is in the Network's best interest. Why not just put a footnote under the table describing the problem?

Jon E. Tyson, MD, MPH  
Center for Clinical Research & Evidence-Based Medicine  
UT Medical School at Houston  
6431 Fannin St., MSB 2.106  
Houston, TX 77030  
voice 713-500-5651  
fax 713-500-0519

---

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
Sent: Tuesday, February 23, 2010 2:11 PM  
To: 'Cunningham, Meg'; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; Wallace, Dennis; cotte010@mc.duke.edu; Tyson, Jon E; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; bbatton@siumed.edu  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; lmoore@med.wayne.edu; pamela.neville@duke.edu; gonza025@mc.duke.edu; Smith, Nancy M; Brenda Vecchio; msumner@peds.uab.edu; Archer, Stephanie (NIH/NICHD) [E]  
Subject: RE: Steering Committee Call Tomorrow

If you joined the call already in progress, please send us an email so we can count your attendance.

Rose

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From: Cunningham, Meg [mailto:mcunningham@rti.org]  
Sent: Monday, February 22, 2010 9:59 AM  
To: [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; Higgins, Rosemary (NIH/NICHD) [E]; ifrantz@tuftsmedicalcenter.org; Kathleen.A.Kennedy@uth.tmc.edu; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; Wallace, Dennis; cotte010@mc.duke.edu; jon.e.tyson@uth.tmc.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; bbatton@siumed.edu  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; lmoore@med.wayne.edu; pamela.neville@duke.edu; gonza025@mc.duke.edu; Nancy.M.Smith@uth.tmc.edu; Brenda Vecchio; msumner@peds.uab.edu; Archer, Stephanie (NIH/NICHD) [E]

Subject: Steering Committee Call Tomorrow

Dear All -

The next standing Steering Committee call is scheduled for tomorrow, Tuesday, February 23rd at 3:00pm ET.

Please Dial:

Outside the USA 1-203-310 (b) (6)

or Within the USA 866-675 (b) (6)

Then, enter Participant Passcode: (b) (6)

Steering Committee Conference Call Agenda 02/23/2010

1. Early BP discussion (attached are a brief description of the time limited data collection proposal and a draft of the form which would be used.)
2. SUPPORT manuscript discussion and update
3. New Business

Thanks,  
Meg

Meg Cunningham  
RTI International  
701 13th St. NW, Ste. 750  
Washington, DC 20005  
tel: 202-974-7837  
fax: 202-728-2095  
www.rti.org<<http://www.rti.org>>

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** FW: \*\*\*\*\* Important -Follow Up ON BPD and Oximeters\*\*\*\*\*  
**Date:** Monday, March 01, 2010 11:32:00 AM

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**From:** Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]  
**Sent:** Monday, March 01, 2010 11:32 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: \*\*\*\*\* Important -Follow Up ON BPD and Oximeters\*\*\*\*\*

No, do not include

Wally Carlo, M.D.  
Edwin M. Dixon Professor of Pediatrics  
University of Alabama at Birmingham  
Director, Division of Neonatology  
Director, Newborn Nurseries  
619 South 20th Street  
525 New Hillman Building  
Birmingham, AL 35233-7335  
Phone: 205 934 4680  
FAX: 205 934 3100  
Cell: 205 266 (b)

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**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Monday, March 01, 2010 10:00 AM  
**To:** Wally Carlo, M.D.; 'Finer, Neil'; alaptook@WIHRI.org; Roger.Faix@hsc.utah.edu; Bradley Yoder; kurt.schibler@cchmc.org; adas@rti.org; nancy.newman; Rich, Wade; Gantz, Marie; mcw3@case.edu; Dennis Wallace  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin  
**Subject:** \*\*\*\*\* Important -Follow Up ON BPD and Oximeters\*\*\*\*\*  
**Importance:** High

To the SUPPORT Subcommittee

Given the email exchange, the subcommittee will need to ascertain whether or not to indicate in the SUPPORT papers whether or not a bias could have existed in reporting the secondary outcome of BPD based on oximeter. Previously the subcommittee had reviewed the oximeter use on a conference call and decided to defer this to a secondary paper. There has been discussion on the SC call and via email subsequently.

**Therefore, please send me a yes/no vote to include this in the paper by March 2.**

Thanks  
Rose

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**From:** Tyson, Jon E [mailto:Jon.E.Tyson@uth.tmc.edu]  
**Sent:** Friday, February 26, 2010 6:28 PM

**To:** Wallace, Dennis; Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; Stevenson David (E-mail); Finer, Neil; Rich, Wade; Gantz, Marie  
**Cc:** Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: Follow Up ON BPD and Oximeters

I don't understand your statement "Controlling for center adjusts for differences between centers including differences in the BPD oximeter used." To simplify the discussion, suppose every center always used the study oximeter in designating who had BPD by oxygen saturation. Because the true saturation that would prompt oxygen administration would differ in the two treatment groups, there would be systematic bias toward administering oxygen to more infants in the high sat group than in the low sat group. This is inherent in the study design. Whatever differences there were between centers, this bias would occur in every center and would not be eliminated by controlling for center. And if I understand the analysis, there would be no interaction between treatment oximeter and BPD oximeter because they would be the same in every baby in every center.

You indicate that 5 centers used the study oximeter in almost every baby. In saying "it's not possible to tease out the effect of the BPD oximeter from other between-center differences" (a statement that I certainly accept), aren't you saying that the effect of the study oximeter on the difference in the incidence of BPD by oxygen administration between high and low sat groups (i.e., the bias) can not be distinguished from the effect of the myriad of other factors in those centers that might affect that difference in incidence? If so, why would you expect to be able to discern that bias (the signal) from all the noise resulting from other factors? I understand from what you said that the same approach was used in virtually all infants in each center which makes the effective n to be based on the number of centers rather than the number of babies. As I understand the analysis, the power to assess an interaction would then be quite low.

The issue here is whether is simply whether to report somewhere in the paper (which could be noted under the table and wouldn't increase the word count for the text) a bias in evaluating a secondary outcome. This can be done with no delay in submitting the manuscript or waiting for Maria to return. *If we had other real or potential sources of bias—say, a breaking of the blind for some infants, open label administration of a study drug to the control group, or differential loss to follow-up, we would certainly report it as a matter of course, whether or not there was a significant or near significant difference in the outcome and without testing and whether or not we assessed or found any interaction or other statistical evidence that this potential source of bias affected the results!*

Jon E. Tyson, MD, MPH  
Center for Clinical Research & Evidence-Based Medicine  
UT Medical School at Houston  
6431 Fannin St., MSB 2.106  
Houston, TX 77030  
voice 713-500-5651  
fax 713-500-0519

---

**From:** Wallace, Dennis [mailto:dwallace@rti.org]  
**Sent:** Friday, February 26, 2010 1:56 PM  
**To:** Wallace, Dennis; Tyson, Jon E; Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A;

kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; Stevenson David (E-mail); Finer, Neil; Rich, Wade; Gantz, Marie

**Cc:** Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]

**Subject:** RE: Follow Up ON BPD and Oximeters

Hello all,

I accidentally hit the send button before finishing editing this response so ignore the earlier e-mail and see the response below.

Dennis

Dennis Wallace  
Senior Research Statistician  
Cox 241  
RTI International  
3040 Cornwallis Rd  
Research Triangle Park, NC 27709-2104  
Voice: 919-541-6271  
Fax: 919-541-6416

---

**From:** Wallace, Dennis

**Sent:** Friday, February 26, 2010 2:53 PM

**To:** 'Tyson, Jon E'; Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; 'Stevenson David (E-mail)'; 'Finer, Neil'; Rich, Wade; Gantz, Marie

**Cc:** Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]

**Subject:** RE: Follow Up ON BPD and Oximeters

Jon,

Marie flew out on a long-scheduled vacation after completing these analyses late Tuesday evening and has very limited e-mail and cell phone access. However, she has taken time to provide a preliminary response that I've outlined below with some added thoughts of my own in red font below. Based on these responses, I do believe that the critical concerns about bias have been addressed sufficiently for this initial manuscript, but if you think we need to have a more full discussion, we can talk after Marie returns next week. Because the programming for these outcome measures is relatively complicated, I'm hesitant to try to do any additional analyses prior to her return. However, as I indicated above, I don't think that we need to delay any submissions while trying to iron on the small details.

Dennis Wallace  
Senior Research Statistician  
Cox 241  
RTI International  
3040 Cornwallis Rd  
Research Triangle Park, NC 27709-2104  
Voice: 919-541-6271  
Fax: 919-541-6416

-----Original Message-----

From: Tyson, Jon E [mailto:Jon.E.Tyson@uth.tmc.edu]  
Sent: Thursday, February 25, 2010 12:45 AM

To: Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; Wallace, Dennis; cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; 'Stevenson David (E-mail)'; 'Finer, Neil'; Rich, Wade; Gantz, Marie  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]  
Subject: RE: Follow Up ON BPD and Oximeters

Rose, before we can understand and interpret this information noted in the mail, we really need to know more about what was done and answers to questions like those below:

1. Which trial result was addressed - whether the evaluation of BPD was biased in the analyses of CPAP/limited ventilation vs. surfactant/conventional ventilation arm (not the analysis for which there is concern) or the analyses of the high vs. low oxygen saturation goal.

Although models were run for the different arms of the factorial design, the trial result that was addressed in the earlier e-mail was the impact of different oximeters on the comparison of the effects high vs. low oxygen saturation targets on BPD and BPD/death outcomes, which we believe is the question of interest.

2. Do we have reliable data to know whether individual infants were monitored on the study oximeter or on the clinical oximeter on the day the infant was 36 weeks and 0 and whether the oximeter was changed part way through that 24 hour period? What was done if the infant was switched on that day. As I understand it, the diagnosis of BPD was based on the entire 24 hours the day the infant was 36 weeks 0 days. Though the results of the survey weren't distributed, my impression from responses to my earlier e mails was that even the procedure usually followed in individual centers was not necessarily clear.

We can determine from form PHY02 what oximeter was used to determine the physiologic definition of BPD, but we do not have the detailed level of information that you described. However, based on the survey results, we do know that only 5 sites used the study oximeter for an oxygen-based definition, and only 3 used the study oximeter for challenge.

3. What variables in the model when the BPD oximeter was added? What variables were in the model when a BPD oximeter x study treatment group was added?

Variables in the model were treatment oximeter (low vs. high), center, GA group. Familial clustering was adjusted for as a random effect. I added BPD oximeter and also looked at the interaction between BPD oximeter and treatment oximeter. These factors were identical to the factors used in the models for which secondary outcomes were reported in the manuscript.

4. Do I understand Maria and you to conclude that because centers tended to be consistent in their oximeter use, controlling for center would prevent a biased assessment of the effect on BPD by oxygen administration?

This comment makes me wonder if the analysis was done for the wrong comparison. This conclusion would be correct for analyses of the effect of CPAP/limited ventilation vs. surfactant/ conventional ventilation on BPD by oxygen delivery (because each treatment arm would contain equal numbers of infants in the high and low sat groups). However, this isn't the comparison in question. This conclusion would certainly not be correct in analyzing the effect of high vs low sat goals on BPD. In this analysis, centers that used the study oximeter would be systematically more likely to administer oxygen to the high sat group than to the low sat group. The problem wouldn't go away by controlling for center, and the more centers that used the study

oximeter, the more biased the result would be. How many centers were there that used the study oximeter?

Controlling for center adjusts for differences between centers including differences in the BPD oximeter used. Thus, adding a covariate for BPD oximeter does not change the estimates for the treatment oximeter effect. We are not arguing that the BPD oximeter used did not have an impact. We did find that BPD oximeter was significant in the models, as was center. However, since center and BPD oximeter are strongly confounded (in fact we have almost complete aliasing of center and clinical/study oximeter), it's not possible to tease out the effect of the BPD oximeter from other between-center differences. In addition, the interaction between BPD oximeter and treatment oximeter was not significant. This indicates that the impact of treatment oximeter on the BPD outcomes was not significantly different in the centers that used the study oximeters to determine BPD and those that used the clinical oximeters.

5. What is the basis for believing that there would be anything near reasonable power to assess a oximeter x treatment group interaction?

Clearly, these analyses were conducted from a post-hoc perspective, and the study was never designed to have the power to determine that the interaction in our data set is statistically significant for a pre-specified interaction effect size. But, that is not a shortcoming unless the magnitude of the interaction effect is such that it represents an important scientific bias in study interpretation. Our preliminary analyses indicate that biases of such magnitude are not present in this data set. We can do more detailed analyses of the level of bias that might have been introduced after Marie returns from vacation, but nothing in the analyses conducted to date suggest that those magnitudes warrant delay of submission of this manuscript.

I know that everyone is anxious to get this paper submitted. While I have an external advisory committee tomorrow, I will try to respond tomorrow night if the information requested above is sent tomorrow during the day.

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]  
Sent: Wednesday, February 24, 2010 7:53 AM  
To: Tyson, Jon E; 'Cunningham, Meg'; [SCRN] Stoll, Barbara;  
alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik;  
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Rich, Wade; Gantz, Marie  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman,  
Jamie; Archer, Stephanie (NIH/NICHD) [E]  
Subject: Follow Up ON BPD and Oximeters

Hi all -

In follow up to yesterday's discussion, Marie spent a great deal of time last evening running additional analyses to address (and now alleviate) Jon's concern as described:

We have looked into the question of whether the oximeter used to determine BPD impacted the BPD and death/BPD outcomes by adding a covariate for the BPD oximeter (study or clinical) to the statistical models. We found that the effect of the BPD oximeter was significant; however, the interaction between BPD oximeter and treatment oximeter (low or high SpO2 target range) was not significant in any model, indicating that, if there was a BPD oximeter effect, it was not different in the two treatment groups. In addition, it should be noted that BPD oximeter is confounded with center (centers tended to be consistent in their use of the study or clinical oximeters to determine BPD). Therefore, by including center in the original models, we have already accounted for the effect of the BPD oximeter the center chose to use. Finally, because center and BPD oximeter are confounded, we cannot know whether the significant BPD oximeter effect is due to the BPD oximeters themselves or other characteristics that differ between centers.

From: Tyson, Jon E [mailto:Jon.E.Tyson@uth.tmc.edu]  
Sent: Tuesday, February 23, 2010 4:33 PM  
To: Higgins, Rosemary (NIH/NICHD) [E]; 'Cunningham, Meg'; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; Wallace, Dennis; cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; bbatton@siumed.edu  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; lmoore@med.wayne.edu; pamela.neville@duke.edu; gonza025@mc.duke.edu; Smith, Nancy M; Brenda Vecchio; msumner@peds.uab.edu; Archer, Stephanie (NIH/NICHD) [E]  
Subject: RE: Steering Committee Call Tomorrow

While it may seem that I am fixated on an unimportant issue regarding a not quite significant difference, I think we undermine the credibility of Network studies if we are not completely forthright about problems in measuring what everyone would agree is an important secondary outcome. Not reporting that the assessment of BPD by oxygen administration could be biased by continued use of the study oximeters would seem to be in the category of not reporting protocol deviations and not something that is in the Network's best interest. Why not just put a footnote under the table describing the problem?

Jon E. Tyson, MD, MPH  
Center for Clinical Research & Evidence-Based Medicine  
UT Medical School at Houston  
6431 Fannin St., MSB 2.106  
Houston, TX 77030  
voice 713-500-5651  
fax 713-500-0519

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
Sent: Tuesday, February 23, 2010 2:11 PM  
To: 'Cunningham, Meg'; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; Wallace, Dennis; cotte010@mc.duke.edu; Tyson, Jon E; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; bbatton@siumed.edu  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; lmoore@med.wayne.edu; pamela.neville@duke.edu; gonza025@mc.duke.edu; Smith, Nancy M; Brenda Vecchio; msumner@peds.uab.edu; Archer, Stephanie (NIH/NICHD) [E]  
Subject: RE: Steering Committee Call Tomorrow

If you joined the call already in progress, please send us an email so we can count your attendance.

Rose

From: Cunningham, Meg [mailto:mcunningham@rti.org]  
Sent: Monday, February 22, 2010 9:59 AM  
To: [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; Higgins, Rosemary (NIH/NICHD) [E]; ifrantz@tuftsmedicalcenter.org; Kathleen.A.Kennedy@uth.tmc.edu; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; Wallace, Dennis; cotte010@mc.duke.edu; jon.e.tyson@uth.tmc.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; bbatton@siumed.edu



Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; lmoore@med.wayne.edu; pamela.neville@duke.edu; gonza025@mc.duke.edu; Nancy.M.Smith@uth.tmc.edu; Brenda Vecchio; msumner@peds.uab.edu; Archer, Stephanie (NIH/NICHD) [E]  
Subject: Steering Committee Call Tomorrow

Dear All -

The next standing Steering Committee call is scheduled for tomorrow, Tuesday, February 23rd at 3:00pm ET.

Please Dial:

Outside the USA 1-203-310 (b) (6)

or Within the USA 866-675 (b) (6)

Then, enter Participant Passcode: (b) (6) ■

Steering Committee Conference Call Agenda 02/23/2010

1. Early BP discussion (attached are a brief description of the time limited data collection proposal and a draft of the form which would be used.)
2. SUPPORT manuscript discussion and update
3. New Business

Thanks,  
Meg

Meg Cunningham  
RTI International  
701 13th St. NW, Ste. 750  
Washington, DC 20005  
tel: 202-974-7837  
fax: 202-728-2095  
www.rti.org<<http://www.rti.org>>

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** FW: \*\*\*\*\* Important -Follow Up ON BPD and Oximeters\*\*\*\*\*  
**Date:** Monday, March 01, 2010 11:26:00 AM

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**From:** Bradley Yoder [mailto:Bradley.Yoder@hsc.utah.edu]  
**Sent:** Monday, March 01, 2010 11:18 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: \*\*\*\*\* Important -Follow Up ON BPD and Oximeters\*\*\*\*\*

I would vote yes; and I agree with Jon's idea about adding it as a sub-text to the Table.

Brad Yoder  
Division of Neonatology  
University of Utah SOM

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Monday, March 01, 2010 9:00 AM  
**To:** 'Wally Carlo, M.D.'; 'Finer, Neil'; alaptook@WIHRI.org; Roger Faix; Bradley Yoder; kurt.schibler@cchmc.org; adas@rti.org; nancy newman; Rich, Wade; Gantz, Marie; mcw3@case.edu; Dennis Wallace  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin  
**Subject:** \*\*\*\*\* Important -Follow Up ON BPD and Oximeters\*\*\*\*\*  
**Importance:** High

To the SUPPORT Subcommittee

Given the email exchange, the subcommittee will need to ascertain whether or not to indicate in the SUPPORT papers whether or not a bias could have existed in reporting the secondary outcome of BPD based on oximeter. Previously the subcommittee had reviewed the oximeter use on a conference call and decided to defer this to a secondary paper. There has been discussion on the SC call and via email subsequently.

**Therefore, please send me a yes/no vote to include this in the paper by March 2.**

Thanks  
Rose

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**From:** Tyson, Jon E [mailto:Jon.E.Tyson@uth.tmc.edu]  
**Sent:** Friday, February 26, 2010 6:28 PM  
**To:** Wallace, Dennis; Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org;

Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; Stevenson David (E-mail); Finer, Neil; Rich, Wade; Gantz, Marie  
**Cc:** Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: Follow Up ON BPD and Oximeters

I don't understand your statement "Controlling for center adjusts for differences between centers including differences in the BPD oximeter used." To simplify the discussion, suppose every center always used the study oximeter in designating who had BPD by oxygen saturation. Because the true saturation that would prompt oxygen administration would differ in the two treatment groups, there would be systematic bias toward administering oxygen to more infants in the high sat group than in the low sat group. This is inherent in the study design. Whatever differences there were between centers, this bias would occur in every center and would not be eliminated by controlling for center. And if I understand the analysis, there would be no interaction between treatment oximeter and BPD oximeter because they would be the same in every baby in every center.

You indicate that 5 centers used the study oximeter in almost every baby. In saying "it's not possible to tease out the effect of the BPD oximeter from other between-center differences" (a statement that I certainly accept), aren't you saying that the effect of the study oximeter on the difference in the incidence of BPD by oxygen administration between high and low sat groups (i.e., the bias) can not be distinguished from the effect of the myriad of other factors in those centers that might affect that difference in incidence? If so, why would you expect to be able to discern that bias (the signal) from all the noise resulting from other factors? I understand from what you said that the same approach was used in virtually all infants in each center which makes the effective n to be based on the number of centers rather than the number of babies. As I understand the analysis, the power to assess an interaction would then be quite low.

The issue here is whether is simply whether to report somewhere in the paper (which could be noted under the table and wouldn't increase the word count for the text) a bias in evaluating a secondary outcome. This can be done with no delay in submitting the manuscript or waiting for Maria to return. *If we had other real or potential sources of bias—say, a breaking of the blind for some infants, open label administration of a study drug to the control group, or differential loss to follow-up, we would certainly report it as a matter of course, whether or not there was a significant or near significant difference in the outcome and without testing and whether or not we assessed or found any interaction or other statistical evidence that this potential source of bias affected the results!*

Jon E. Tyson, MD, MPH  
Center for Clinical Research & Evidence-Based Medicine  
UT Medical School at Houston  
6431 Fannin St., MSB 2.106  
Houston, TX 77030  
voice 713-500-5651  
fax 713-500-0519

---

**From:** Wallace, Dennis [mailto:dwallace@rti.org]

**Sent:** Friday, February 26, 2010 1:56 PM

**To:** Wallace, Dennis; Tyson, Jon E; Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu;

Stevenson David (E-mail); Finer, Neil; Rich, Wade; Gantz, Marie  
**Cc:** Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: Follow Up ON BPD and Oximeters

Hello all,

I accidentally hit the send button before finishing editing this response so ignore the earlier e-mail and see the response below.

Dennis

Dennis Wallace  
Senior Research Statistician  
Cox 241  
RTI International  
3040 Cornwallis Rd  
Research Triangle Park, NC 27709-2104  
Voice: 919-541-6271  
Fax: 919-541-6416

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**From:** Wallace, Dennis  
**Sent:** Friday, February 26, 2010 2:53 PM  
**To:** 'Tyson, Jon E'; Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; 'Stevenson David (E-mail)'; 'Finer, Neil'; Rich, Wade; Gantz, Marie  
**Cc:** Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: Follow Up ON BPD and Oximeters

Jon,

Marie flew out on a long-scheduled vacation after completing these analyses late Tuesday evening and has very limited e-mail and cell phone access. However, she has taken time to provide a preliminary response that I've outlined below with some added thoughts of my own in red font below. Based on these responses, I do believe that the critical concerns about bias have been addressed sufficiently for this initial manuscript, but if you think we need to have a more full discussion, we can talk after Marie returns next week. Because the programming for these outcome measures is relatively complicated, I'm hesitant to try to do any additional analyses prior to her return. However, as I indicated above, I don't think that we need to delay any submissions while trying to iron on the small details.

Dennis Wallace  
Senior Research Statistician  
Cox 241  
RTI International  
3040 Cornwallis Rd  
Research Triangle Park, NC 27709-2104  
Voice: 919-541-6271  
Fax: 919-541-6416

-----Original Message-----

From: Tyson, Jon E [mailto:Jon.E.Tyson@uth.tmc.edu]  
Sent: Thursday, February 25, 2010 12:45 AM  
To: Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org;

Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu;  
Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu;  
vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; Wallace, Dennis;  
cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu;  
Luc.Brion@utsouthwestern.edu; 'Stevenson David (E-mail)'; 'Finer, Neil';  
Rich, Wade; Gantz, Marie  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman,  
Jamie; Archer, Stephanie (NIH/NICHD) [E]  
Subject: RE: Follow Up ON BPD and Oximeters

Rose, before we can understand and interpret this information noted in the mail, we really need to know more about what was done and answers to questions like those below:

1. Which trial result was addressed - whether the evaluation of BPD was biased in the analyses of CPAP/limited ventilation vs. surfactant/conventional ventilation arm (not the analysis for which there is concern) or the analyses of the high vs. low oxygen saturation goal.

Although models were run for the different arms of the factorial design, the trial result that was addressed in the earlier e-mail was the impact of different oximeters on the comparison of the effects high vs. low oxygen saturation targets on BPD and BPD/death outcomes, which we believe is the question of interest.

2. Do we have reliable data to know whether individual infants were monitored on the study oximeter or on the clinical oximeter on the day the infant was 36 weeks and 0 and whether the oximeter was changed part way through that 24 hour period? What was done if the infant was switched on that day. As I understand it, the diagnosis of BPD was based on the entire 24 hours the day the infant was 36 weeks 0 days. Though the results of the survey weren't distributed, my impression from responses to my earlier e mails was that even the procedure usually followed in individual centers was not necessarily clear.

We can determine from form PHY02 what oximeter was used to determine the physiologic definition of BPD, but we do not have the detailed level of information that you described. However, based on the survey results, we do know that only 5 sites used the study oximeter for an oxygen-based definition, and only 3 used the study oximeter for challenge.

3. What variables in the model when the BPD oximeter was added? What variables were in the model when a BPD oximeter x study treatment group was added?

Variables in the model were treatment oximeter (low vs. high), center, GA group. Familial clustering was adjusted for as a random effect. I added BPD oximeter and also looked at the interaction between BPD oximeter and treatment oximeter. These factors were identical to the factors used in the models for which secondary outcomes were reported in the manuscript.

4. Do I understand Maria and you to conclude that because centers tended to be consistent in their oximeter use, controlling for center would prevent a biased assessment of the effect on BPD by oxygen administration?

This comment makes me wonder if the analysis was done for the wrong comparison, This conclusion would be correct for analyses of the effect of CPAP/limited ventilation vs. surfactant/ conventional ventilation on BPD by oxygen delivery (because each treatment arm would contain equal numbers of infants in the high and low sat groups). However, this isn't the comparison in question. This conclusion would certainly not be correct in analyzing the effect of high vs low sat goals on BPD. In this analysis, centers that used the study oximeter would be systematically more likely to administer oxygen to the high sat group than to the low sat group. The problem wouldn't go away by controlling for center, and the more centers that used the study oximeter, the more biased the result would be. How many centers were there that used the study oximeter?

Controlling for center adjusts for differences between centers including differences in the BPD oximeter used. Thus, adding a covariate for BPD

oximeter does not change the estimates for the treatment oximeter effect. We are not arguing that the BPD oximeter used did not have an impact. We did find that BPD oximeter was significant in the models, as was center. However, since center and BPD oximeter are strongly confounded (in fact we have almost complete aliasing of center and clinical/study oximeter), it's not possible to tease out the effect of the BPD oximeter from other between-center differences. In addition, the interaction between BPD oximeter and treatment oximeter was not significant. This indicates that the impact of treatment oximeter on the BPD outcomes was not significantly different in the centers that used the study oximeters to determine BPD and those that used the clinical oximeters.

5. What is the basis for believing that there would be anything near reasonable power to assess a oximeter x treatment group interaction?

Clearly, these analyses were conducted from a post-hoc perspective, and the study was never designed to have the power to determine that the interaction in our data set is statistically significant for a pre-specified interaction effect size. But, that is not a shortcoming unless the magnitude of the interaction effect is such that it represents an important scientific bias in study interpretation. Our preliminary analyses indicate that biases of such magnitude are not present in this data set. We can do more detailed analyses of the level of bias that might have been introduced after Marie returns from vacation, but nothing in the analyses conducted to date suggest that those magnitudes warrant delay of submission of this manuscript.

I know that everyone is anxious to get this paper submitted. While I have an external advisory committee tomorrow, I will try to respond tomorrow night if the information requested above is sent tomorrow during the day.

---

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]  
Sent: Wednesday, February 24, 2010 7:53 AM  
To: Tyson, Jon E; 'Cunningham, Meg'; [SCRN] Stoll, Barbara;  
alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik;  
goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A;  
kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu;  
matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org;  
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Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu;  
vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; Wallace, Dennis;  
cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu;  
Luc.Brion@utsouthwestern.edu; 'Stevenson David (E-mail)'; 'Finer, Neil';  
Rich, Wade; Gantz, Marie  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman,  
Jamie; Archer, Stephanie (NIH/NICHD) [E]  
Subject: Follow Up ON BPD and Oximeters

Hi all -

In Follow up to yesterday's discussion, Marie spent a great deal of time last evening running additional analyses to address (and now alleviate) Jon's concern as described:

We have looked into the question of whether the oximeter used to determine BPD impacted the BPD and death/BPD outcomes by adding a covariate for the BPD oximeter (study or clinical) to the statistical models. We found that the effect of the BPD oximeter was significant; however, the interaction between BPD oximeter and treatment oximeter (low or high SpO2 target range) was not significant in any model, indicating that, if there was a BPD oximeter effect, it was not different in the two treatment groups. In addition, it should be noted that BPD oximeter is confounded with center (centers tended to be consistent in their use of the study or clinical oximeters to determine BPD). Therefore, by including center in the original models, we have already accounted for the effect of the BPD oximeter the center chose to use. Finally, because center and BPD oximeter are confounded, we cannot know whether the significant BPD oximeter effect is due to the BPD oximeters themselves or other characteristics that differ between centers.

---

From: Tyson, Jon E [mailto:Jon.E.Tyson@uth.tmc.edu]  
Sent: Tuesday, February 23, 2010 4:33 PM  
To: Higgins, Rosemary (NIH/NICHD) [E]; 'Cunningham, Meg'; [SCRN] Stoll,

Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; Wallace, Dennis; cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; bbatton@siumed.edu  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; lmoore@med.wayne.edu; pamela.neville@duke.edu; gonza025@mc.duke.edu; Smith, Nancy M; Brenda Vecchio; msumner@peds.uab.edu; Archer, Stephanie (NIH/NICHD) [E]  
Subject: RE: Steering Committee Call Tomorrow

While it may seem that I am fixated on an unimportant issue regarding a not quite significant difference, I think we undermine the credibility of Network studies if we are not completely forthright about problems in measuring what everyone would agree is an important secondary outcome. Not reporting that the assessment of BPD by oxygen administration could be biased by continued use of the study oximeters would seem to be in the category of not reporting protocol deviations and not something that is in the Network's best interest. Why not just put a footnote under the table describing the problem?

Jon E. Tyson, MD, MPH  
Center for Clinical Research & Evidence-Based Medicine  
UT Medical School at Houston  
6431 Fannin St., MSB 2.106  
Houston, TX 77030  
voice 713-500-5651  
fax 713-500-0519

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
Sent: Tuesday, February 23, 2010 2:11 PM  
To: 'Cunningham, Meg'; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; Wallace, Dennis; cotte010@mc.duke.edu; Tyson, Jon E; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; bbatton@siumed.edu  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; lmoore@med.wayne.edu; pamela.neville@duke.edu; gonza025@mc.duke.edu; Smith, Nancy M; Brenda Vecchio; msumner@peds.uab.edu; Archer, Stephanie (NIH/NICHD) [E]  
Subject: RE: Steering Committee Call Tomorrow

If you joined the call already in progress, please send us an email so we can count your attendance.

Rose

From: Cunningham, Meg [mailto:mcunningham@rti.org]  
Sent: Monday, February 22, 2010 9:59 AM  
To: [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; Higgins, Rosemary (NIH/NICHD) [E]; ifrantz@tuftsmedicalcenter.org; Kathleen.A.Kennedy@uth.tmc.edu; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; Wallace, Dennis; cotte010@mc.duke.edu; jon.e.tyson@uth.tmc.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; bbatton@siumed.edu  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; lmoore@med.wayne.edu; pamela.neville@duke.edu; gonza025@mc.duke.edu; Nancy.M.Smith@uth.tmc.edu; Brenda Vecchio; msumner@peds.uab.edu; Archer, Stephanie (NIH/NICHD) [E]  
Subject: Steering Committee Call Tomorrow

Dear All -

The next standing Steering Committee call is scheduled for tomorrow, Tuesday, February 23rd at 3:00pm ET.

Please Dial:

Outside the USA 1-203-310-(b)

or Within the USA 866-675-(b)

Then, enter Participant Passcode: (b) (6)

Steering Committee Conference Call Agenda 02/23/2010

1. Early BP discussion (attached are a brief description of the time limited data collection proposal and a draft of the form which would be used.)
2. SUPPORT manuscript discussion and update
3. New Business

Thanks,  
Meg

Meg Cunningham  
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701 13th St. NW, Ste. 750  
Washington, DC 20005  
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fax: 202-728-2095  
[www.rti.org](http://www.rti.org)<<http://www.rti.org>>



**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** FW: \*\*\*\*\* Important -Follow Up ON BPD and Oximeters\*\*\*\*\*  
**Date:** Monday, March 01, 2010 11:04:00 AM

---

Neil also Voted NO over the weekend; I vote NO

---

**From:** Rich, Wade [mailto:wrich@ucsd.edu]  
**Sent:** Monday, March 01, 2010 11:01 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: \*\*\*\*\* Important -Follow Up ON BPD and Oximeters\*\*\*\*\*

No.

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Monday, March 01, 2010 8:00 AM  
**To:** 'Wally Carlo, M.D.'; Finer, Neil; alaptook@WIHRI.org; Roger.Faix@hsc.utah.edu; Bradley Yoder; kurt.schibler@cchmc.org; adas@rti.org; nancy newman; Rich, Wade; Gantz, Marie; mcw3@case.edu; Dennis Wallace  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin  
**Subject:** \*\*\*\*\* Important -Follow Up ON BPD and Oximeters\*\*\*\*\*  
**Importance:** High

To the SUPPORT Subcommittee

Given the email exchange, the subcommittee will need to ascertain whether or not to indicate in the SUPPORT papers whether or not a bias could have existed in reporting the secondary outcome of BPD based on oximeter. Previously the subcommittee had reviewed the oximeter use on a conference call and decided to defer this to a secondary paper. There has been discussion on the SC call and via email subsequently.

**Therefore, please send me a yes/no vote to include this in the paper by March 2.**

Thanks  
Rose

---

**From:** Tyson, Jon E [mailto:Jon.E.Tyson@uth.tmc.edu]  
**Sent:** Friday, February 26, 2010 6:28 PM  
**To:** Wallace, Dennis; Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; Stevenson David (E-mail); Finer, Neil; Rich, Wade; Gantz, Marie  
**Cc:** Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: Follow Up ON BPD and Oximeters

I don't understand your statement "Controlling for center adjusts for differences between centers including differences in the BPD oximeter used." To simplify the discussion, suppose every center always used the study oximeter in designating who had BPD by oxygen saturation. Because the true saturation that would prompt oxygen administration would differ in the two treatment groups, there would be systematic bias toward administering oxygen to more infants in the high sat group than in the low sat group. This is inherent in the study design. Whatever differences there were between centers, this bias would occur in every center and would not be eliminated by controlling for center. And if I understand the analysis, there would be no interaction between treatment oximeter and BPD oximeter because they would be the same in every baby in every center.

You indicate that 5 centers used the study oximeter in almost every baby. In saying "it's not possible to tease out the effect of the BPD oximeter from other between-center differences" (a statement that I certainly accept), aren't you saying that the effect of the study oximeter on the difference in the incidence of BPD by oxygen administration between high and low sat groups (i.e., the bias) can not be distinguished from the effect of the myriad of other factors in those centers that might affect that difference in incidence? If so, why would you expect to be able to discern that bias (the signal) from all the noise resulting from other factors? I understand from what you said that the same approach was used in virtually all infants in each center which makes the effective n to be based on the number of centers rather than the number of babies. As I understand the analysis, the power to assess an interaction would then be quite low.

The issue here is whether is simply whether to report somewhere in the paper (which could be noted under the table and wouldn't increase the word count for the text) a bias in evaluating a secondary outcome. This can be done with no delay in submitting the manuscript or waiting for Maria to return. *If we had other real or potential sources of bias—say, a breaking of the blind for some infants, open label administration of a study drug to the control group, or differential loss to follow-up, we would certainly report it as a matter of course, whether or not there was a significant or near significant difference in the outcome and without testing and whether or not we assessed or found any interaction or other statistical evidence that this potential source of bias affected the results!*

Jon E. Tyson, MD, MPH  
Center for Clinical Research & Evidence-Based Medicine  
UT Medical School at Houston  
6431 Fannin St., MSB 2.106  
Houston, TX 77030  
voice 713-500-5651  
fax 713-500-0519

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**From:** Wallace, Dennis [mailto:dwallace@rti.org]  
**Sent:** Friday, February 26, 2010 1:56 PM  
**To:** Wallace, Dennis; Tyson, Jon E; Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; Stevenson David (E-mail); Finer, Neil; Rich, Wade; Gantz, Marie  
**Cc:** Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: Follow Up ON BPD and Oximeters

Hello all,

I accidentally hit the send button before finishing editing this response so ignore the earlier e-mail

and see the response below.  
Dennis

Dennis Wallace  
Senior Research Statistician  
Cox 241  
RTI International  
3040 Cornwallis Rd  
Research Triangle Park, NC 27709-2104  
Voice: 919-541-6271  
Fax: 919-541-6416

---

**From:** Wallace, Dennis  
**Sent:** Friday, February 26, 2010 2:53 PM  
**To:** 'Tyson, Jon E'; Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; 'Stevenson David (E-mail)'; 'Finer, Neil'; Rich, Wade; Gantz, Marie  
**Cc:** Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: Follow Up ON BPD and Oximeters

Jon,  
Marie flew out on a long-scheduled vacation after completing these analyses late Tuesday evening and has very limited e-mail and cell phone access. However, she has taken time to provide a preliminary response that I've outlined below with some added thoughts of my own in red font below. Based on these responses, I do believe that the critical concerns about bias have been addressed sufficiently for this initial manuscript, but if you think we need to have a more full discussion, we can talk after Marie returns next week. Because the programming for these outcome measures is relatively complicated, I'm hesitant to try to do any additional analyses prior to her return. However, as I indicated above, I don't think that we need to delay any submissions while trying to iron on the small details.

Dennis Wallace  
Senior Research Statistician  
Cox 241  
RTI International  
3040 Cornwallis Rd  
Research Triangle Park, NC 27709-2104  
Voice: 919-541-6271  
Fax: 919-541-6416

-----Original Message-----

**From:** Tyson, Jon E [mailto:Jon.E.Tyson@uth.tmc.edu]  
**Sent:** Thursday, February 25, 2010 12:45 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; Wallace, Dennis; cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; 'Stevenson David (E-mail)'; 'Finer, Neil'; Rich, Wade; Gantz, Marie  
**Cc:** Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: Follow Up ON BPD and Oximeters

Rose, before we can understand and interpret this information noted in the mail, we really need to know more about what was done and answers to questions like those below:

1. Which trial result was addressed - whether the evaluation of BPD was biased in the analyses of CPAP/limited ventilation vs. surfactant/conventional ventilation arm (not the analysis for which there is concern) or the analyses of the high vs. low oxygen saturation goal.

Although models were run for the different arms of the factorial design, the trial result that was addressed in the earlier e-mail was the impact of different oximeters on the comparison of the effects high vs. low oxygen saturation targets on BPD and BPD/death outcomes, which we believe is the question of interest.

2. Do we have reliable data to know whether individual infants were monitored on the study oximeter or on the clinical oximeter on the day the infant was 36 weeks and 0 and whether the oximeter was changed part way through that 24 hour period? What was done if the infant was switched on that day. As I understand it, the diagnosis of BPD was based on the entire 24 hours the day the infant was 36 weeks 0 days. Though the results of the survey weren't distributed, my impression from responses to my earlier e-mails was that even the procedure usually followed in individual centers was not necessarily clear.

We can determine from form PHY02 what oximeter was used to determine the physiologic definition of BPD, but we do not have the detailed level of information that you described. However, based on the survey results, we do know that only 5 sites used the study oximeter for an oxygen-based definition, and only 3 used the study oximeter for challenge.

3. What variables in the model when the BPD oximeter was added? What variables were in the model when a BPD oximeter x study treatment group was added?

Variables in the model were treatment oximeter (low vs. high), center, GA group. Familial clustering was adjusted for as a random effect. I added BPD oximeter and also looked at the interaction between BPD oximeter and treatment oximeter. These factors were identical to the factors used in the models for which secondary outcomes were reported in the manuscript.

4. Do I understand Maria and you to conclude that because centers tended to be consistent in their oximeter use, controlling for center would prevent a biased assessment of the effect on BPD by oxygen administration?

This comment makes me wonder if the analysis was done for the wrong comparison. This conclusion would be correct for analyses of the effect of CPAP/limited ventilation vs. surfactant/conventional ventilation on BPD by oxygen delivery (because each treatment arm would contain equal numbers of infants in the high and low sat groups). However, this isn't the comparison in question. This conclusion would certainly not be correct in analyzing the effect of high vs low sat goals on BPD. In this analysis, centers that used the study oximeter would be systematically more likely to administer oxygen to the high sat group than to the low sat group. The problem wouldn't go away by controlling for center, and the more centers that used the study oximeter, the more biased the result would be. How many centers were there that used the study oximeter?

Controlling for center adjusts for differences between centers including differences in the BPD oximeter used. Thus, adding a covariate for BPD oximeter does not change the estimates for the treatment oximeter effect. We are not arguing that the BPD oximeter used did not have an impact. We did find that BPD oximeter was significant in the models, as was center. However, since center and BPD oximeter are strongly confounded (in fact we have almost complete aliasing of center and clinical/study oximeter), it's not possible to tease out the effect of the BPD oximeter from other between-center differences. In addition, the interaction between BPD oximeter and treatment oximeter was not significant. This indicates that the impact of treatment oximeter on the BPD outcomes was not significantly different in

the centers that used the study oximeters to determine BPD and those that used the clinical oximeters.

5. What is the basis for believing that there would be anything near reasonable power to assess a oximeter x treatment group interaction?

Clearly, these analyses were conducted from a post-hoc perspective, and the study was never designed to have the power to determine that the interaction in our data set is statistically significant for a pre-specified interaction effect size. But, that is not a shortcoming unless the magnitude of the interaction effect is such that it represents an important scientific bias in study interpretation. Our preliminary analyses indicate that biases of such magnitude are not present in this data set. We can do more detailed analyses of the level of bias that might have been introduced after Marie returns from vacation, but nothing in the analyses conducted to date suggest that those magnitudes warrant delay of submission of this manuscript.

I know that everyone is anxious to get this paper submitted. While I have an external advisory committee tomorrow, I will try to respond tomorrow night if the information requested above is sent tomorrow during the day.

---

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]  
Sent: Wednesday, February 24, 2010 7:53 AM  
To: Tyson, Jon E; 'Cunningham, Meg'; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; Wallace, Dennis; cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; 'Stevenson David (E-mail)'; 'Finer, Neil'; Rich, Wade; Gantz, Marie  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]  
Subject: Follow Up ON BPD and Oximeters

Hi all -

In Follow up to yesterday's discussion, Marie spent a great deal of time last evening running additional analyses to address (and now alleviate) Jon's concern as described:

We have looked into the question of whether the oximeter used to determine BPD impacted the BPD and death/BPD outcomes by adding a covariate for the BPD oximeter (study or clinical) to the statistical models. We found that the effect of the BPD oximeter was significant; however, the interaction between BPD oximeter and treatment oximeter (low or high SpO2 target range) was not significant in any model, indicating that, if there was a BPD oximeter effect, it was not different in the two treatment groups. In addition, it should be noted that BPD oximeter is confounded with center (centers tended to be consistent in their use of the study or clinical oximeters to determine BPD). Therefore, by including center in the original models, we have already accounted for the effect of the BPD oximeter the center chose to use. Finally, because center and BPD oximeter are confounded, we cannot know whether the significant BPD oximeter effect is due to the BPD oximeters themselves or other characteristics that differ between centers.

---

From: Tyson, Jon E [mailto:Jon.E.Tyson@uth.tmc.edu]  
Sent: Tuesday, February 23, 2010 4:33 PM  
To: Higgins, Rosemary (NIH/NICHD) [E]; 'Cunningham, Meg'; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; Wallace, Dennis; cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; bbatton@siumed.edu

Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; lmoore@med.wayne.edu; pamela.neville@duke.edu; gonza025@mc.duke.edu; Smith, Nancy M; Brenda Vecchio; msumner@peds.uab.edu; Archer, Stephanie (NIH/NICHD) [E]  
Subject: RE: Steering Committee Call Tomorrow

While it may seem that I am fixated on an unimportant issue regarding a not quite significant difference, I think we undermine the credibility of Network studies if we are not completely forthright about problems in measuring what everyone would agree is an important secondary outcome. Not reporting that the assessment of BPD by oxygen administration could be biased by continued use of the study oximeters would seem to be in the category of not reporting protocol deviations and not something that is in the Network's best interest. Why not just put a footnote under the table describing the problem?

Jon E. Tyson, MD, MPH  
Center for Clinical Research & Evidence-Based Medicine  
UT Medical School at Houston  
6431 Fannin St., MSB 2.106  
Houston, TX 77030  
voice 713-500-5651  
fax 713-500-0519

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
Sent: Tuesday, February 23, 2010 2:11 PM  
To: 'Cunningham, Meg'; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; Wallace, Dennis; cotte010@mc.duke.edu; Tyson, Jon E; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; bbatton@siumed.edu  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; lmoore@med.wayne.edu; pamela.neville@duke.edu; gonza025@mc.duke.edu; Smith, Nancy M; Brenda Vecchio; msumner@peds.uab.edu; Archer, Stephanie (NIH/NICHD) [E]  
Subject: RE: Steering Committee Call Tomorrow

If you joined the call already in progress, please send us an email so we can count your attendance.

Rose

From: Cunningham, Meg [mailto:mcunningham@rti.org]  
Sent: Monday, February 22, 2010 9:59 AM  
To: [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; Higgins, Rosemary (NIH/NICHD) [E]; ifrantz@tuftsmedicalcenter.org; Kathleen.A.Kennedy@uth.tmc.edu; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; Wallace, Dennis; cotte010@mc.duke.edu; jon.e.tyson@uth.tmc.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; bbatton@siumed.edu  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; lmoore@med.wayne.edu; pamela.neville@duke.edu; gonza025@mc.duke.edu; Nancy.M.Smith@uth.tmc.edu; Brenda Vecchio; msumner@peds.uab.edu; Archer, Stephanie (NIH/NICHD) [E]  
Subject: Steering Committee Call Tomorrow

Dear All -

The next standing Steering Committee call is scheduled for tomorrow, Tuesday, February 23rd at 3:00pm ET.

Please Dial:  
Outside the USA 1-203-310-(b)  
or Within the USA 866-675-(b)(6)

Then, enter Participant Passcode: (b) (6)

Steering Committee Conference Call Agenda 02/23/2010

1. Early BP discussion (attached are a brief description of the time limited data collection proposal and a draft of the form which would be used.)
2. SUPPORT manuscript discussion and update
3. New Business

Thanks,  
Meg

Meg Cunningham  
RTI International  
701 13th St. NW, Ste. 750  
Washington, DC 20005  
tel: 202-974-7837  
fax: 202-728-2095  
[www.rti.org](http://www.rti.org)<<http://www.rti.org>>

**From:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**To:** "Wally Carlo, M.D."; "Finer, Neil"  
**Cc:** [Archer, Stephanie \(NIH/NICHD\) \[E\]](#)  
**Subject:** FW: All forms in for Support papers  
**Date:** Monday, March 01, 2010 11:03:00 AM

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This looks to have been taken care of –  
Thanks for all the help

Rose

---

**From:** Abel, Brendan [mailto:[babel@nejm.org](mailto:babel@nejm.org)]  
**Sent:** Monday, March 01, 2010 11:01 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Finer, Neil; Wally Carlo, M.D.  
**Subject:** All forms in for Support papers

Hi Rose,

Wanted to let you know that all forms have now been received for both (b) (6) and (b) (6). Thank you VERY much for all of your help in tracking down the forms.

Let me know if you have any questions (forms related, or not).

Best,

Brendan

Brendan Abel  
Editorial Assistant  
New England Journal of Medicine  
(617) 487-6584

This email message is a private communication. The information transmitted, including attachments, is intended only for the person or entity to which it is addressed and may contain confidential, privileged, and/or proprietary material. Any review, duplication, retransmission, distribution, or other use of, or taking of any action in reliance upon, this information by persons or entities other than the intended recipient is unauthorized by the sender and is prohibited. If you have received this message in error, please contact the sender immediately by return email and delete the original message from all computer systems. Thank you.



**From:** [Wally Carlo, M.D.](#)  
**To:** [Neil Finer](#); [Duara, Shahnaz](#); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Abhik Das](#); [Everett, Ruth](#); [wrich@ucsd.edu](#); [Michele Walsh](#); [Poole Kenneth \(E-mail\)](#); [edward.donovan@chmcc.org](#); [Jobe Alan \(E-mail\)](#)  
**Cc:** [petrie@rti.org](#); [Hastings, Betty J.](#)  
**Subject:** RE: 2 28 05 DSMC Monitoring adrev  
**Date:** Monday, February 28, 2005 9:53:45 PM

---

Because your primary outcome is combining both strata, we may want the analysis the same way. wally

-----Original Message-----

From: Neil Finer [<mailto:nfiner@ucsd.edu>]  
Sent: Monday, February 28, 2005 7:55 PM  
To: Duara, Shahnaz, Rosemary (NIH/NICHD); Abhik Das; Everett, Ruth; Wally Carlo, M.D.; [wrich@ucsd.edu](#); Michele Walsh; Poole Kenneth (E-mail); [edward.donovan@chmcc.org](#); Jobe Alan (E-mail)  
Cc: [petrie@rti.org](#); Hastings, Betty J.  
Subject: Re: 2 28 05 DSMC Monitoring adrev

Hi Shahnaz

I would hope that we use strata specific data as in the tables - then we could close an individual arm in a strata if needed.

Neil

----- Original Message -----

From: "Duara, Shahnaz" <[SDuara@med.miami.edu](mailto:SDuara@med.miami.edu)>  
To: "Neil Finer" <[nfiner@ucsd.edu](mailto:nfiner@ucsd.edu)>; "Higgins, Rosemary (NIH/NICHD)" <[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)>; "Abhik Das" <[adas@rti.org](mailto:adas@rti.org)>; "Everett, Ruth" <[REverett@med.miami.edu](mailto:REverett@med.miami.edu)>; "Carlo Waldemar (E-mail)" <[wcarlo@peds.uab.edu](mailto:wcarlo@peds.uab.edu)>; <[wrich@ucsd.edu](mailto:wrich@ucsd.edu)>; "Michele Walsh" <[mcw3@case.edu](mailto:mcw3@case.edu)>; "Poole Kenneth (E-mail)" <[poo@rti.org](mailto:poo@rti.org)>; <[edward.donovan@chmcc.org](mailto:edward.donovan@chmcc.org)>; "Jobe Alan (E-mail)" <[Jobea0@chmcc.org](mailto:Jobea0@chmcc.org)>  
Cc: <[petrie@rti.org](mailto:petrie@rti.org)>; "Hastings, Betty J." <[bkh@rti.org](mailto:bkh@rti.org)>  
Sent: Monday, February 28, 2005 3:17 PM  
Subject: RE: 2 28 05 DSMC Monitoring adrev

Hi,

Question - is it implicit in the design that stopping rules apply within GA strata? Shouldn't differences between treatment groups in one GA strata lead to stoppage for that strata but continuation of the study in the other? Do the numbers require an all or none position with respect to continuation of the study?

Shahnaz

-----Original Message-----

From: Neil Finer [<mailto:nfiner@ucsd.edu>]  
Sent: Monday, February 28, 2005 1:38 PM  
To: Higgins, Rosemary (NIH/NICHD); Abhik Das; Everett, Ruth; Carlo Waldemar (E-mail); [wrich@ucsd.edu](#); Duara, Shahnaz; Michele Walsh; Poole Kenneth (E-mail); [edward.donovan@chmcc.org](#); Jobe Alan (E-mail)  
Cc: [petrie@rti.org](#); Hastings, Betty J.  
Subject: Re: 2 28 05 DSMC Monitoring adrev

Hi Rose

I made a few changes in yellow.

Neil

----- Original Message -----

From: "Higgins, Rosemary (NIH/NICHD)" <higginsr@mail.nih.gov>  
To: "Abhik Das" <adas@rti.org>; "Neil Finer" <nfiner@ucsd.edu>; "Everett, Ruth" <REverett@med.miami.edu>; "Carlo Waldemar (E-mail)" <wcarlo@peds.uab.edu>; <wrich@ucsd.edu>; "Duara, Shahnaz" <SDuara@med.miami.edu>; "Michele Walsh" <mcw3@case.edu>; "Poole Kenneth (E-mail)" <poo@rti.org>; <edward.donovan@chmcc.org>; "Jobe Alan (E-mail)" <Jobea0@chmcc.org>  
Cc: <petrie@rti.org>; "Hastings, Betty J." <bkh@rti.org>  
Sent: Monday, February 28, 2005 7:09 AM  
Subject: 2 28 05 DSMC Monitoring adrev

>  
> Hi,  
> Last call for changes on the SUPPORT DSMC document. I would like to  
> get  
> it  
> to the steering committee by the end of the Week (march 4). Thanks for  
  
> all the input!! Rose  
> <<2 28 05 DSMC Monitoring adrev.doc>>  
>

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Incoming mail is certified Virus Free.  
Checked by AVG anti-virus system (<http://www.grisoft.com>).  
Version: 6.0.857 / Virus Database: 584 - Release Date: 2/10/2005

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Outgoing mail is certified Virus Free.  
Checked by AVG anti-virus system (<http://www.grisoft.com>).  
Version: 6.0.857 / Virus Database: 584 - Release Date: 2/10/2005

## **Higgins, Rosemary (NIH/NICHD) [E]**

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**From:** Finer, Neil <nfiner@ucsd.edu>  
**Sent:** Saturday, February 27, 2010 6:30 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** wcarlo@peds.uab.edu; dwallace@rti.org; Rich, Wade  
**Subject:** Re: Follow Up ON BPD and Oximeters

That's fine Rose  
My vote is to proceed without any changes Neil

Sent from my iPhone

On Feb 27, 2010, at 4:14 PM, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov<mailto:higginsr@mail.nih.gov>> wrote:

The subcommittee should decide. I will send an email getting input from them on Monday - this is the proper way to go.

Thanks  
Rose

---

**From:** Finer, Neil <nfiner@ucsd.edu<mailto:nfiner@ucsd.edu>>  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Wally Carlo, M.D. <WCarlo@peds.uab.edu<mailto:WCarlo@peds.uab.edu>>; Wallace, Dennis <dwallace@rti.org<mailto:dwallace@rti.org>>; Rich, Wade <wrich@ucsd.edu<mailto:wrich@ucsd.edu>>  
**Sent:** Sat Feb 27 17:10:53 2010  
**Subject:** RE: Follow Up ON BPD and Oximeters

Rose

Are you contemplating that Wally should add some kind of disclaimer?  
Let's not forget that BPD was not a primary outcome in the Saturation paper, that the differences in BPD were not significant in spite of Jon's comments – as he tends to blow with the wind relative to p values >than significance – If it suits his purpose he calls it a trend but he very opposed to us using the word trend in the CPAP when our p value was at the same level. In addition he is not an author nor is he apparently on the boilerplate.  
I guess I remain puzzled why this getting so much airtime This has moved beyond listening to his issues and he circulates all his responses to all the Pls I hope that this can be brought to closure in the very near future Neil

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Saturday, February 27, 2010 11:54 AM  
**To:** 'Jon.E.Tyson@uth.tmc.edu<mailto:Jon.E.Tyson@uth.tmc.edu>'; 'dwallace@rti.org<mailto:dwallace@rti.org>'; 'mcunningham@rti.org<mailto:mcunningham@rti.org>'; 'barbara\_stoll@oz.ped.emory.edu<mailto:barbara\_stoll@oz.ped.emory.edu>'; 'alaptook@WIHRI.org<mailto:alaptook@WIHRI.org>'; 'edward-bell@uiowa.edu<mailto:edward-bell@uiowa.edu>'; 'bpoindex@iupui.edu<mailto:bpoindex@iupui.edu>'; 'adas@rti.org<mailto:adas@rti.org>'; 'goldb008@mc.duke.edu<mailto:goldb008@mc.duke.edu>'; 'ifrantz@tuftsmedicalcenter.org<mailto:ifrantz@tuftsmedicalcenter.org>';

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'Bradley.yoder@hsc.utah.edu<mailto:'Bradley.yoder@hsc.utah.edu>;  
'rohls@salud.unm.edu<mailto:'rohls@salud.unm.edu>;  
'Luc.Brion@UTSouthwestern.edu<mailto:'Luc.Brion@UTSouthwestern.edu>;  
'dstevenson@stanford.edu<mailto:'dstevenson@stanford.edu>; Finer, Neil; Rich, Wade;  
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Cc: 'kzaterka@rti.org<mailto:'kzaterka@rti.org>; 'airene@rti.org<mailto:'airene@rti.org>;  
'petrie@rti.org<mailto:'petrie@rti.org>; 'newman@rti.org<mailto:'newman@rti.org>; Archer, Stephanie (NIH/NICHD)  
[E]  
Subject: Re: Follow Up ON BPD and Oximeters

Jon,  
Marie will return mid-week and the subcommittee can make a recommendation. The papers remain under review/revision at this point.

Rose

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From: Tyson, Jon E <Jon.E.Tyson@uth.tmc.edu<mailto:Jon.E.Tyson@uth.tmc.edu>>  
To: Wallace, Dennis <dwallace@rti.org<mailto:dwallace@rti.org>>; Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg <mcunningham@rti.org<mailto:mcunningham@rti.org>>; [SCRN] Stoll, Barbara <barbara\_stoll@oz.ped.emory.edu<mailto:barbara\_stoll@oz.ped.emory.edu>>; alaptook@WIHRI.org<mailto:alaptook@WIHRI.org> <alaptook@WIHRI.org<mailto:alaptook@WIHRI.org>>; Bell, Edward <edward-bell@uiowa.edu<mailto:edward-bell@uiowa.edu>>; bpoindex@iupui.edu<mailto:bpoindex@iupui.edu> <bpoindex@iupui.edu<mailto:bpoindex@iupui.edu>>; Das, Abhik <adas@rti.org<mailto:adas@rti.org>>; goldb008@mc.duke.edu<mailto:goldb008@mc.duke.edu> <goldb008@mc.duke.edu<mailto:goldb008@mc.duke.edu>>; ifrantz@tuftsmedicalcenter.org<mailto:ifrantz@tuftsmedicalcenter.org> <ifrantz@tuftsmedicalcenter.org<mailto:ifrantz@tuftsmedicalcenter.org>>; Kennedy, Kathleen A <Kathleen.A.Kennedy@uth.tmc.edu<mailto:Kathleen.A.Kennedy@uth.tmc.edu>>; kurt.schibler@cchmc.org<mailto:kurt.schibler@cchmc.org> <kurt.schibler@cchmc.org<mailto:kurt.schibler@cchmc.org>>; kwatterberg@salud.unm.edu<mailto:kwatterberg@salud.unm.edu> <kwatterberg@salud.unm.edu<mailto:kwatterberg@salud.unm.edu>>; matthew.bizzarro@yale.edu<mailto:matthew.bizzarro@yale.edu> <matthew.bizzarro@yale.edu<mailto:matthew.bizzarro@yale.edu>>; mcw3@cwru.edu<mailto:mcw3@cwru.edu> <mcw3@cwru.edu<mailto:mcw3@cwru.edu>>; mcaplan@northshore.org<mailto:mcaplan@northshore.org> <mcaplan@northshore.org<mailto:mcaplan@northshore.org>>; Pablo.Sanchez@UTSouthwestern.edu<mailto:Pablo.Sanchez@UTSouthwestern.edu> <Pablo.Sanchez@UTSouthwestern.edu<mailto:Pablo.Sanchez@UTSouthwestern.edu>>; richard.ehrenkranz@yale.edu<mailto:richard.ehrenkranz@yale.edu> <richard.ehrenkranz@yale.edu<mailto:richard.ehrenkranz@yale.edu>>;

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Jamie <newman@rti.org<mailto:newman@rti.org>>; Archer, Stephanie (NIH/NICHD) [E]  
Sent: Fri Feb 26 18:27:31 2010

Subject: RE: Follow Up ON BPD and Oximeters I don't understand your statement "Controlling for center adjusts for differences between centers including differences in the BPD oximeter used." To simplify the discussion, suppose every center always used the study oximeter in designating who had BPD by oxygen saturation. Because the true saturation that would prompt oxygen administration would differ in the two treatment groups, there would be systematic bias toward administering oxygen to more infants in the high sat group than in the low sat group. This is inherent in the study design. Whatever differences there were between centers, this bias would occur in every center and would not be eliminated by controlling for center. And if I understand the analysis, there would be no interaction between treatment oximeter and BPD oximeter because they would be the same in every baby in every center.

You indicate that 5 centers used the study oximeter in almost every baby. In saying "it's not possible to tease out the effect of the BPD oximeter from other between-center differences" (a statement that I certainly accept), aren't you saying that the effect of the study oximeter on the difference in the incidence of BPD by oxygen administration between high and low sat groups (i.e., the bias) can not be distinguished from the effect of the myriad of other factors in those centers that might affect that difference in incidence? If so, why would you expect to be able to discern that bias (the signal) from all the noise resulting from other factors? I understand from what you said that the same approach was used in virtually all infants in each center which makes the effective n to be based on the number of centers rather than the number of babies. As I understand the analysis, the power to assess an interaction would then be quite low.

The issue here is whether is simply whether to report somewhere in the paper (which could be noted under the table and wouldn't increase the word count for the text) a bias in evaluating a secondary outcome. This can be done with no delay in submitting the manuscript or waiting for Maria to return. If we had other real or potential sources of bias—say, a breaking of the blind for some infants, open label administration of a study drug to the control group, or differential loss to follow-up, we would certainly report it as a matter of course, whether or not there was a significant or near significant difference in the outcome and without testing and whether or not we assessed or found any interaction or other statistical evidence that this potential source of bias affected the results!

Jon E. Tyson, MD, MPH  
Center for Clinical Research & Evidence-Based Medicine UT Medical School at Houston  
6431 Fannin St., MSB 2.106  
Houston, TX 77030  
voice 713-500-5651  
fax 713-500-0519

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From: Wallace, Dennis [mailto:dwallace@rti.org]  
Sent: Friday, February 26, 2010 1:56 PM  
To: Wallace, Dennis; Tyson, Jon E; Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara; alaptook@WIHRI.org<mailto:alaptook@WIHRI.org>; Bell, Edward; bpoindex@iupui.edu<mailto:bpoindex@iupui.edu>; Das, Abhik; goldb008@mc.duke.edu<mailto:goldb008@mc.duke.edu>; ifrantz@tuftsmedicalcenter.org<mailto:ifrantz@tuftsmedicalcenter.org>; Kennedy, Kathleen A; kurt.schibler@cchmc.org<mailto:kurt.schibler@cchmc.org>; kwatterberg@salud.unm.edu<mailto:kwatterberg@salud.unm.edu>; matthew.bizarro@yale.edu<mailto:matthew.bizarro@yale.edu>; mcw3@cwru.edu<mailto:mcw3@cwru.edu>; mcaplan@northshore.org<mailto:mcaplan@northshore.org>; Pablo.Sanchez@UTSouthwestern.edu<mailto:Pablo.Sanchez@UTSouthwestern.edu>; richard.ehrenkranz@yale.edu<mailto:richard.ehrenkranz@yale.edu>; Roger.Faix@hsc.utah.edu<mailto:Roger.Faix@hsc.utah.edu>; sshankar@med.wayne.edu<mailto:sshankar@med.wayne.edu>; vanmeurs@leland.stanford.edu<mailto:vanmeurs@leland.stanford.edu>; Wally Carlo, M.D.; cotte010@mc.duke.edu<mailto:cotte010@mc.duke.edu>; Bradley Yoder; rohls@salud.unm.edu<mailto:rohls@salud.unm.edu>; Luc.Brion@utsouthwestern.edu<mailto:Luc.Brion@utsouthwestern.edu>; Stevenson David (E-mail); Finer, Neil; Rich, Wade; Gantz, Marie  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]  
Subject: RE: Follow Up ON BPD and Oximeters

Hello all,

I accidentally hit the send button before finishing editing this response so ignore the earlier e-mail and see the response below.

Dennis

Dennis Wallace  
Senior Research Statistician  
Cox 241  
RTI International  
3040 Cornwallis Rd  
Research Triangle Park, NC 27709-2104  
Voice: 919-541-6271  
Fax: 919-541-6416

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From: Wallace, Dennis  
Sent: Friday, February 26, 2010 2:53 PM  
To: 'Tyson, Jon E'; Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara; alaptook@WIHRI.org<mailto:alaptook@WIHRI.org>; Bell, Edward; bpoindex@iupui.edu<mailto:bpoindex@iupui.edu>; Das, Abhik; goldb008@mc.duke.edu<mailto:goldb008@mc.duke.edu>; ifrantz@tuftsmedicalcenter.org<mailto:ifrantz@tuftsmedicalcenter.org>; Kennedy, Kathleen A; kurt.schibler@cchmc.org<mailto:kurt.schibler@cchmc.org>; kwatterberg@salud.unm.edu<mailto:kwatterberg@salud.unm.edu>; matthew.bizarro@yale.edu<mailto:matthew.bizarro@yale.edu>; mcw3@cwru.edu<mailto:mcw3@cwru.edu>; mcaplan@northshore.org<mailto:mcaplan@northshore.org>; Pablo.Sanchez@UTSouthwestern.edu<mailto:Pablo.Sanchez@UTSouthwestern.edu>; richard.ehrenkranz@yale.edu<mailto:richard.ehrenkranz@yale.edu>; Roger.Faix@hsc.utah.edu<mailto:Roger.Faix@hsc.utah.edu>;

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Luc.Brion@utsouthwestern.edu<mailto:Luc.Brion@utsouthwestern.edu>; 'Stevenson David (E-mail)'; 'Finer, Neil'; Rich,  
Wade; Gantz, Marie  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]  
Subject: RE: Follow Up ON BPD and Oximeters

Jon,

Marie flew out on a long-scheduled vacation after completing these analyses late Tuesday evening and has very limited e-mail and cell phone access. However, she has taken time to provide a preliminary response that I've outlined below with some added thoughts of my own in red font below. Based on these responses, I do believe that the critical concerns about bias have been addressed sufficiently for this initial manuscript, but if you think we need to have a more full discussion, we can talk after Marie returns next week. Because the programming for these outcome measures is relatively complicated, I'm hesitant to try to do any additional analyses prior to her return. However, as I indicated above, I don't think that we need to delay any submissions while trying to iron on the small details.

Dennis Wallace

Senior Research Statistician

Cox 241

RTI International

3040 Cornwallis Rd

Research Triangle Park, NC 27709-2104

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-----Original Message-----

From: Tyson, Jon E [mailto:Jon.E.Tyson@uth.tmc.edu]

Sent: Thursday, February 25, 2010 12:45 AM

To: Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara;

alaptook@WIHRI.org<mailto:alaptook@WIHRI.org>; Bell, Edward; bpoindex@iupui.edu<mailto:bpoindex@iupui.edu>;

Das, Abhik; goldb008@mc.duke.edu<mailto:goldb008@mc.duke.edu>;

ifrantz@tuftsmedicalcenter.org<mailto:ifrantz@tuftsmedicalcenter.org>; Kennedy, Kathleen A;

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Luc.Brion@utsouthwestern.edu<mailto:Luc.Brion@utsouthwestern.edu>; 'Stevenson David (E-mail)'; 'Finer, Neil'; Rich,  
Wade; Gantz, Marie  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]  
Subject: RE: Follow Up ON BPD and Oximeters

Rose, before we can understand and interpret this information noted in the mail, we really need to know more about what was done and answers to questions like those below:

1. Which trial result was addressed – whether the evaluation of BPD was biased in the analyses of CPAP/limited ventilation vs. surfactant/conventional ventilation arm (not the analysis for which there is concern) or the analyses of the high vs. low oxygen saturation goal.

Although models were run for the different arms of the factorial design, the trial result that was addressed in the earlier e-mail was the impact of different oximeters on the comparison of the effects high vs. low oxygen saturation targets on BPD and BPD/death outcomes, which we believe is the question of interest.

2. Do we have reliable data to know whether individual infants were monitored on the study oximeter or on the clinical oximeter on the day the infant was 36 weeks and 0 and whether the oximeter was changed part way through that 24 hour period? What was done if the infant was switched on that day. As I understand it, the diagnosis of BPD was based on the entire 24 hours the day the infant was 36 weeks 0 days. Though the results of the survey weren't distributed, my impression from responses to my earlier e mails was that even the procedure usually followed in individual centers was not necessarily clear.

We can determine from form PHY02 what oximeter was used to determine the physiologic definition of BPD, but we do not have the detailed level of information that you described. However, based on the survey results, we do know that only 5 sites used the study oximeter for an oxygen-based definition, and only 3 used the study oximeter for challenge.

3. What variables in the model when the BPD oximeter was added? What variables were in the model when a BPD oximeter x study treatment group was added?



Variables in the model were treatment oximeter (low vs. high), center, GA group. Familial clustering was adjusted for as a random effect. I added BPD oximeter and also looked at the interaction between BPD oximeter and treatment oximeter. These factors were identical to the factors used in the models for which secondary outcomes were reported in the manuscript.

4. Do I understand Maria and you to conclude that because centers tended to be consistent in their oximeter use, controlling for center would prevent a biased assessment of the effect on BPD by oxygen administration?

This comment makes me wonder if the analysis was done for the wrong comparison. This conclusion would be correct for analyses of the effect of CPAP/limited ventilation vs. surfactant/ conventional ventilation on BPD by oxygen delivery (because each treatment arm would contain equal numbers of infants in the high and low sat groups). However, this isn't the comparison in question. This conclusion would certainly not be correct in analyzing the effect of high vs low sat goals on BPD. In this analysis, centers that used the study oximeter would be systematically more likely to administer oxygen to the high sat group than to the low sat group. The problem wouldn't go away by controlling for center, and the more centers that used the study oximeter, the more biased the result would be. How many centers were there that used the study oximeter?

Controlling for center adjusts for differences between centers including differences in the BPD oximeter used. Thus, adding a covariate for BPD oximeter does not change the estimates for the treatment oximeter effect. We are not arguing that the BPD oximeter used did not have an impact. We did find that BPD oximeter was significant in the models, as was center. However, since center and BPD oximeter are strongly confounded (in fact we have almost complete aliasing of center and clinical/study oximeter), it's not possible to tease out the effect of the BPD oximeter from other between-center differences. In addition, the interaction between BPD oximeter and treatment oximeter was not significant. This indicates that the impact of treatment oximeter on the BPD outcomes was not significantly different in the centers that used the study oximeters to determine BPD and those that used the clinical oximeters.

5. What is the basis for believing that there would be anything near reasonable power to assess a oximeter x treatment group interaction?

Clearly, these analyses were conducted from a post-hoc perspective, and the study was never designed to have the power to determine that the interaction in our data set is statistically significant for a pre-specified interaction effect size. But, that is not a shortcoming unless the magnitude of the interaction effect is such that it represents an important scientific bias in study interpretation. Our preliminary analyses indicate that biases of such magnitude are not present in this data set. We can do more detailed analyses of the level of bias that might have been introduced after Marie returns

from vacation, but nothing in the analyses conducted to date suggest that those magnitudes warrant delay of submission of this manuscript.

I know that everyone is anxious to get this paper submitted. While I have an external advisory committee tomorrow, I will try to respond tomorrow night if the information requested above is sent tomorrow during the day.

---

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]

Sent: Wednesday, February 24, 2010 7:53 AM

To: Tyson, Jon E; 'Cunningham, Meg'; [SCRN] Stoll, Barbara; alaptook@WIHRI.org<mailto:alaptook@WIHRI.org>; Bell, Edward; bpoindex@iupui.edu<mailto:bpoindex@iupui.edu>; Das, Abhik; goldb008@mc.duke.edu<mailto:goldb008@mc.duke.edu>; ifrantz@tuftsmedicalcenter.org<mailto:ifrantz@tuftsmedicalcenter.org>; Kennedy, Kathleen A; kurt.schibler@cchmc.org<mailto:kurt.schibler@cchmc.org>; kwatterberg@salud.unm.edu<mailto:kwatterberg@salud.unm.edu>; matthew.bizzarro@yale.edu<mailto:matthew.bizzarro@yale.edu>; mcw3@cwru.edu<mailto:mcw3@cwru.edu>; mcaplan@northshore.org<mailto:mcaplan@northshore.org>; Pablo.Sanchez@UTSouthwestern.edu<mailto:Pablo.Sanchez@UTSouthwestern.edu>; richard.ehrenkranz@yale.edu<mailto:richard.ehrenkranz@yale.edu>; Roger.Faix@hsc.utah.edu<mailto:Roger.Faix@hsc.utah.edu>; sshankar@med.wayne.edu<mailto:sshankar@med.wayne.edu>; vanmeurs@leland.stanford.edu<mailto:vanmeurs@leland.stanford.edu>; Wally Carlo, M.D.; Wallace, Dennis; cotte010@mc.duke.edu<mailto:cotte010@mc.duke.edu>; Bradley Yoder; rohls@salud.unm.edu<mailto:rohls@salud.unm.edu>; Luc.Brion@utsouthwestern.edu<mailto:Luc.Brion@utsouthwestern.edu>; 'Stevenson David (E-mail)'; 'Finer, Neil'; Rich, Wade; Gantz, Marie

Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]

Subject: Follow Up ON BPD and Oximeters

Hi all –

In Follow up to yesterday's discussion, Marie spent a great deal of time last evening running additional analyses to address (and now alleviate) Jon's concern as described:

We have looked into the question of whether the oximeter used to determine BPD impacted the BPD and death/BPD outcomes by adding a covariate for the BPD oximeter (study or clinical) to the statistical models. We found that the effect of the BPD oximeter was significant; however, the interaction between BPD oximeter and treatment oximeter

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---

From: Tyson, Jon E [mailto:Jon.E.Tyson@uth.tmc.edu]

Sent: Tuesday, February 23, 2010 4:33 PM

To: Higgins, Rosemary (NIH/NICHD) [E]; 'Cunningham, Meg'; [SCRN] Stoll, Barbara; alaptook@WIHRI.org<mailto:alaptook@WIHRI.org>; Bell, Edward; bpoindex@iupui.edu<mailto:bpoindex@iupui.edu>; Das, Abhik; goldb008@mc.duke.edu<mailto:goldb008@mc.duke.edu>; ifrantz@tuftsmedicalcenter.org<mailto:ifrantz@tuftsmedicalcenter.org>; Kennedy, Kathleen A; kurt.schibler@cchmc.org<mailto:kurt.schibler@cchmc.org>; kwatterberg@salud.unm.edu<mailto:kwatterberg@salud.unm.edu>; matthew.bizarro@yale.edu<mailto:matthew.bizarro@yale.edu>; mcw3@cwru.edu<mailto:mcw3@cwru.edu>; mcaplan@northshore.org<mailto:mcaplan@northshore.org>; Pablo.Sanchez@UTSouthwestern.edu<mailto:Pablo.Sanchez@UTSouthwestern.edu>; richard.ehrenkranz@yale.edu<mailto:richard.ehrenkranz@yale.edu>; Roger.Faix@hsc.utah.edu<mailto:Roger.Faix@hsc.utah.edu>; sshankar@med.wayne.edu<mailto:sshankar@med.wayne.edu>; vanmeurs@leland.stanford.edu<mailto:vanmeurs@leland.stanford.edu>; Wally Carlo, M.D.; Wallace, Dennis; cotte010@mc.duke.edu<mailto:cotte010@mc.duke.edu>; Bradley Yoder; rohls@salud.unm.edu<mailto:rohls@salud.unm.edu>; Luc.Brion@utsouthwestern.edu<mailto:Luc.Brion@utsouthwestern.edu>; <mailto:bbatton@siumed.edu> bbatton@siumed.edu<mailto:bbatton@siumed.edu>

Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; lmoore@med.wayne.edu<mailto:lmoore@med.wayne.edu>; pamela.neville@duke.edu<mailto:pamela.neville@duke.edu>; gonza025@mc.duke.edu<mailto:gonza025@mc.duke.edu>; Smith, Nancy M; Brenda Vecchio; msumner@peds.uab.edu<mailto:msumner@peds.uab.edu>; Archer, Stephanie (NIH/NICHD) [E]

Subject: RE: Steering Committee Call Tomorrow

While it may seem that I am fixated on an unimportant issue regarding a not quite significant difference, I think we undermine the credibility of Network studies if we are not completely forthright about problems in measuring what everyone would agree is an important secondary outcome. Not reporting that the assessment of BPD by oxygen administration could be biased by continued use of the study oximeters would seem to be in the category of not reporting protocol deviations and not something that is in the Network's best interest. Why not just put a footnote under the table describing the problem?

Jon E. Tyson, MD, MPH

Center for Clinical Research & Evidence-Based Medicine

UT Medical School at Houston

6431 Fannin St., MSB 2.106

Houston, TX 77030

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---

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]

Sent: Tuesday, February 23, 2010 2:11 PM

To: 'Cunningham, Meg'; [SCRN] Stoll, Barbara; alaptook@WIHRI.org<mailto:alaptook@WIHRI.org>; Bell, Edward; bpoindex@iupui.edu<mailto:bpoindex@iupui.edu>; Das, Abhik; goldb008@mc.duke.edu<mailto:goldb008@mc.duke.edu>; ifrantz@tuftsmedicalcenter.org<mailto:ifrantz@tuftsmedicalcenter.org>; Kennedy, Kathleen A; kurt.schibler@cchmc.org<mailto:kurt.schibler@cchmc.org>; kwatterberg@salud.unm.edu<mailto:kwatterberg@salud.unm.edu>; matthew.bizarro@yale.edu<mailto:matthew.bizarro@yale.edu>; mcw3@cwru.edu<mailto:mcw3@cwru.edu>; mcaplan@northshore.org<mailto:mcaplan@northshore.org>; Pablo.Sanchez@UTSouthwestern.edu<mailto:Pablo.Sanchez@UTSouthwestern.edu>; richard.ehrenkranz@yale.edu<mailto:richard.ehrenkranz@yale.edu>; Roger.Faix@hsc.utah.edu<mailto:Roger.Faix@hsc.utah.edu>; sshankar@med.wayne.edu<mailto:sshankar@med.wayne.edu>; vanmeurs@leland.stanford.edu<mailto:vanmeurs@leland.stanford.edu>; Wally Carlo, M.D.; Wallace, Dennis; cotte010@mc.duke.edu<mailto:cotte010@mc.duke.edu>; Tyson, Jon E; Bradley Yoder; rohls@salud.unm.edu<mailto:rohls@salud.unm.edu>; Luc.Brion@utsouthwestern.edu<mailto:Luc.Brion@utsouthwestern.edu>; <mailto:bbatton@siumed.edu> bbatton@siumed.edu<mailto:bbatton@siumed.edu>

Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; lmoore@med.wayne.edu<mailto:lmoore@med.wayne.edu>; pamela.neville@duke.edu<mailto:pamela.neville@duke.edu>; gonza025@mc.duke.edu<mailto:gonza025@mc.duke.edu>; Smith, Nancy M; Brenda Vecchio; msumner@peds.uab.edu<mailto:msumner@peds.uab.edu>; Archer, Stephanie (NIH/NICHD) [E]

Subject: RE: Steering Committee Call Tomorrow

If you joined the call already in progress, please send us an email so we can count your attendance.

Rose

---

From: Cunningham, Meg [mailto:mcunningham@rti.org]

Sent: Monday, February 22, 2010 9:59 AM

To: [SCRN] Stoll, Barbara; alaptook@WIHRI.org<mailto:alaptook@WIHRI.org>; Bell, Edward; bpoindex@iupui.edu<mailto:bpoindex@iupui.edu>; Das, Abhik; goldb008@mc.duke.edu<mailto:goldb008@mc.duke.edu>; Higgins, Rosemary (NIH/NICHD) [E]; ifrantz@tuftsmedicalcenter.org<mailto:ifrantz@tuftsmedicalcenter.org>; Kathleen.A.Kennedy@uth.tmc.edu<mailto:Kathleen.A.Kennedy@uth.tmc.edu>; kurt.schibler@cchmc.org<mailto:kurt.schibler@cchmc.org>; kwatterberg@salud.unm.edu<mailto:kwatterberg@salud.unm.edu>; matthew.bizarro@yale.edu<mailto:matthew.bizarro@yale.edu>; mcw3@cwru.edu<mailto:mcw3@cwru.edu>; mcaplan@northshore.org<mailto:mcaplan@northshore.org>; Pablo.Sanchez@UTSouthwestern.edu<mailto:Pablo.Sanchez@UTSouthwestern.edu>; richard.ehrenkranz@yale.edu<mailto:richard.ehrenkranz@yale.edu>; Roger.Faix@hsc.utah.edu<mailto:Roger.Faix@hsc.utah.edu>; sshankar@med.wayne.edu<mailto:sshankar@med.wayne.edu>; vanmeurs@leland.stanford.edu<mailto:vanmeurs@leland.stanford.edu>; Wally Carlo, M.D.; Wallace, Dennis; cotte010@mc.duke.edu<mailto:cotte010@mc.duke.edu>; jon.e.tyson@uth.tmc.edu<mailto:jon.e.tyson@uth.tmc.edu>; Bradley Yoder; rohls@salud.unm.edu<mailto:rohls@salud.unm.edu>; Luc.Brion@utsouthwestern.edu<mailto:Luc.Brion@utsouthwestern.edu>; <mailto:bbatton@siumed.edu> bbatton@siumed.edu<mailto:bbatton@siumed.edu>

Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; lmoore@med.wayne.edu<mailto:lmoore@med.wayne.edu>; pamela.neville@duke.edu<mailto:pamela.neville@duke.edu>; gonza025@mc.duke.edu<mailto:gonza025@mc.duke.edu>; Nancy.M.Smith@uth.tmc.edu<mailto:Nancy.M.Smith@uth.tmc.edu>; Brenda Vecchio; msumner@peds.uab.edu<mailto:msumner@peds.uab.edu>; Archer, Stephanie (NIH/NICHD) [E]

Subject: Steering Committee Call Tomorrow

Dear All -

The next standing Steering Committee call is scheduled for tomorrow, Tuesday, February 23rd at 3:00pm ET.

Please Dial:

Outside the USA 1-203-310-(b)

or Within the USA 866-675-(b)

Then, enter Participant Passcode: (b) (6)

#### Steering Committee Conference Call Agenda 02/23/2010

1. Early BP discussion (attached are a brief description of the time limited data collection proposal and a draft of the form which would be used.)
2. SUPPORT manuscript discussion and update
3. New Business

Thanks,

Meg

Meg Cunningham

RTI International

701 13th St. NW, Ste. 750

Washington, DC 20005

tel: 202-974-7837

fax: 202-728-2095

www.rti.org<<http://www.rti.org>><<http://www.rti.org>>

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "dwallace@rti.org"  
**Subject:** Re: Follow Up ON BPD and Oximeters  
**Date:** Saturday, February 27, 2010 2:41:49 PM

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We should probably wait until Marie returns.

---

**From:** Wallace, Dennis <dwallace@rti.org>  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Sat Feb 27 14:31:51 2010  
**Subject:** RE: Follow Up ON BPD and Oximeters

It obviously didn't work, as I got back into the office for a few minutes today to find the e-mail from Jon and a voice mail wanting him to call. I need to get to the hospital this afternoon to see my father-in-law, but I'll try to respond to his e-mail either this evening or tomorrow morning. My strategy with this next e-mail is that we always have some potential for many sources of bias in any trial that isn't a random selection from the full population of subjects, but we don't try to address all of those in the primary manuscript. We don't see the potential as substantial for this issue, and don't see a reason to highlight it in this manuscript. However, when Marie returns, we'll do some added analyses to present to the steering committee to try to address his concerns. I don't see what else we can do at this point, but I'll take any suggestions you have.

Dennis

Dennis Wallace  
Senior Research Statistician  
Cox 241  
RTI International  
3040 Cornwallis Rd  
Research Triangle Park, NC 27709-2104  
Voice: 919-541-6271  
Fax: 919-541-6416

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Friday, February 26, 2010 2:58 PM  
**To:** Wallace, Dennis  
**Subject:** RE: Follow Up ON BPD and Oximeters

BLESS YOU!!!

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network

---

**From:** Wallace, Dennis [mailto:dwallace@rti.org]  
**Sent:** Friday, February 26, 2010 2:57 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Follow Up ON BPD and Oximeters

Rose,

The text on this one probably doesn't make much sense as I hit send accidentally while editing. I sent a follow-up that's completely edited.

Dennis

Dennis Wallace

Senior Research Statistician  
Cox 241  
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3040 Cornwallis Rd  
Research Triangle Park, NC 27709-2104  
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---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Friday, February 26, 2010 2:54 PM  
**To:** Wallace, Dennis  
**Subject:** RE: Follow Up ON BPD and Oximeters

Thank you!!!

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network

---

**From:** Wallace, Dennis [mailto:dwallace@rti.org]  
**Sent:** Friday, February 26, 2010 2:53 PM  
**To:** Tyson, Jon E; Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; Stevenson David (E-mail); Finer, Neil; Rich, Wade; Gantz, Marie  
**Cc:** Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: Follow Up ON BPD and Oximeters

Jon,

Marie flew out on a long-scheduled vacation after completing these analyses late Tuesday evening and has very limited e-mail and cell phone access. However, she has taken time to provide a preliminary response that I've outlined below with some added thoughts of my own in red font below. Based on these responses, I do believe that the critical concerns about bias have been addressed sufficiently for this initial manuscript, but if you think we need to have a more full discussion, we can talk after Marie returns next week. Because the programming for these outcome measures is relatively complicated, I'm hesitant to try to do any additional analyses prior to her return. Because of the g I did try to call yesterday without success, so I'll try to give the best responses I can to your e-mail based on review of her programs. I wasn't able to find her actual output, but I'll keep trying to touch base and perhaps be able to provide more complete answers after I talk with her.

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Voice: 919-541-6271  
Fax: 919-541-6416

-----Original Message-----

**From:** Tyson, Jon E [mailto:Jon.E.Tyson@uth.tmc.edu]  
**Sent:** Thursday, February 25, 2010 12:45 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A;



kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu;  
matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org;  
Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu;  
Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu;  
vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; Wallace, Dennis;  
cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu;  
Luc.Brion@utsouthwestern.edu; 'Stevenson David (E-mail)'; 'Finer, Neil';  
Rich, Wade; Gantz, Marie

Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]  
Subject: RE: Follow Up ON BPD and Oximeters

Rose, before we can understand and interpret this information noted in the mail, we really need to know more about what was done and answers to questions like those below:

1. Which trial result was addressed - whether the evaluation of BPD was biased in the analyses of CPAP/limited ventilation vs. surfactant/conventional ventilation arm (not the analysis for which there is concern) or the analyses of the high vs. low oxygen saturation goal.

Although models were run for the different arms of the factorial design, the trial result that was addressed in the earlier e-mail was the impact of different oximeters on the comparison of the effects high vs. low oxygen saturation targets on BPD and BPD/death outcomes, which we believe is the question of interest.

2. Do we have reliable data to know whether individual infants were monitored on the study oximeter or on the clinical oximeter on the day the infant was 36 weeks and 0 and whether the oximeter was changed part way through that 24 hour period? What was done if the infant was switched on that day. As I understand it, the diagnosis of BPD was based on the entire 24 hours the day the infant was 36 weeks 0 days. Though the results of the survey weren't distributed, my impression from responses to my earlier e mails was that even the procedure usually followed in individual centers was not necessarily clear.

We can determine from form PHY02 what oximeter was used to determine the physiologic definition of BPD, but we do not have the detailed level of information that you described. However, based on the survey results, we do know that only 5 sites used the study oximeter for an oxygen-based definition, and only 3 used the study oximeter for challenge.

3. What variables in the model when the BPD oximeter was added? What variables were in the model when a BPD oximeter x study treatment group was added?

Variables in the model were treatment oximeter (low vs. high), center, GA group. Familial clustering was adjusted for as a random effect. I added BPD oximeter and also looked at the interaction between BPD oximeter and treatment oximeter. These factors were identical to the factors used in the models for which secondary outcomes were reported in the manuscript.

4. Do I understand Maria and you to conclude that because centers tended to be consistent in their oximeter use, controlling for center would prevent a biased assessment of the effect on BPD by oxygen administration?

This comment makes me wonder if the analysis was done for the wrong comparison, This conclusion would be correct for analyses of the effect of CPAP/limited ventilation vs. surfactant/ conventional ventilation on BPD by oxygen delivery (because each treatment arm would contain equal numbers of infants in the high and low sat groups). However, this isn't the comparison in question. This conclusion would certainly not be correct in analyzing the effect of high vs low sat goals on BPD. In this analysis, centers that used the study oximeter would be systematically more likely to administer oxygen to the high sat group than to the low sat group. The problem wouldn't go away by controlling for center, and the more centers that used the study oximeter, the more biased the result would be. How many centers were there that used the study oximeter?

Controlling for center adjusts for differences between centers including differences in the BPD oximeter used. Thus, adding a covariate for BPD oximeter does not change the estimates for the treatment oximeter effect. We are not arguing that the BPD oximeter used did not have an impact. We did find that BPD oximeter was significant in the models, as was center. However, since center and BPD oximeter are strongly confounded (in fact we have almost complete aliasing of center and clinical/study oximeter), it's not possible to tease out the effect of the BPD oximeter from other between-center differences. In addition, the interaction between BPD oximeter and treatment oximeter was not significant. This indicates that the impact of treatment oximeter on the BPD outcomes was not significantly different in the centers that used the study oximeters to determine BPD and those that used the clinical oximeters.

5. What is the basis for believing that there would be anything near reasonable power to assess a oximeter x treatment group interaction?

Clearly, these analyses were conducted from a post-hoc perspective, and the study was never designed to have the power to determine that the interaction in our data set is statistically significant for a pre-specified interaction effect size. But, that is not a shortcoming unless the magnitude of the interaction effect is such that it represents an important scientific bias in study interpretation. Our preliminary analyses indicate that biases of such magnitude are not present in this data set. We can do more detailed analyses of the level of bias that might have been introduced after Marie returns from vacation, but nothing in the analyses conducted to date suggest that those magnitudes warrant delay of submission of this manuscript.

I know that everyone is anxious to get this paper submitted. While I have an external advisory committee tomorrow, I will try to respond tomorrow night if the information requested above is sent tomorrow during the day.

---

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]  
Sent: Wednesday, February 24, 2010 7:53 AM  
To: Tyson, Jon E; 'Cunningham, Meg'; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; Wallace, Dennis; cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; 'Stevenson David (E-mail)'; 'Finer, Neil'; Rich, Wade; Gantz, Marie  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]  
Subject: Follow Up ON BPD and Oximeters

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From: Tyson, Jon E [mailto:Jon.E.Tyson@uth.tmc.edu]

Sent: Tuesday, February 23, 2010 4:33 PM  
To: Higgins, Rosemary (NIH/NICHD) [E]; 'Cunningham, Meg'; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; Wallace, Dennis; cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; bbatton@siumed.edu  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; lmoore@med.wayne.edu; pamela.neville@duke.edu; gonza025@mc.duke.edu; Smith, Nancy M; Brenda Vecchio; msumner@peds.uab.edu; Archer, Stephanie (NIH/NICHD) [E]  
Subject: RE: Steering Committee Call Tomorrow

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Jon E. Tyson, MD, MPH  
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UT Medical School at Houston  
6431 Fannin St., MSB 2.106  
Houston, TX 77030  
voice 713-500-5651  
fax 713-500-0519

---

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Sent: Tuesday, February 23, 2010 2:11 PM  
To: 'Cunningham, Meg'; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; Wallace, Dennis; cotte010@mc.duke.edu; Tyson, Jon E; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; bbatton@siumed.edu  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; lmoore@med.wayne.edu; pamela.neville@duke.edu; gonza025@mc.duke.edu; Smith, Nancy M; Brenda Vecchio; msumner@peds.uab.edu; Archer, Stephanie (NIH/NICHD) [E]  
Subject: RE: Steering Committee Call Tomorrow

If you joined the call already in progress, please send us an email so we can count your attendance.

Rose

---

From: Cunningham, Meg [mailto:mcunningham@rti.org]  
Sent: Monday, February 22, 2010 9:59 AM  
To: [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; Higgins, Rosemary (NIH/NICHD) [E]; ifrantz@tuftsmedicalcenter.org; Kathleen.A.Kennedy@uth.tmc.edu; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; Wallace, Dennis; cotte010@mc.duke.edu; jon.e.tyson@uth.tmc.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; bbatton@siumed.edu  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; lmoore@med.wayne.edu; pamela.neville@duke.edu; gonza025@mc.duke.edu; Nancy.M.Smith@uth.tmc.edu; Brenda Vecchio; msumner@peds.uab.edu; Archer,

Stephanie (NIH/NICHD) [E]  
Subject: Steering Committee Call Tomorrow

Dear All -

The next standing Steering Committee call is scheduled for tomorrow, Tuesday, February 23rd at 3:00pm ET.

Please Dial:

Outside the USA 1-203-310-(b)

or Within the USA 866-675-(b)

Then, enter Participant Passcode: (b) (6) ■

Steering Committee Conference Call Agenda 02/23/2010

1. Early BP discussion (attached are a brief description of the time limited data collection proposal and a draft of the form which would be used.)
2. SUPPORT manuscript discussion and update
3. New Business

Thanks,  
Meg

Meg Cunningham  
RTI International  
701 13th St. NW, Ste. 750  
Washington, DC 20005  
tel: 202-974-7837  
fax: 202-728-2095  
www.rti.org<<http://www.rti.org>>

**From:** [Kristi Watterberg](#)  
**To:** [Michele Walsh](#); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Ronald N Goldberg](#); [matt\\_laughon@med.unc.edu](mailto:matt_laughon@med.unc.edu); [Dennis Wallace](#); [Kathleen A Kennedy](#); [richard.ehrenkranz@yale.edu](mailto:richard.ehrenkranz@yale.edu)  
**Subject:** Re: RE: RE: SUPPORT data  
**Date:** Saturday, February 27, 2010 11:48:27 AM

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Ron, if HC works, all the outcome and side effect data would support its use as the primary drug, superceding dex. If it doesn't work, we would have that answer cleanly, and could then proceed to look at dex again in a separate trial - which would again give us a clean answer. We take the risk of futility (as always), but the benefit of a clear answer, a much shorter time line, and a more do-able study. Kristi

>>> Ronald N Goldberg <goldb008@mc.duke.edu> 2/25/2010 9:01 AM >>>

Hi Dennis,

As there is much experience with dexamethasone why can't a Bayesian (spelling?) approach be used to allow us to answer this question with fewer patients.

I think including an arm for dex is essential.

Ron

---

**From:** "Wallace, Dennis" [dwallace@rti.org]  
**Sent:** 02/24/2010 06:07 PM EST  
**To:** "Kristi Watterberg" <KWatterberg@salud.unm.edu>; "Rosemary (NIH/NICHD) Higgins" <higginsr@mail.nih.gov>; Ronald Goldberg; <matt\_laughon@med.unc.edu>; "Michelle Walsh" <mcw3@po.cwru.edu>; "Das, Abhik" <adas@rti.org>; <Kathleen.A.Kennedy@uth.tmc.edu>; <richard.ehrenkranz@yale.edu>  
**Subject:** RE: RE: RE: SUPPORT data

Kristi,

Thanks for forwarding these. As a consequence of (b) (6), I'm behind on getting the formal power calculations for a three-arm trial done. As I said in the earlier e-mail, I know that the sample size for 3 arms will be between 1200 and 1440 and probably about half way between. If we're seriously going to consider a 3-arm design, I'll go ahead with the programming for that, although it looks like it will take a bit more work than I originally thought. However, if we're not going to consider that design, then I'm not sure of the benefit of trying to refine these numbers. What are your thoughts? I'd also like to comment on Matt's suggestion regarding doing the 3-arm study with a plan to compare the HC and Dex arms while acknowledging that we haven't powered the study to do that. Assuming that the prevalence of an outcome of interest is in the 40% to 60% range, the half width of 95% confidence interval for the difference in prevalence of the outcomes is about 7%, which is 70% of the magnitude of the treatment effect that we're powering the study to find compared to placebo.

I really have concerns about planning to do an analysis that provides such imprecise information for comparing two active treatment arms, when an effect of that magnitude is clearly clinically significant. I'm concerned that taking such an approach will damage the scientific reputation of the Network. If we really want to compare two active treatments, we need to define a region of clinical indifference (whether that be 3%, 5%, or 7%) and then design the study to ensure that we have the power to demonstrate equivalence if the two treatments are really clinically equivalent.

Dennis

Dennis Wallace  
Senior Research Statistician  
Cox 241  
RTI International  
3040 Cornwallis Rd  
Research Triangle Park, NC 27709-2104  
Voice: 919-541-6271

Fax: 919-541-6416

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**From:** Kristi Watterberg [mailto:KWatterberg@salud.unm.edu]

**Sent:** Wednesday, February 24, 2010 4:24 PM

**To:** Rosemary (NIH/NICHD) Higgins; goldb008@mc.duke.edu; matt\_laughon@med.unc.edu; Michelle Walsh; Das, Abhik; Wallace, Dennis; Kathleen.A.Kennedy@uth.tmc.edu; richard.ehrenkranz@yale.edu

**Subject:** Fwd: RE: RE: SUPPORT data

Matt's comments ~ Kristi

**From:** [Kristi Watterberg](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Subject:** RE: RE: SUPPORT data  
**Date:** Saturday, February 27, 2010 8:13:56 AM

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thanks!

>>> "Higgins, Rosemary (NIH/NICHD) [E]" <[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)> 2/25/2010 8:55 AM >>>

The advisory board approved the study as a two armed trial. I have attached the version of the protocol that was sent to the advisory board/outside reviewers.

Rose

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**From:** Kristi Watterberg [<mailto:KWatterberg@salud.unm.edu>]  
**Sent:** Wednesday, February 24, 2010 11:20 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; [goldb008@mc.duke.edu](mailto:goldb008@mc.duke.edu); [matt\\_laughon@med.unc.edu](mailto:matt_laughon@med.unc.edu); Michelle Walsh; [adas@rti.org](mailto:adas@rti.org); Dennis Wallace; [Kathleen.A.Kennedy@uth.tmc.edu](mailto:Kathleen.A.Kennedy@uth.tmc.edu); [richard.ehrenkranz@yale.edu](mailto:richard.ehrenkranz@yale.edu)  
**Subject:** Fwd: RE: SUPPORT data

Hello, all. I am forwarding Marie's data regarding infants who remain on mechanical ventilation at 14 days and their BPD/death outcomes. As you will see, about 44% of the enrolled infants were on mechanical ventilation at that time (526). Of those, 30% survived without BPD, which is very close to the data provided by Abhik (24% of babies with at least 14 days of mechanical ventilation survived without BPD).

This is reassuring for our sample size estimation - if survival without BPD was 25%, as from Abhik's data, the total sample size to detect a 10% difference would be 658; if survival without BPD had improved to 35%, we would need 750. Because we cannot be sure of the baseline incidence at the time we start the study, we proposed a conservative sample size of 800. The SUPPORT data are between those two estimates, so the proposed sample size should be appropriate.

To make the best use of our conference call time on Monday, I would like to get a current poll of the subcommittee regarding inclusion of dexamethasone in the study before the call, so we can make a decision and go forward.

As I see it, a straight HC/placebo trial will give us a reasonable chance of enrolling an adequate sample size in less than 3 years within the network. We run the risk of futility - but if HC doesn't work to facilitate extubation and decrease BPD, that's a very important finding. A three-way trial will stretch the capability of the network to enroll, and still would not give us a large enough sample size to compare HC/Dex anyway for non-inferiority.

so I think we are better off running a straight HC/placebo trial to find out if it works. If it does, we have lots of evidence to say HC is better for neurodevelopmental outcomes, and this trial will add to the evidence available regarding outcome after HC Rx. If it doesn't, then we could proceed to a straight dex/placebo trial in a subsequent protocol. After all our e-mail discussion regarding a three-arm protocol comparing each drug to the same placebo group, I know Kathleen and Michelle favor a single drug (HC) trial. Rich, have you changed your position after all the back and forth? Others?

Rose, what is our position in responding to the outside reviewers in this regard?

Thanks, Kristi

## **Higgins, Rosemary (NIH/NICHD) [E]**

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**From:** Finer, Neil <nfiner@ucsd.edu>  
**Sent:** Friday, February 26, 2010 6:37 PM  
**To:** Wallace, Dennis; Higgins, Rosemary (NIH/NICHD) [E]; 'wcarlo@peds.uab.edu'  
**Cc:** Rich, Wade  
**Subject:** FW: Follow Up ON BPD and Oximeters

Hi Everyone

For the record I oppose adding any statement to the oximeter paper

I will go along with Wally and Rose if they want to do this, but I believe that you have more than responded to Jon Neil

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**From:** Tyson, Jon E [mailto:Jon.E.Tyson@uth.tmc.edu]

**Sent:** Friday, February 26, 2010 3:28 PM

**To:** Wallace, Dennis; Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; Stevenson David (E-mail); Finer, Neil; Rich, Wade; Gantz, Marie

**Cc:** Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]

**Subject:** RE: Follow Up ON BPD and Oximeters

I don't understand your statement "Controlling for center adjusts for differences between centers including differences in the BPD oximeter used." To simplify the discussion, suppose every center always used the study oximeter in designating who had BPD by oxygen saturation. Because the true saturation that would prompt oxygen administration would differ in the two treatment groups, there would be systematic bias toward administering oxygen to more infants in the high sat group than in the low sat group. This is inherent in the study design. Whatever differences there were between centers, this bias would occur in every center and would not be eliminated by controlling for center. And if I understand the analysis, there would be no interaction between treatment oximeter and BPD oximeter because they would be the same in every baby in every center.

You indicate that 5 centers used the study oximeter in almost every baby. In saying "it's not possible to tease out the effect of the BPD oximeter from other between-center differences" (a statement that I certainly accept), aren't you saying that the effect of the study oximeter on the difference in the incidence of BPD by oxygen administration between high and low sat groups (i.e., the bias) can not be distinguished from the effect of the myriad of other factors in those centers that might affect that difference in incidence? If so, why would you expect to be able to discern that bias (the signal) from all the noise resulting from other factors? I understand from what you said that the same approach was used in virtually all infants in each center which makes the effective n to be based on the number of centers rather than the number of babies. As I understand the analysis, the power to assess an interaction would then be quite low.

The issue here is whether is simply whether to report somewhere in the paper (which could be noted under the table and wouldn't increase the word count for the text) a bias in evaluating a secondary outcome. This can be done with no delay in submitting the manuscript or waiting for Maria to return. *If we had other real or potential sources of bias—say, a breaking of the blind for some infants, open label administration of a study drug to the control group, or differential loss to follow-up, we would certainly report it as a matter of course, whether or not there was a significant or near significant*



*difference in the outcome and without testing and whether or not we assessed or found any interaction or other statistical evidence that this potential source of bias affected the results!*

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6431 Fannin St., MSB 2.106  
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voice 713-500-5651  
fax 713-500-0519

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**From:** Wallace, Dennis [mailto:dwallace@rti.org]  
**Sent:** Friday, February 26, 2010 1:56 PM  
**To:** Wallace, Dennis; Tyson, Jon E; Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; Stevenson David (E-mail); Finer, Neil; Rich, Wade; Gantz, Marie  
**Cc:** Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: Follow Up ON BPD and Oximeters

Hello all,

I accidentally hit the send button before finishing editing this response so ignore the earlier e-mail and see the response below.  
Dennis

Dennis Wallace  
Senior Research Statistician  
Cox 241  
RTI International  
3040 Cornwallis Rd  
Research Triangle Park, NC 27709-2104  
Voice: 919-541-6271  
Fax: 919-541-6416

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**From:** Wallace, Dennis  
**Sent:** Friday, February 26, 2010 2:53 PM  
**To:** 'Tyson, Jon E'; Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; 'Stevenson David (E-mail)'; 'Finer, Neil'; Rich, Wade; Gantz, Marie  
**Cc:** Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: Follow Up ON BPD and Oximeters

Jon,

Marie flew out on a long-scheduled vacation after completing these analyses late Tuesday evening and has very limited e-mail and cell phone access. However, she has taken time to provide a preliminary response that I've outlined below with some added thoughts

of my own in red font below. Based on these responses, I do believe that the critical concerns about bias have been addressed sufficiently for this initial manuscript, but if you think we need to have a more full discussion, we can talk after Marie returns next week. Because the programming for these outcome measures is relatively complicated, I'm hesitant to try to do any additional analyses prior to her return. However, as I indicated above, I don't think that we need to delay any submissions while trying to iron on the small details.

Dennis Wallace  
Senior Research Statistician  
Cox 241  
RTI International  
3040 Cornwallis Rd  
Research Triangle Park, NC 27709-2104  
Voice: 919-541-6271  
Fax: 919-541-6416

-----Original Message-----

From: Tyson, Jon E [mailto:Jon.E.Tyson@uth.tmc.edu]  
Sent: Thursday, February 25, 2010 12:45 AM  
To: Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; Wallace, Dennis; cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; 'Stevenson David (E-mail)'; 'Finer, Neil'; Rich, Wade; Gantz, Marie  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]  
Subject: RE: Follow Up ON BPD and Oximeters

Rose, before we can understand and interpret this information noted in the mail, we really need to know more about what was done and answers to questions like those below:

1. Which trial result was addressed - whether the evaluation of BPD was biased in the analyses of CPAP/limited ventilation vs. surfactant/conventional ventilation arm (not the analysis for which there is concern) or the analyses of the high vs. low oxygen saturation goal.

Although models were run for the different arms of the factorial design, the trial result that was addressed in the earlier e-mail was the impact of different oximeters on the comparison of the effects high vs. low oxygen saturation targets on BPD and BPD/death outcomes, which we believe is the question of interest.

2. Do we have reliable data to know whether individual infants were monitored on the study oximeter or on the clinical oximeter on the day the infant was 36 weeks and 0 and whether the oximeter was changed part way through that 24 hour period? What was done if the infant was switched on that day. As I understand it, the diagnosis of BPD was based on the entire 24 hours the day the infant was 36 weeks 0 days. Though the results of the survey weren't distributed, my impression from responses to my earlier e mails was that even the procedure usually followed in individual centers was not necessarily clear.

We can determine from form PHY02 what oximeter was used to determine the physiologic definition of BPD, but we do not have the detailed level of information that you described. However, based on the survey results, we do know that only 5 sites used the study oximeter for an oxygen-based definition, and only 3 used the study oximeter for challenge.

3. What variables in the model when the BPD oximeter was added? What variables were in the model when a BPD oximeter x study treatment group was added?

Variables in the model were treatment oximeter (low vs. high), center, GA group. Familial clustering was adjusted for as a random effect. I added BPD oximeter and also looked at the interaction between BPD oximeter and treatment oximeter. These factors were identical to the factors used in the models for which secondary outcomes were reported in the manuscript.

4. Do I understand Maria and you to conclude that because centers tended to be consistent in their oximeter use, controlling for center would prevent a biased assessment of the effect on BPD by oxygen administration?

This comment makes me wonder if the analysis was done for the wrong comparison. This conclusion would be correct for analyses of the effect of CPAP/limited ventilation vs. surfactant/ conventional ventilation on BPD by oxygen delivery (because each treatment arm would contain equal numbers of infants in the high and low sat groups). However, this isn't the comparison in question. This conclusion would certainly not be correct in analyzing the effect of high vs low sat goals on BPD. In this analysis, centers that used the study oximeter would be systematically more likely to administer oxygen to the high sat group than to the low sat group. The problem wouldn't go away by controlling for center, and the more centers that used the study oximeter, the more biased the result would be. How many centers were there that used the study oximeter?

Controlling for center adjusts for differences between centers including differences in the BPD oximeter used. Thus, adding a covariate for BPD oximeter does not change the estimates for the treatment oximeter effect. We are not arguing that the BPD oximeter used did not have an impact. We did find that BPD oximeter was significant in the models, as was center. However, since center and BPD oximeter are strongly confounded (in fact we have almost complete aliasing of center and clinical/study oximeter), it's not possible to tease out the effect of the BPD oximeter from other between-center differences. In addition, the interaction between BPD oximeter and treatment oximeter was not significant. This indicates that the impact of treatment oximeter on the BPD outcomes was not significantly different in the centers that used the study oximeters to determine BPD and those that used the clinical oximeters.

5. What is the basis for believing that there would be anything near reasonable power to assess a oximeter x treatment group interaction?

Clearly, these analyses were conducted from a post-hoc perspective, and the study was never designed to have the power to determine that the interaction in our data set is statistically significant for a pre-specified interaction effect size. But, that is not a shortcoming unless the magnitude of the interaction effect is such that it represents an important scientific bias in study interpretation. Our preliminary analyses indicate that biases of such magnitude are not present in this data set. We can do more detailed analyses of the level of bias that might have been introduced after Marie returns from vacation, but nothing in the analyses conducted to date suggest that those magnitudes warrant delay of submission of this manuscript.

I know that everyone is anxious to get this paper submitted. While I have an external advisory committee tomorrow, I will try to respond tomorrow night if the information requested above is sent tomorrow during the day.

---

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]  
Sent: Wednesday, February 24, 2010 7:53 AM

To: Tyson, Jon E; 'Cunningham, Meg'; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; Wallace, Dennis; cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; 'Stevenson David (E-mail)'; 'Finer, Neil'; Rich, Wade; Gantz, Marie  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]  
Subject: Follow Up ON BPD and Oximeters

Hi all -

In Follow up to yesterday's discussion, Marie spent a great deal of time last evening running additional analyses to address (and now alleviate) Jon's concern as described:

We have looked into the question of whether the oximeter used to determine BPD impacted the BPD and death/BPD outcomes by adding a covariate for the BPD oximeter (study or clinical) to the statistical models. We found that the effect of the BPD oximeter was significant; however, the interaction between BPD oximeter and treatment oximeter (low or high SpO2 target range) was not significant in any model, indicating that, if there was a BPD oximeter effect, it was not different in the two treatment groups. In addition, it should be noted that BPD oximeter is confounded with center (centers tended to be consistent in their use of the study or clinical oximeters to determine BPD). Therefore, by including center in the original models, we have already accounted for the effect of the BPD oximeter the center chose to use. Finally, because center and BPD oximeter are confounded, we cannot know whether the significant BPD oximeter effect is due to the BPD oximeters themselves or other characteristics that differ between centers.

---

From: Tyson, Jon E [mailto:Jon.E.Tyson@uth.tmc.edu]  
Sent: Tuesday, February 23, 2010 4:33 PM  
To: Higgins, Rosemary (NIH/NICHD) [E]; 'Cunningham, Meg'; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; Wallace, Dennis; cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; bbatton@siumed.edu  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; lmoore@med.wayne.edu; pamela.neville@duke.edu; gonza025@mc.duke.edu; Smith, Nancy M; Brenda Vecchio; msumner@peds.uab.edu; Archer, Stephanie (NIH/NICHD) [E]  
Subject: RE: Steering Committee Call Tomorrow

While it may seem that I am fixated on an unimportant issue regarding a not quite significant difference, I think we undermine the credibility of Network studies if we are not completely forthright about problems in measuring what everyone would agree is an important secondary outcome. Not reporting that the assessment of BPD by oxygen administration could be biased by continued use of the study oximeters would seem to be in the category of not reporting protocol deviations and not something that is in the Network's best interest. Why not just put a footnote under the table describing the problem?

Jon E. Tyson, MD, MPH  
Center for Clinical Research & Evidence-Based Medicine  
UT Medical School at Houston  
6431 Fannin St., MSB 2.106  
Houston, TX 77030  
voice 713-500-5651  
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From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
Sent: Tuesday, February 23, 2010 2:11 PM  
To: 'Cunningham, Meg'; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; Wallace, Dennis; cotte010@mc.duke.edu; Tyson, Jon E; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; bbatton@siumed.edu  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; lmoore@med.wayne.edu; pamela.neville@duke.edu; gonza025@mc.duke.edu; Smith, Nancy M; Brenda Vecchio; msumner@peds.uab.edu; Archer, Stephanie (NIH/NICHD) [E]  
Subject: RE: Steering Committee Call Tomorrow

If you joined the call already in progress, please send us an email so we can count your attendance.

Rose

From: Cunningham, Meg [mailto:mcunningham@rti.org]  
Sent: Monday, February 22, 2010 9:59 AM  
To: [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; Higgins, Rosemary (NIH/NICHD) [E]; ifrantz@tuftsmedicalcenter.org; Kathleen.A.Kennedy@uth.tmc.edu; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; Wallace, Dennis; cotte010@mc.duke.edu; jon.e.tyson@uth.tmc.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; bbatton@siumed.edu  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; lmoore@med.wayne.edu; pamela.neville@duke.edu; gonza025@mc.duke.edu; Nancy.M.Smith@uth.tmc.edu; Brenda Vecchio; msumner@peds.uab.edu; Archer, Stephanie (NIH/NICHD) [E]  
Subject: Steering Committee Call Tomorrow

Dear All -

The next standing Steering Committee call is scheduled for tomorrow, Tuesday, February 23rd at 3:00pm ET.

Please Dial:

Outside the USA 1-203-310 (b) (6)  
or Within the USA 866-675 (b) (6)

Then, enter Participant Passcode: (b) (6)

Steering Committee Conference Call Agenda 02/23/2010

1. Early BP discussion (attached are a brief description of the time limited data collection proposal and a draft of the form which would be used.)
2. SUPPORT manuscript discussion and update
3. New Business

Thanks,  
Meg

Meg Cunningham  
RTI International  
701 13th St. NW, Ste. 750

Washington, DC 20005

tel: 202-974-7837

fax: 202-728-2095

www.rti.org<<http://www.rti.org>>

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "debra.camputaro@yale.edu"  
**Cc:** "Ehrenkranz Richard (E-mail)"  
**Subject:** FW: URGENT REQUEST:: SUPPORT forms  
**Date:** Friday, February 26, 2010 4:22:00 PM  
**Attachments:** ICMJE sat paper.pdf

---

Hi Debbie –

Here is the form – he likely filled one in earlier but it needs to be done on a computer, saved and emailed to Brendan Able ([babel@nejm.org](mailto:babel@nejm.org)). If you have any questions, I can be reached at 703-395-0183 or 703-827-6548.

Thanks for all your help!!

Rose

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Friday, February 26, 2010 9:32 AM  
**To:** 'richard.ehrenkranz@yale.edu'; 'poo@rti.org'; 'ambal@uab.edu'; 'Pablo.Sanchez@UTSouthwestern.edu'; 'vanmeurs@leland.stanford.edu'; 'kwatterberg@salud.unm.edu'  
**Cc:** 'kzaterka@rti.org'  
**Subject:** URGENT REQUEST:: SUPPORT forms

Hi,

Brendan is missing your form for the saturation paper - please submit the fillable form (attached) and email it to Him today at [babel@nejm.org](mailto:babel@nejm.org).

Thanks

Rose

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** richard.ehrenkranz@yale.edu <richard.ehrenkranz@yale.edu>; Vivek Narendran <Vivek.Narendran@cchmc.org>; Phelps, Dale <Dale\_Phelps@URMC.Rochester.edu>; Anthony Piazza (Anthony.Piazza@oz.ped.emory.edu) <Anthony.Piazza@oz.ped.emory.edu>  
**Cc:** 'Abel, Brendan' <babel@nejm.org>  
**Sent:** Wed Feb 24 12:11:30 2010  
**Subject:** SUPPORT forms

Hi all,

Please fill out the attached form, save the form, and email it to Brendan Abel at NEJM. I have copied Brendan on this email, so you have his email address. The form must be filled out and submitted in the interactive form. **Please do this today or tomorrow.**

Thanks for all your help!

Rose

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network  
Pregnancy and Perinatology Branch  
Center for Developmental Biology and Perinatal Medicine

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**Eunice Kennedy Shriver National Institute of Child Health and Human Development  
National Institutes of Health  
6100 Executive Blvd., Room 4B03  
MSC 7510  
Bethesda, MD 20892  
For overnight delivery use Rockville, MD 20852  
301-496-5575  
301-496-3790 (FAX)  
higginsr@mail.nih.gov**





## **ICMJE Uniform Disclosure Form for Potential Conflicts of Interest**

### **INSTRUCTIONS:**

The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. The form has five parts.

#### **1. Identifying information.**

Each author should submit a separate form. Provide complete information and double-check the manuscript number. If you are NOT the corresponding author please insert his or her name.

#### **2. The work under consideration for publication.**

Please provide information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The idea is to provide for the reader information about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. If you check the "No" box it means that you did the work without receiving any financial support from any third party -- that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds to pay you. If you or your institution did receive funds from a third party to support the work, check "Yes" along with the appropriate boxes to indicate the type of support and whether you or your institution received it.

#### **3. Relevant financial activities outside the submitted work.**

Please report all sources of revenue relevant to the submitted work that accrued either directly to you or were paid to your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. If there is any question, it is usually better to disclose a relationship than not to do so. Please note that your interactions with the work's sponsor outside the submitted work should be listed here. For each category list each entity on a separate line. Use as many lines as necessary to provide complete information. In addition, please disclose relationships that fall outside the 36-month window that readers may want to know about and could reasonably criticize you for not disclosing (for example, long-term financial relationships that are now ended).

The goal of this section is to provide information for our reviewers and readers about your interactions with entities in the biomedical arena that could be perceived to influence, or that give the appearance of potentially influencing, what you wrote in the submitted work. You should disclose interactions with ANY entity that could be considered broadly relevant to the work. For example, if your article is about testing an epidermal growth factor receptor (EGFR) antagonist in lung cancer, you should report all associations with entities pursuing diagnostic or therapeutic strategies in cancer in general, not just in the area of EGFR or lung cancer. For grants you have received for work outside the submitted work, you should disclose support ONLY from entities that could be perceived to benefit financially from the published work, such as drug companies, or foundations supported by entities that could be perceived to have a financial stake in the outcome. Public funding sources, such as the NIH or the MRC, need not be disclosed. For example, if the NIH sponsored a piece of work you have been involved in but drugs were provided by a pharmaceutical company, you need only list the pharmaceutical company.

#### **4. Financial relationships involving your spouse or partner or your children (under 18 years of age).**

If monies from the types of relationships listed in Section 3 were paid to your spouse or partner or dependent children, please list the type of activity and source of the money.

#### **5. Nonfinancial associations.**

Please report any personal, professional, political, institutional, religious, or other associations that a reasonable reader would want to know about in relation to the submitted work.



## ICMJE Uniform Disclosure Form for Potential Conflicts of Interest

### Section 1. Identifying Information.

Given Name:  
(or first)

Surname:  
(or last)

Effective Date:

Format example: 07-August-2008

Are you the corresponding author?  Yes  No

Manuscript Title:

A Randomized Trial of Oxygen Saturation Targets in Extremely Preterm Infants

Manuscript Identifying Number (if you know it):

09-11781

### Section 2. Information about the support of the work under consideration for publication.

Did you or your institution at any time receive payment or support in kind for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc...)?

No

Yes, specify nature of compensation

### Section 3. Information about relevant financial relationships outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with any entities that have an interest related to the submitted work. Use one line for each entity; add as many lines as you need. Use the comments column to indicate any additional information that you think a reader or editor would want to know about the compensation. Report relationships that were present during the 36 months prior to submission. In addition please disclose relationships that fall outside the 36-month window that readers may want to know about and could reasonably criticize you for not disclosing (for example, long-term financial relationships that are now ended).

If you have more than one relationship, click "Add +" to add a row. Click "Del x" to delete an extra row.

Type of Relationship (in alphabetical order)	No	Money Paid to You	Money to Your Institution	Entity	Comments	
Board membership	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del x
						Add +
Consultancy	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del x
						Add +
Employment	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del x
						Add +
Expert testimony	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del x
						Add +



# ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

## ICMJE Uniform Disclosure Form for Potential Conflicts of Interest

Type of Relationship (in alphabetical order)	No	Money Paid to You	Money to Your institution	Entity	Comments	
Gifts	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del x
						Add +
Grants/grants pending	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del x
						Add +
Honoraria	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del x
						Add +
Payment for manuscript preparation	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del x
						Add +
Patents (planned, pending or issued)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del x
						Add +
Royalties	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del x
						Add +
Payment for development of educational presentations including service on speakers' bureaus	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del x
						Add +
Stock/stock options	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del x
						Add +
Travel/accommodations expenses covered or reimbursed	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del x
						Add +
Other (err on the side of full disclosure)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del x
						Add +



## ICMJE Uniform Disclosure Form for Potential Conflicts of Interest

### Section 4. Information about financial relationships involving your spouse or partner or your children (under 18 years of age).

Do your children or your spouse or partner have financial relationships with entities that have an interest in the content of the submitted work?

- No other relationships/conditions/circumstances that present potential conflict of interest
- Yes, the following relationships/conditions/circumstances are present (explain below):

### Section 5. Information about relevant nonfinancial associations.

Do you have any relevant nonfinancial associations or interests (personal, professional, political, institutional, religious, or other) that a reasonable reader would want to know about in relation to the submitted work?

- No relevant nonfinancial relationships/conditions/circumstances to report.
- Yes, the following relevant nonfinancial relationships/conditions/circumstances are present (explain below):

At the time of manuscript acceptance, journals will ask authors to confirm and, if necessary, update their disclosure statements. On occasion, journals may ask authors to disclose further information about reported relationships.

Save Form

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "dwallace@rti.org"; "nfiner@ucsd.edu"; "mgantz@rti.org"  
**Cc:** "wcarlo@peds.uab.edu"; "adas@rti.org"; "kzaterka@rti.org"; "wrich@ucsd.edu"  
**Subject:** Re: Follow Up ON BPD and Oximeters  
**Date:** Friday, February 26, 2010 1:46:17 PM

---

Ok  
You can send it

Thanks  
Rose

----- Original Message -----

**From:** Wallace, Dennis <dwallace@rti.org>  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu <nfiner@ucsd.edu>; Gantz, Marie <mgantz@rti.org>  
**Cc:** wcarlo@peds.uab.edu <wcarlo@peds.uab.edu>; Das, Abhik <adas@rti.org>; Zaterka-Baxter, Kristin <kzaterka@rti.org>; wrich@ucsd.edu <wrich@ucsd.edu>  
**Sent:** Fri Feb 26 13:39:39 2010  
**Subject:** RE: Follow Up ON BPD and Oximeters

Rose,

I had sent a couple of e-mails to Marie, and I'm waiting for a final response. I'm online waiting now and I'm happy to combine her response and what I'd started putting together into a final e-mail for Jon this afternoon if you'd rather that I do that.

Dennis

Dennis Wallace  
Senior Research Statistician  
Cox 241  
RTI International  
3040 Cornwallis Rd  
Research Triangle Park, NC 27709-2104  
Voice: 919-541-6271  
Fax: 919-541-6416

-----Original Message-----

**From:** Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]  
**Sent:** Friday, February 26, 2010 1:36 PM  
**To:** 'nfiner@ucsd.edu'; Gantz, Marie  
**Cc:** 'wcarlo@peds.uab.edu'; Das, Abhik; Wallace, Dennis; Zaterka-Baxter, Kristin; 'wrich@ucsd.edu'  
**Subject:** Re: Follow Up ON BPD and Oximeters

I will send an email this afternoon. We had lost power last night and it just came back on- our offices are being renovated so we were told to telecommute today so I have been using dial up internet and a battery pack for my computer. It's 55 degrees in our house.

As soon as we get our cable modum reset, I will get this out.

I agree, the subcommittee has been very responsive.

Thanks for everyon's patience!!  
Rose

----- Original Message -----

From: Finer, Neil <nfiner@ucsd.edu>  
To: Gantz, Marie <mgantz@rti.org>; Higgins, Rosemary (NIH/NICHD) [E]  
Cc: Wally Carlo, M.D. <WCarlo@peds.uab.edu>; Das, Abhik <adas@rti.org>;  
Wallace, Dennis <dwallace@rti.org>; Zaterka-Baxter, Kristin  
<kzaterka@rti.org>; Rich, Wade <wrich@ucsd.edu>  
Sent: Fri Feb 26 13:29:37 2010  
Subject: RE: Follow Up ON BPD and Oximeters

Again Many thanks Marie  
Rose when do you think we can put these questions to sleep??  
I think Marie and the rest of us have been more than responsive.  
There was simply no evidence to suggest that the use of either a normal  
or study oximeter at the time of the BPD diagnosis or test for the  
Physiologic was significant on a center adjusted basis. We will never  
have the individual patient data for this - BUT the protocol did specify  
that the study oximeter should stop at 36 weeks and most centers got it  
right!!  
Finally the argument that there was a trend in the SpO2 paper for BPD  
and that we should stress this, but that the same p value in the CPAP  
paper for BPD by the oxygen definition should not be described as a  
trend is very intriguing to me.  
Neil

-----Original Message-----

From: Gantz, Marie [<mailto:mgantz@rti.org>]  
Sent: Friday, February 26, 2010 10:03 AM  
To: Higgins, Rosemary (NIH/NICHD) [E]  
Cc: Finer, Neil; Wally Carlo, M.D.; Das, Abhik; Wallace, Dennis;  
Zaterka-Baxter, Kristin; Rich, Wade  
Subject: FW: Follow Up ON BPD and Oximeters

Here are some brief answers to Jon's questions.

Marie

Marie Gantz, Ph.D.  
Research Statistician  
RTI International  
[mgantz@rti.org](mailto:mgantz@rti.org)  
828-254-6255

-----Original Message-----

From: Tyson, Jon E [<mailto:Jon.E.Tyson@uth.tmc.edu>]  
Sent: Thursday, February 25, 2010 12:45 AM  
To: Higgins, Rosemary (NIH/NICHD) [E]; Cunningham, Meg; [SCRN] Stoll,  
Barbara; [alaptook@WIHRI.org](mailto:alaptook@WIHRI.org); Bell, Edward; [bpointex@iupui.edu](mailto:bpointex@iupui.edu); Das,  
Abhik; [goldb008@mc.duke.edu](mailto:goldb008@mc.duke.edu); [ifrantz@tuftsmedicalcenter.org](mailto:ifrantz@tuftsmedicalcenter.org); Kennedy,  
Kathleen A; [kurt.schibler@cchmc.org](mailto:kurt.schibler@cchmc.org); [kwatterberg@salud.unm.edu](mailto:kwatterberg@salud.unm.edu);  
[matthew.bizzarro@yale.edu](mailto:matthew.bizzarro@yale.edu); [mew3@cwru.edu](mailto:mew3@cwru.edu); [mcaplan@northshore.org](mailto:mcaplan@northshore.org);  
[Pablo.Sanchez@UTSouthwestern.edu](mailto:Pablo.Sanchez@UTSouthwestern.edu); [richard.ehrenkranz@yale.edu](mailto:richard.ehrenkranz@yale.edu);  
[Roger.Faix@hsc.utah.edu](mailto:Roger.Faix@hsc.utah.edu); [sshankar@med.wayne.edu](mailto:sshankar@med.wayne.edu);  
[vanmeurs@leland.stanford.edu](mailto:vanmeurs@leland.stanford.edu); Wally Carlo, M.D.; Wallace, Dennis;  
[cotte010@mc.duke.edu](mailto:cotte010@mc.duke.edu); Bradley Yoder; [rohls@salud.unm.edu](mailto:rohls@salud.unm.edu);  
[Luc.Brion@utsouthwestern.edu](mailto:Luc.Brion@utsouthwestern.edu); 'Stevenson David (E-mail)'; 'Finer, Neil';

Rich, Wade; Gantz, Marie

Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie;

Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]

Subject: RE: Follow Up ON BPD and Oximeters

Rose, before we can understand and interpret this information noted in the mail, we really need to know more about what was done and answers to questions like those below:

1. Which trial result was addressed - whether the evaluation of BPD was biased in the analyses of CPAP/limited ventilation vs. surfactant/conventional ventilation arm (not the analysis for which there is concern) or the analyses of the high vs. low oxygen saturation goal.

MG: The trial result that was addressed was the impact of the high vs. low oxygen saturation targets on BPD and BPD/death outcomes.

2. Do we have reliable data to know whether individual infants were monitored on the study oximeter or on the clinical oximeter on the day the infant was 36 weeks and 0 and whether the oximeter was changed part way through that 24 hour period? What was done if the infant was switched on that day. As I understand it, the diagnosis of BPD was based on the entire 24 hours the day the infant was 36 weeks 0 days. Though the results of the survey weren't distributed, my impression from responses to my earlier e mails was that even the procedure usually followed in individual centers was not necessarily clear.

MG: No, we do not have this information.

3. What variables in the model when the BPD oximeter was added? What variables were in the model when a BPD oximeter x study treatment group was added?

MG: Variables in the model were treatment oximeter (low vs. high), center, GA group. Familial clustering was adjusted for as a random effect. I added BPD oximeter and also looked at the interaction between BPD oximeter and treatment oximeter.

4. Do I understand Maria and you to conclude that because centers tended to be consistent in their oximeter use, controlling for center would prevent a biased assessment of the effect on BPD by oxygen administration?

This comment makes me wonder if the analysis was done for the wrong comparison, This conclusion would be correct for analyses of the effect of CPAP/limited ventilation vs. surfactant/ conventional ventilation on BPD by oxygen delivery (because each treatment arm would contain equal numbers of infants in the high and low sat groups). However, this isn't the comparison in question. This conclusion would certainly not be correct in analyzing the effect of high vs low sat goals on BPD. In this analysis, centers that used the study oximeter would be systematically more likely to administer oxygen to the high sat group than to the low sat group. The problem wouldn't go away by controlling for center, and the more centers that used the study oximeter, the more biased the result would be. How many centers were there that used the study oximeter?

MG: Controlling for center adjusts for differences between centers including differences in the BPD oximeter used. Thus, adding a covariate for BPD oximeter does not change the estimates for the treatment oximeter effect. We are not arguing that the BPD oximeter used did not have an impact. We did find that BPD oximeter was significant in the models, as was center. However, since center and BPD oximeter are confounded, it's not possible to completely tease out the effect of the BPD oximeter from other between-center differences. In addition, the interaction between BPD oximeter and treatment oximeter was not significant. This indicates that the impact of treatment oximeter on the BPD outcomes was not significantly different in the centers that used the study oximeters to determine BPD and those that used the clinical oximeters.

5. What is the basis for believing that there would be anything near reasonable power to assess a oximeter x treatment group interaction?

MG: As always, the question of statistical power can only be answered with respect to the effect size you are attempting to detect. Clearly, from a post-hoc perspective, we do not have the power to determine that the interaction in our data set is statistically significant. But, that is not a shortcoming unless the interaction that is present is clinically significant.

I know that everyone is anxious to get this paper submitted. While I have an external advisory committee tomorrow, I will try to respond tomorrow night if the information requested above is sent tomorrow during the day.

---

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]  
Sent: Wednesday, February 24, 2010 7:53 AM  
To: Tyson, Jon E; 'Cunningham, Meg'; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; Wallace, Dennis; cotte010@mc.duke.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; 'Stevenson David (E-mail)'; 'Finer, Neil'; Rich, Wade; Gantz, Marie  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]  
Subject: Follow Up ON BPD and Oximeters

Hi all -

In Follow up to yesterday's discussion, Marie spent a great deal of time last evening running additional analyses to address (and now alleviate) Jon's concern as described:

We have looked into the question of whether the oximeter used to determine BPD impacted the BPD and death/BPD outcomes by adding a covariate for the BPD oximeter (study or clinical) to the statistical



models. We found that the effect of the BPD oximeter was significant; however, the interaction between BPD oximeter and treatment oximeter (low or high SpO2 target range) was not significant in any model, indicating that, if there was a BPD oximeter effect, it was not different in the two treatment groups. In addition, it should be noted that BPD oximeter is confounded with center (centers tended to be consistent in their use of the study or clinical oximeters to determine BPD). Therefore, by including center in the original models, we have already accounted for the effect of the BPD oximeter the center chose to use. Finally, because center and BPD oximeter are confounded, we cannot know whether the significant BPD oximeter effect is due to the BPD oximeters themselves or other characteristics that differ between centers.

---

From: Tyson, Jon E [<mailto:Jon.E.Tyson@uth.tmc.edu>]  
Sent: Tuesday, February 23, 2010 4:33 PM  
To: Higgins, Rosemary (NIH/NICHD) [E]; 'Cunningham, Meg'; [SCRN] Stoll, Barbara; [alaptook@WIHRI.org](mailto:alaptook@WIHRI.org); Bell, Edward; [bpoindex@iupui.edu](mailto:bpoindex@iupui.edu); Das, Abhik; [goldb008@mc.duke.edu](mailto:goldb008@mc.duke.edu); [ifrantz@tuftsmedicalcenter.org](mailto:ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; [kurt.schibler@cchmc.org](mailto:kurt.schibler@cchmc.org); [kwatterberg@salud.unm.edu](mailto:kwatterberg@salud.unm.edu); [matthew.bizzarro@yale.edu](mailto:matthew.bizzarro@yale.edu); [mew3@cwru.edu](mailto:mew3@cwru.edu); [mcaplan@northshore.org](mailto:mcaplan@northshore.org); [Pablo.Sanchez@UTSouthwestern.edu](mailto:Pablo.Sanchez@UTSouthwestern.edu); [richard.ehrenkranz@yale.edu](mailto:richard.ehrenkranz@yale.edu); [Roger.Faix@hsc.utah.edu](mailto:Roger.Faix@hsc.utah.edu); [sshankar@med.wayne.edu](mailto:sshankar@med.wayne.edu); [vanmeurs@leland.stanford.edu](mailto:vanmeurs@leland.stanford.edu); Wally Carlo, M.D.; Wallace, Dennis; [cotte010@mc.duke.edu](mailto:cotte010@mc.duke.edu); Bradley Yoder; [rohls@salud.unm.edu](mailto:rohls@salud.unm.edu); [Luc.Brion@utsouthwestern.edu](mailto:Luc.Brion@utsouthwestern.edu); [bbatton@siumed.edu](mailto:bbatton@siumed.edu)  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; [lmoore@med.wayne.edu](mailto:lmoore@med.wayne.edu); [pamela.neville@duke.edu](mailto:pamela.neville@duke.edu); [gonza025@mc.duke.edu](mailto:gonza025@mc.duke.edu); Smith, Nancy M; Brenda Vecchio; [msumner@peds.uab.edu](mailto:msumner@peds.uab.edu); Archer, Stephanie (NIH/NICHD) [E]  
Subject: RE: Steering Committee Call Tomorrow

While it may seem that I am fixated on an unimportant issue regarding a not quite significant difference, I think we undermine the credibility of Network studies if we are not completely forthright about problems in measuring what everyone would agree is an important secondary outcome. Not reporting that the assessment of BPD by oxygen administration could be biased by continued use of the study oximeters would seem to be in the category of not reporting protocol deviations and not something that is in the Network's best interest. Why not just put a footnote under the table describing the problem?

Jon E. Tyson, MD, MPH  
Center for Clinical Research & Evidence-Based Medicine  
UT Medical School at Houston  
6431 Fannin St., MSB 2.106  
Houston, TX 77030  
voice 713-500-5651  
fax 713-500-0519

---

From: Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]  
Sent: Tuesday, February 23, 2010 2:11 PM  
To: 'Cunningham, Meg'; [SCRN] Stoll, Barbara; [alaptook@WIHRI.org](mailto:alaptook@WIHRI.org); Bell, Edward; [bpoindex@iupui.edu](mailto:bpoindex@iupui.edu); Das, Abhik; [goldb008@mc.duke.edu](mailto:goldb008@mc.duke.edu); [ifrantz@tuftsmedicalcenter.org](mailto:ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A;

kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu;  
matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org;  
Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu;  
Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu;  
vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; Wallace, Dennis;  
cotte010@mc.duke.edu; Tyson, Jon E; Bradley Yoder; rohls@salud.unm.edu;  
Luc.Brion@utsouthwestern.edu; bbatton@siumed.edu  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie;  
Newman, Jamie; lmoore@med.wayne.edu; pamelaneville@duke.edu;  
gonza025@mc.duke.edu; Smith, Nancy M; Brenda Vecchio;  
msummer@peds.uab.edu; Archer, Stephanie (NIH/NICHD) [E]  
Subject: RE: Steering Committee Call Tomorrow

If you joined the call already in progress, please send us an email so we can count your attendance.

Rose

---

From: Cunningham, Meg [mailto:mcunningham@rti.org]  
Sent: Monday, February 22, 2010 9:59 AM  
To: [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward;  
bpointex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; Higgins, Rosemary (NIH/NICHD) [E]; ifrantz@tuftsmedicalcenter.org;  
Kathleen.A.Kennedy@uth.tmc.edu; kurt.schibler@cchmc.org;  
kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu;  
mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu;  
richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu;  
sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.;  
Wallace, Dennis; cotte010@mc.duke.edu; jon.e.tyson@uth.tmc.edu; Bradley  
Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu;  
bbatton@siumed.edu  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie;  
Newman, Jamie; lmoore@med.wayne.edu; pamelaneville@duke.edu;  
gonza025@mc.duke.edu; Nancy.M.Smith@uth.tmc.edu; Brenda Vecchio;  
msummer@peds.uab.edu; Archer, Stephanie (NIH/NICHD) [E]  
Subject: Steering Committee Call Tomorrow

Dear All -

The next standing Steering Committee call is scheduled for tomorrow, Tuesday, February 23rd at 3:00pm ET.

Please Dial:

Outside the USA 1-203-310 (b)

or Within the USA 866-675 (b)

Then, enter Participant Passcode: (b) (6)

Steering Committee Conference Call Agenda 02/23/2010

1. Early BP discussion (attached are a brief description of the time limited data collection proposal and a draft of the form which would be used.)
2. SUPPORT manuscript discussion and update
3. New Business

Thanks,

Meg

Meg Cunningham  
RTI International  
701 13th St. NW, Ste. 750  
Washington, DC 20005  
tel: 202-974-7837  
fax: 202-728-2095  
www.rti.org<<http://www.rti.org>>

**From:** Newman, Jamie  
**To:** Vohr, Betty; Susan Hintz  
**Cc:** Hammond, Jane; Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: SUPPORT Spanish speaking at sites at 18m  
**Date:** Friday, February 26, 2010 1:11:08 PM

---

Marie Gantz is out of the office until Wednesday. We should be able to get back to you with the # Spanish-speaking per site late next week.  
Thanks, Jamie

-----Original Message-----

From: Vohr, Betty [mailto:BVohr@WIHRI.org]  
Sent: Friday, February 26, 2010 8:03 AM  
To: Susan Hintz; Newman, Jamie  
Cc: Hammond, Jane; Rosemary Higgins  
Subject: RE: SUPPORT Spanish speaking at sites at 18m

10.6 % of the population. Will be interested to see how they are clustered at sites.

-----Original Message-----

From: Susan Hintz [mailto:srhintz@stanford.edu]  
Sent: Thursday, February 25, 2010 8:26 PM  
To: Newman, Jamie  
Cc: Vohr, Betty; Hammond, Jane; Rosemary Higgins  
Subject: Re: SUPPORT Spanish speaking at sites at 18m

Hi Jamie

Yes, that would be great.

S

Sent from my iPhone

On Feb 25, 2010, at 12:47 PM, "Newman, Jamie" <newman@rti.org> wrote:

- > In Sept 2008 Marie Gantz looked into how many SUPPORT pts at 18 months
- > were Spanish speaking and found:
- > Out of 237 SUPPORT kids who have had the Bayley III exam, 26 exams
- > have not been conducted in English, and the primary language is
- > Spanish of 19 of those 26 kids. Another 2 of the kids with non-English
- > exams had a primary language of English and secondary language of
- > Spanish.
- >
- > I can ask her to re-run this with the most recent data but first want
- > to confirm that this is what you are looking for?
- > Thanks, Jamie
- >
- > -----Original Message-----
- > From: Vohr, Betty [mailto:BVohr@WIHRI.org]
- > Sent: Thursday, February 25, 2010 3:19 PM

> To: Susan Hintz; Newman, Jamie  
> Cc: Hammond, Jane; Rosemary Higgins  
> Subject: RE: Gold Standards for SUPPORT MRI School Age  
>  
> Glad you are thinking ahead. Can we get a printout from RTI of the  
> "n"  
> of Spanish speaking at sites at 18m ? This might provide a feel for  
> the extent of the problem.  
> BV  
>

> -----Original Message-----

> From: Susan Hintz [<mailto:srhintz@stanford.edu>]  
> Sent: Thursday, February 25, 2010 1:41 PM  
> To: Newman, Jamie  
> Cc: Jane Hammond; Rosemary Higgins; Vohr, Betty  
> Subject: Re: Gold Standards for SUPPORT MRI School Age  
>

> Hi,  
>

> In response to questions about Gold Standards for the the school age  
> SUPPORT neuroimaging and outcomes study - For the Bateria III and  
> Spanish version of the WISC, I had previously said that perhaps the  
> psychologist at New Mexico and our Spanish-speaking psychologist Maria  
> Elena might be interested in this. However, I know that, as you have  
> said before, there are no current "Spanish" gold standard examiners in  
> the extended Hypothermia WISC group. I think we may need to re-think  
> this for the SUPPORT Neuroimaging and Outcomes follow-up (now called  
> the NEURO cohort). We have a lot more patients (expected) than in the  
> Hypothermia extended follow-up, and at least we should have a "point  
> person" or two for questions if they come up on the Spanish version.  
> Maybe they don't need to be designated as a "gold standard" per se,  
> and certainly I do NOT think that SEPARATE certification videos are  
> required.  
>

> Input on this would be appreciated  
>

> As we have been discussing by email over the past weeks-months, the M-  
> ABC-II gold standard examiners will certainly include myself, Betty  
> Vohr, one of our physical therapists (Elish Burne) and it appears that  
> one of the PT's at Tufts may be interested from what I am hearing.  
> I am  
> in the process of trying to hone in on date for one of the developers  
> of the test (David Sugden) to come to do a "gold standard"  
> training.  
>

> Susan  
>  
>  
>

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**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "edward.donovan@cchmc.org"  
**Cc:** "kurt.schibler@cchmc.org"  
**Subject:** Re: Fw: SUPPORT copyright for CPAP Paper  
**Date:** Friday, February 26, 2010 10:04:40 AM

---

Thanks - I also sent another email for the icmje fillable form that can be emailed.

Thanks  
Rose

----- Original Message -----

**From:** Edward Donovan <Edward.Donovan@cchmc.org>  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Kurt Schibler <Kurt.Schibler@cchmc.org>  
**Sent:** Fri Feb 26 10:03:40 2010  
**Subject:** Re: Fw: SUPPORT copyright for CPAP Paper

It's on the way. Sorry for the delay.

Edward F. Donovan, M.D.  
Ohio Perinatal Quality Collaborative  
www.OPQC.net

Child Policy Research Center  
Children's Hospital Medical Center  
3333 Burnet Avenue, ML 7014  
Cincinnati, OH 45229-3039  
Phone 513-636-0169  
Fax 513-636-0171  
www.cincinnatichildrens.org/cprc

>>> "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> 2/26/2010 9:28 AM >>>

Ed

NEJM is missing your copyright form. Please complete the form and sign TODAY! You should fax it directly to NEJM at the number on the form.

Thanks  
Rose

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** 'Ed Donovan' <edward.donovan@cchmc.org>; 'Brenda Morris' (b) (6) Laroia, Nirupama <Nirupama\_Laroia@URMC.Rochester.edu>; 'Poindexter, Brenda B' <bpoindex@iupui.edu>  
**Cc:** 'Abel, Brendan' <babel@nejm.org>; Archer, Stephanie (NIH/NICHD) [E]  
**Sent:** Wed Feb 24 16:52:57 2010  
**Subject:** SUPPORT copyright for CPAP Paper

Hi,

NEJM is missing your copyright form for the CPAP surf paper. Please fill in the information and either fax it (781) 207.6529 or email a pdf with your signature to Brendan Abel. The information for the manuscript is as follows:

Manuscript number 09-11783

Author - Neil Finer

Title Early CPAP versus Surfactant in Extremely Preterm Infants

Thanks for your prompt attention

Rose

Rosemary D. Higgins, MD

Program Scientist for the Neonatal Research Network

Pregnancy and Perinatology Branch

Center for Developmental Biology and Perinatal Medicine

Eunice Kennedy Shriver National Institute of Child Health and Human Development

National Institutes of Health

6100 Executive Blvd., Room 4B03

MSC 7510

Bethesda, MD 20892

For overnight delivery use Rockville, MD 20852

301-496-5575

301-496-3790 (FAX)

[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)



**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "babel@nejm.org"  
**Cc:** "wcarlo@peds.uab.edu"; "nfiner@ucsd.edu"  
**Subject:** Re: New England Journal of Medicine 09-11783.R1 SUPPORT Protocol  
**Date:** Friday, February 26, 2010 9:59:57 AM

---

I have sent the reminders.

Thanks for your help

Rose

----- Original Message -----

From: Abel, Brendan <babel@nejm.org>  
To: Higgins, Rosemary (NIH/NICHD) [E]  
Cc: 'wcarlo@peds.uab.edu' <wcarlo@peds.uab.edu>; 'Finer, Neil' <nfiner@ucsd.edu>  
Sent: Fri Feb 26 09:11:51 2010  
Subject: RE: New England Journal of Medicine 09-11783.R1 SUPPORT Protocol

Hi Rose,

Here is the most updated list. We're getting closer- would love to get the remaining forms in today.

Thanks,

Brendan

-----Original Message-----

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
Sent: Friday, February 26, 2010 8:38 AM  
To: Abel, Brendan; 'nfiner@ucsd.edu'; NEJM Editorial  
Cc: 'wcarlo@peds.uab.edu'; 'wrich@ucsd.edu'  
Subject: Re: New England Journal of Medicine 09-11783.R1 SUPPORT Protocol

Thanks

Let us know if you need any additional items.

Rose

----- Original Message -----

From: Abel, Brendan <babel@nejm.org>  
To: 'Finer, Neil' <nfiner@ucsd.edu>; NEJM Editorial <editorial@nejm.org>  
Cc: Wally Carlo, M.D. <WCarlo@peds.uab.edu>; Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade <wrich@ucsd.edu>  
Sent: Fri Feb 26 08:34:27 2010  
Subject: RE: New England Journal of Medicine 09-11783.R1 SUPPORT Protocol

Thanks, Dr. Finer. I'll pass it right along to Caren Solomon.

Brendan

-----Original Message-----

From: Finer, Neil [mailto:nfiner@ucsd.edu]  
Sent: Friday, February 26, 2010 7:23 AM  
To: Abel, Brendan; NEJM Editorial

Cc: Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade  
Subject: RE: New England Journal of Medicine 09-11783.R1 SUPPORT Protocol

Hello Brendan

I am currently in Ireland and I received a message from Dr Solomon that she wanted the SUPPORT Protocol I am sorry that we did not send in before as thought we had done this - I have attached this - will you kindly send to Dr Solomon - I cannot access her email address from here Many thanks Neil Finer

-----Original Message-----

From: Abel, Brendan [mailto:[babel@nejm.org](mailto:babel@nejm.org)]  
Sent: Wednesday, February 24, 2010 6:26 AM  
To: Finer, Neil  
Subject: RE: New England Journal of Medicine 09-11783.R1

Dear Dr. Finer,

Thank you for sending along. Please also be sure to submit formally through the manuscript submission site. All you need to do is log into <http://mc.manuscriptcentral.com/nejm> and enter For Authors, where you will find a button to "Submit a Revision."

Let me know if you have any questions. And please keep working on sending all of the required forms.

Thanks,

Brendan

-----

Brendan Abel  
Editorial Assistant  
New England Journal of Medicine  
(617) 487-6584

-----Original Message-----

From: Finer, Neil [mailto:[nfiner@ucsd.edu](mailto:nfiner@ucsd.edu)]  
Sent: Tuesday, February 23, 2010 7:14 PM  
To: NEJM Editorial  
Cc: Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade; Gantz, Marie  
Subject: RE: New England Journal of Medicine 09-11783.R1

Dear Dr. Solomon

Thank you for your detailed responses and suggestions I am attaching 2 manuscripts for you - one with your comments and our responses and a clean copy The manuscript is now < 2700 words and the Abstract is 241 words We have addressed all your comments and those in your letter and made a response to each of these and acknowledged this in your comment. We inserted a comment regarding the suggestions in your letter. I on behalf of my collaborators, thank you for your diligence in reviewing this work. We hope that this revision is acceptable for publication in the Journal Yours truly Neil Finer

-----Original Message-----

From: [onbehalfof+editorial+nejm.org@manuscriptcentral.com](mailto:onbehalfof+editorial+nejm.org@manuscriptcentral.com)  
[mailto:[onbehalfof+editorial+nejm.org@manuscriptcentral.com](mailto:onbehalfof+editorial+nejm.org@manuscriptcentral.com)] On Behalf Of [editorial@nejm.org](mailto:editorial@nejm.org)  
Sent: Monday, February 22, 2010 11:36 AM  
To: Finer, Neil  
Subject: New England Journal of Medicine 09-11783.R1

Dear Dr. Finer:

I am writing again about your manuscript, "Early CPAP versus Surfactant in Extremely Preterm Infants: The SUPPORT Trial." Your revision has been evaluated by the editors and addresses several but not all concerns raised earlier. We must ask for some further changes before it could be accepted for publication.

At this point I am attaching a partially edited version of your manuscript in which I have inserted editorial comments and queries. (These comments are most easily viewed in Word by viewing in "reading layout" or "print layout.") In general, the changes I have suggested should be incorporated, unless there are places where I have inadvertently changed your meaning.

I would call your attention in particular to the following requests, which are also included in inserted comments in the text: (1) Please address the prior comment of the statistical reviewer in framing your results (ie We believe that providing in the Discussion section comment on the plausible increase or decrease in risk of the primary outcome consistent with your results, based on the 95% CI, would be interpretable by readers and would avoid any implication that the study proved non inferiority, which, as you note, was not the design.) 2) We continue to be concerned that the subgroup results by gestational age are overemphasized. Please include in reporting/discussing your subgroup results by gestational age the p value for interaction, and the number of analyses performed, and whether analyses prespecified, and acknowledge that these results must be viewed as hypothesis generating.

When you send in your revised manuscript, it is not necessary to provide a letter with responses to the inserted editorial comments, but please note anywhere that you did not make suggested changes (and why); it is fine to insert any responses in the associated comment box. Please return two copies of the revision: one in which the changes you have made are highlighted, and the other a clean copy.

Please include a word count for the text. As you know, the word count for text should not exceed 2700 words, and there should be no more than 5 tables or figures in the print version of the manuscript, though it is fine to include additional "web only" appendix tables.

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Please recall that the Journal requires that neither an article under consideration nor any part of its essential substance, tables, or figures has been or will be published or submitted elsewhere before appearing in the Journal.

We look forward to receiving your revised manuscript and will plan a prompt evaluation when it arrives. Please do not hesitate to contact me if you have questions.

Thank you again for your work.

Sincerely,

Caren Solomon

Caren G. Solomon, MD  
Deputy Editor

New England Journal of Medicine  
10 Shattuck Street  
Boston, MA 02115  
(617) 734-9800  
Fax: (617) 739-9864  
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**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "edward.donovan@cchmc.org"  
**Cc:** "kurt.schibler@cchmc.org"  
**Subject:** Fw: SUPPORT copyright for CPAP Paper  
**Date:** Friday, February 26, 2010 9:28:59 AM  
**Attachments:** NEJM-CTA-2009 (2).pdf

---

Ed

NEJM is missing your copyright form. Please complete the form and sign TODAY! You should fax it directly to NEJM at the number on the form.

Thanks  
Rose

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** 'Ed Donovan' <edward.donovan@cchmc.org>; 'Brenda Morris' (b) (6); Laroia, Nirupama <Nirupama\_Laroia@URMC.Rochester.edu>; 'Poindexter, Brenda B' <bpoindex@iupui.edu>  
**Cc:** 'Abel, Brendan' <babel@nejm.org>; Archer, Stephanie (NIH/NICHD) [E]  
**Sent:** Wed Feb 24 16:52:57 2010  
**Subject:** SUPPORT copyright for CPAP Paper

Hi,

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Manuscript number 09-11783

Author - Neil Finer

Title Early CPAP versus Surfactant in Extremely Preterm Infants

Thanks for your prompt attention

Rose

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network  
Pregnancy and Perinatology Branch  
Center for Developmental Biology and Perinatal Medicine  
Eunice Kennedy Shriver National Institute of Child Health and Human Development  
National Institutes of Health  
6100 Executive Blvd., Room 4B03  
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Bethesda, MD 20892  
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SIGNATURE \_\_\_\_\_

**From:** [Abel, Brendan](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Cc:** ["wcarlo@peds.uab.edu"](#); ["Finer, Neil"](#)  
**Subject:** RE: New England Journal of Medicine 09-11783.R1 SUPPORT Protocol  
**Date:** Friday, February 26, 2010 9:11:56 AM  
**Attachments:** [Support trials form updates.doc](#)

---

Hi Rose,

Here is the most updated list. We're getting closer- would love to get the remaining forms in today.

Thanks,

Brendan

-----Original Message-----

From: Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]  
Sent: Friday, February 26, 2010 8:38 AM  
To: Abel, Brendan; [nfiner@ucsd.edu](mailto:nfiner@ucsd.edu); NEJM Editorial  
Cc: [wcarlo@peds.uab.edu](mailto:wcarlo@peds.uab.edu); [wrich@ucsd.edu](mailto:wrich@ucsd.edu)  
Subject: Re: New England Journal of Medicine 09-11783.R1 SUPPORT Protocol

Thanks

Let us know if you need any additional items.

Rose

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From: Abel, Brendan <[babel@nejm.org](mailto:babel@nejm.org)>  
To: 'Finer, Neil' <[nfiner@ucsd.edu](mailto:nfiner@ucsd.edu)>; NEJM Editorial <[editorial@nejm.org](mailto:editorial@nejm.org)>  
Cc: Wally Carlo, M.D. <[WCarlo@peds.uab.edu](mailto:WCarlo@peds.uab.edu)>; Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade <[wrich@ucsd.edu](mailto:wrich@ucsd.edu)>  
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Brendan

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[<mailto:onbehalfof+editorial+nejm.org@manuscriptcentral.com>] On Behalf Of editorial@nejm.org  
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I would call your attention in particular to the following requests, which are also included in inserted comments in



the text: (1) Please address the prior comment of the statistical reviewer in framing your results (ie We believe that providing in the Discussion section comment on the plausible increase or decrease in risk of the primary outcome consistent with your results , based on the 95% CI, would be interpretable by readers and would avoid any implication that the study proved non inferiority, which, as you note, was not the design.) 2) We continue to be concerned that the subgroup results by gestational age are overemphasized. Please include in reporting/discussing your subgroup results by gestational age the p value for interaction, and the number of analyses performed, and whether analyses prespecified, and acknowledge that these results must be viewed as hypothesis generating.

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We look forward to receiving your revised manuscript and will plan a prompt evaluation when it arrives. Please do not hesitate to contact me if you have questions.

Thank you again for your work.

Sincerely,

Caren Solomon

Caren G. Solomon, MD  
Deputy Editor

New England Journal of Medicine  
10 Shattuck Street  
Boston, MA 02115  
(617) 734-9800  
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**09-11783 Neil Finer**

Early CPAP versus Surfactant in Extremely Preterm Infants: The SUPPORT Trial

**Missing Copyright Transfer Form**

Yoder  
Donovan  
Morris  
Laroia  
Poindexter

**Missing ICMJE Disclosure Form**

Carlo  
Walsh (Rec'd form, but consulting fee row in Sec. 2 not completed.)  
Laptook  
Yoder  
Faix  
Poole  
Ambalavanan  
Donovan  
Newman  
Sanchez  
Poindexter  
Cotton  
Van Muers  
Soed  
Duara  
O'Shea  
Bell  
Bhandari  
Watterberg

**09-11781 Carlo**

Oxygen Saturation Targets in Extremely Preterm Infants: The SUPPORT Trial

**Missing Copyright Transfer Form**

Finer  
Das  
Ambalavanan  
Morris  
Laroia

**Missing ICMJE Disclosure Form**

Carlo

Laptook

Yoder

Faix

Poole

Newman

Ambalavanan

Sanchez

Piazza

Phelps

Poindexter

Cotton

Van Meurs

Duara

Sood

O'Shea

Bell

Ehrenkranz

Watterberg

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "nfiner@ucsd.edu"  
**Subject:** Re: New England Journal of Medicine 09-11783.R1 SUPPORT Protocol  
**Date:** Friday, February 26, 2010 8:40:07 AM

---

Enjoy!  
Have a guinness for me!!

----- Original Message -----

From: Finer, Neil <nfiner@ucsd.edu>  
To: Higgins, Rosemary (NIH/NICHD) [E]  
Sent: Fri Feb 26 08:38:17 2010  
Subject: RE: New England Journal of Medicine 09-11783.R1 SUPPORT Protocol

Hi Rose  
A prayer or 2  
Be well  
Neil

-----Original Message-----

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
Sent: Friday, February 26, 2010 5:38 AM  
To: 'babel@nejm.org'; Finer, Neil; 'editorial@nejm.org'  
Cc: 'wcarlo@peds.uab.edu'; Rich, Wade  
Subject: Re: New England Journal of Medicine 09-11783.R1 SUPPORT Protocol

Thanks  
Let us know if you need any additional items.

Rose

----- Original Message -----

From: Abel, Brendan <babel@nejm.org>  
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## **Higgins, Rosemary (NIH/NICHD) [E]**

---

**From:** Finer, Neil <nfiner@ucsd.edu>  
**Sent:** Friday, February 26, 2010 7:23 AM  
**To:** Abel, Brendan; editorial@nejm.org  
**Cc:** Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade  
**Subject:** RE: New England Journal of Medicine 09-11783.R1 SUPPORT Protocol  
**Attachments:** Protocol.pdf

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[REDACTED]

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**From:** Susan Hintz  
**To:** Newman, Jamie  
**Cc:** Vohr, Betty; Hammond, Jane; Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** Re: SUPPORT Spanish speaking at sites at 18m  
**Date:** Thursday, February 25, 2010 8:25:55 PM

---

Hi Jamie

Yes, that would be great.

S

Sent from my iPhone

On Feb 25, 2010, at 12:47 PM, "Newman, Jamie" <newman@rti.org> wrote:

> In Sept 2008 Marie Gantz looked into how many SUPPORT pts at 18 months  
> were Spanish speaking and found:  
> Out of 237 SUPPORT kids who have had the Bayley III exam, 26 exams  
> have  
> not been conducted in English, and the primary language is Spanish  
> of 19  
> of those 26 kids. Another 2 of the kids with non-English exams had a  
> primary language of English and secondary language of Spanish.

>  
> I can ask her to re-run this with the most recent data but first  
> want to  
> confirm that this is what you are looking for?  
> Thanks, Jamie

>

> -----Original Message-----

> From: Vohr, Betty [mailto:BVohr@WIHRI.org]  
> Sent: Thursday, February 25, 2010 3:19 PM  
> To: Susan Hintz; Newman, Jamie  
> Cc: Hammond, Jane; Rosemary Higgins  
> Subject: RE: Gold Standards for SUPPORT MRI School Age

>

> Glad you are thinking ahead. Can we get a printout from RTI of the  
> "n"  
> of Spanish speaking at sites at 18m ? This might provide a feel for  
> the  
> extent of the problem.

> BV

>

> -----Original Message-----

> From: Susan Hintz [mailto:srhintz@stanford.edu]  
> Sent: Thursday, February 25, 2010 1:41 PM  
> To: Newman, Jamie  
> Cc: Jane Hammond; Rosemary Higgins; Vohr, Betty  
> Subject: Re: Gold Standards for SUPPORT MRI School Age

>

> Hi,

>

> In response to questions about Gold Standards for the the school age  
> SUPPORT neuroimaging and outcomes study - For the Bateria III and

- > Spanish version of the WISC, I had previously said that perhaps the
- > psychologist at New Mexico and our Spanish-speaking psychologist Maria
- > Elena might be interested in this. However, I know that, as you have
- > said before, there are no current "Spanish" gold standard examiners in
- > the extended Hypothermia WISC group. I think we may need to re-think
- > this for the SUPPORT Neuroimaging and Outcomes follow-up (now called
- > the
- > NEURO cohort). We have a lot more patients (expected) than in the
- > Hypothermia extended follow-up, and at least we should have a "point
- > person" or two for questions if they come up on the Spanish version.
- > Maybe they don't need to be designated as a "gold standard" per se,
- > and
- > certainly I do NOT think that SEPARATE certification videos are
- > required.
- >
- > Input on this would be appreciated
- >
- > As we have been discussing by email over the past weeks-months, the M-
- > ABC-II gold standard examiners will certainly include myself, Betty
- > Vohr, one of our physical therapists (Elish Burne) and it appears that
- > one of the PT's at Tufts may be interested from what I am hearing.
- > I am
- > in the process of trying to hone in on date for one of the
- > developers of
- > the test (David Sugden) to come to do a "gold standard"
- > training.
- >
- > Susan
- >
- >
- >
- > This e-mail and any files transmitted with it are confidential and
- > intended solely for the use of the individual
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- > please notify sender by reply e-mail and
- > delete this message and any attachment(s) immediately. Thank you for
- > your consideration in this matter.

**From:** Zaterka-Baxter, Kristin  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: SUPPORT ROP adjudication document summary  
**Date:** Thursday, February 25, 2010 3:21:29 PM  
**Attachments:** [Adjudication Case Review all reviewers.xls](#)  
[Effect of ROP adjudication - 05JAN10.doc](#)

---

No bother at all – please see attached – let me know if these are the ones you need.

Thanks,  
Kris

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Thursday, February 25, 2010 3:19 PM  
**To:** Zaterka-Baxter, Kristin  
**Subject:** SUPPORT ROP adjudication document summary

Kris

Sorry to bother you but can you send me the summary document that Marie generated with respect to the ROP adjudication? I don't have access to all of my files.

Thanks  
Rose

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network

SUPPORT FOR ADJUDICATION CASES

Infant ID	Wallace/Freedman	Markowitz	Hutchinson	Comments
Infant 1	1	3	1	
Infant 2	1	3	1	
Infant 3	1	3	1	
Infant 4	1	3	1	
Infant 5	1	1	1	
Infant 6	1	3	1	
Infant 7	1	3	1	
Infant 8	3	3	1	
Infant 9	3	3	1	
Infant 10	3	3	3	
Infant 11	1	3	1	
Infant 12	1	3	1	
Infant 13	1	1	1	
Infant 14	1	3	1	
Infant 15	1	3	3	
Infant 16	1	1	1	
Infant 17	1	3	1	
Infant 18	3	3	3	
Infant 19	1	3	3	
Infant 20	1	3	1	
Infant 21	1	3	3	but probably not
Infant 22	3	3	1	
Infant 23	1	3	1	
Infant 24	1	3	1	
Infant 25	1	3	1	
Infant 26	1	3	1	
Infant 27	1	3	1	
Infant 28	1	3	1	
Infant 29	1	3	1	
Infant 30	1	3	1	
Infant 31	1	1	1	
Infant 32	1	3	1	
Infant 33	1	3	1	
Infant 34	1	1	1	
Infant 35	1	1	1	
Infant 36	1	1	1	
Infant 37	1	1	1	
Infant 38	1	1	1	
Infant 39	1	3	1	
Infant 40	1	1	1	
Infant 41	1	3	1	
Infant 42	1	3	1	
Infant 43	1	1	1	
Infant 44	1	1	1	
Infant 45	1	1	1	
Infant 46	1	3	1	
Infant 47	1	1	1	
Infant 48	1	3	1	
Infant 49	1	3	1	
Infant 50	1	1	1	
Infant 51	1	3	1	
Infant 52	1	3	1	
Infant 53	3	3	1	
Infant 54	1	3	1	
Infant 55	1	3	1	
Infant 56	3	3	1	
Infant 57	1	3	1	
Infant 58	1	3	1	
Infant 59	3	3	3	

Infant ID	Wallace/Freedman	Markowitz	Hutchinson	Comments
Infant 60	1	3	1	
Infant 61	1	3	1	
Infant 62	1	3	1	
Infant 63	1	3	1	
Infant 64	3	3	1	
Infant 65	1	3	1	
Infant 66	1	3	1	
Infant 67	1	3	1	? This one is a little strange. Why would they suddenly have stage 3 ROP @ 86 weeks that was not there @ 40.9 wks?
Infant 68	3	3	3	
Infant 69	1	3	1	
Infant 70	1	1	1	
Infant 71	1	1	1	
Infant 72	1	3	1	
Infant 73	1	3	1	
Infant 74	1	3	1	
Infant 75	1	3	1	
Infant 76	1	3	1	
Infant 77	1	3	1	
Infant 78	1	3	1	
Infant 79	1	3	1	
Infant 80	1	3	1	
Infant 81	3	3	1	
Infant 82	1	3	1	
Infant 83	1	3	1	
Infant 84	1	3	1	
Infant 85	3	3	1	
Infant 86	3	3	3	
Infant 87	1	3	1	
Infant 88	1	3	1	
Infant 89	1	1	1	
Infant 90	1	3	1	
Infant 91	1	3	1	
Infant 92	1	3	1	
Infant 93	3	3	1	
Infant 94	1	3	1	
Infant 95	1	3	3	



- 1 = Probably never had ROP that met criteria for ROP intervention (laser/cryo) in either eye
- 2 = Probably did meet criteria fro ROP intervention in at least one eye
- 3 = There is no way to know if ROP criteria may have been met

Effect of ROP adjudication for Low vs. High SpO<sub>2</sub>

Characteristic	Low SpO <sub>2</sub> (N=664)	High SpO <sub>2</sub> (N=662)	Relative Risk for Low SpO <sub>2</sub> vs. High SpO <sub>2</sub> (95% CI)	Adjusted P-value
ROP/death without adjudication result	171/605 (28.3)	198/616 (32.1)	0.9 (0.76, 1.06)	0.2050
ROP among survivors without adjudication result	41/475 (8.6)	91/509 (17.9)	0.52 (0.37, 0.73)	0.0002
ROP/death with adjudication result (majority rule)*	171/642 (26.6)	198/656 (30.2)	0.91 (0.77, 1.07)	0.2532
ROP among survivors with adjudication result (majority rule)*	41/512 (8.0)	91/549 (16.6)	0.52 (0.37, 0.73)	0.0002
ROP/death with adjudication result ('unknown' set to ROP=Y)**	183/654 (28.0)	204/662 (30.8)	0.93 (0.79, 1.1)	0.4125
ROP among survivors with adjudication result ('unknown' set to ROP=Y)**	53/524 (10.1)	97/555 (17.5)	0.62 (0.45, 0.84)	0.0019

Relative risks are adjusted for GA stratification, center and familial clustering.

Centers with fewer than 10 infants enrolled and those with an incidence of zero for the outcome in question were combined with the geographically closest site for RR calculation.

\* Majority rule: If 2 reviewers determined that the infant 'Probably never had ROP that met criteria for ROP intervention (laser/cryo) in either eye' then ROP=N; if 2 reviewers determined that 'There is no way to know if ROP criteria may have been met' then ROP=missing.

\*\* 'Unknown' set to ROP=Y: If 2 reviewers determined that the infant 'Probably never had ROP that met criteria for ROP intervention (laser/cryo) in either eye' then ROP=N; if 2 reviewers determined that 'There is no way to know if ROP criteria may have been met' then ROP=Y.

Characteristic	Low SpO <sub>2</sub> (N=276)	High SpO <sub>2</sub> (N=289)	Relative Risk for Low SpO <sub>2</sub> vs High SpO <sub>2</sub> (95% CI)	Adjusted P-value
ROP/death without adjudication result	117/256 (45.7)	139/271 (51.3)	0.88 (0.73, 1.05)	0.1648
ROP among survivors without adjudication result	32/171 (18.7)	66/198 (33.3)	0.58 (0.4, 0.85)	0.0046
ROP/death with adjudication result (majority rule)*	117/270 (43.3)	139/286 (48.6)	0.89 (0.74, 1.07)	0.2022
ROP among survivors with adjudication result (majority rule)*	32/185 (17.3)	66/213 (31.0)	0.58 (0.4, 0.85)	0.0051
ROP/death with adjudication result ('unknown' set to ROP=Y)**	123/276 (44.6)	142/289 (49.1)	0.9 (0.75, 1.08)	0.2768
ROP among survivors with adjudication result ('unknown' set to ROP=Y)**	38/191 (19.9)	69/216 (31.9)	0.64 (0.45, 0.91)	0.0130

Relative risks are adjusted for GA stratification, center and familial clustering.

Centers with fewer than 10 infants enrolled and those with an incidence of zero for the outcome in question were combined with the geographically closest site for RR calculation.

\* Majority rule: If 2 reviewers determined that the infant 'Probably never had ROP that met criteria for ROP intervention (laser/cryo) in either eye' then ROP=N; if 2 reviewers determined that 'There is no way to know if ROP criteria may have been met' then ROP=missing.

\*\* 'Unknown' set to ROP=Y: If 2 reviewers determined that the infant 'Probably never had ROP that met criteria for ROP intervention (laser/cryo) in either eye' then ROP=N; if 2 reviewers determined that 'There is no way to know if ROP criteria may have been met' then ROP=Y.

Characteristic	Low SpO <sub>2</sub> (N=378)	High SpO <sub>2</sub> (N=373)	Relative Risk for Low SpO <sub>2</sub> vs. High SpO <sub>2</sub> (95% CI)	Adjusted P-value
ROP/death without adjudication result	54/349 (15.5)	59/345 (17.1)	0.95 (0.67, 1.34)	0.7575
ROP among survivors without adjudication result	9/304 (3.0)	25/311 (8.0)	0.38 (0.18, 0.79)	0.0098
ROP/death with adjudication result (majority rule)*	54/372 (14.5)	59/370 (15.9)	0.96 (0.68, 1.36)	0.8068
ROP among survivors with adjudication result (majority rule)*	9/327 (2.8)	25/336 (7.4)	0.38 (0.18, 0.8)	0.0108
ROP/death with adjudication result ('unknown' set to ROP=Y)**	60/378 (15.9)	62/373 (16.6)	1 (0.72, 1.4)	0.9831
ROP among survivors with adjudication result ('unknown' set to ROP=Y)**	15/333 (4.5)	28/339 (8.3)	0.56 (0.3, 1.02)	0.0597

Relative risks are adjusted for GA stratification, center and familial clustering.

Centers with fewer than 10 infants enrolled and those with an incidence of zero for the outcome in question were combined with the geographically closest site for RR calculation.

\* Majority rule: If 2 reviewers determined that the infant 'Probably never had ROP that met criteria for ROP intervention (laser/cryo) in either eye' then ROP=N; if 2 reviewers determined that 'There is no way to know if ROP criteria may have been met' then ROP=missing.

\*\* 'Unknown' set to ROP=Y: If 2 reviewers determined that the infant 'Probably never had ROP that met criteria for ROP intervention (laser/cryo) in either eye' then ROP=N; if 2 reviewers determined that 'There is no way to know if ROP criteria may have been met' then ROP=Y.

Effect of ROP adjudication for CPAP vs. Surfactant

Outcome	CPAP (N=663)	Surfactant (N=654)	Relative Risk (95% CI)	Adjusted P-value
ROP/death without adjudication result	176/620 (28.4)	193/601 (32.1)	0.87 (0.74, 1.03)	0.0971
ROP among survivors without adjudication result	67/511 (13.1)	65/473 (13.7)	0.94 (0.69, 1.28)	0.7140
ROP/death with adjudication result (majority rule)*	176/654 (26.9)	193/644 (30.0)	0.89 (0.75, 1.05)	0.1601
ROP among survivors with adjudication result (majority rule)*	67/545 (12.3)	65/516 (12.6)	0.96 (0.7, 1.31)	0.7969
ROP/death with adjudication result ('unknown' set to ROP=Y)**	185/663 (27.9)	202/653 (30.9)	0.89 (0.76, 1.05)	0.1608
ROP among survivors with adjudication result ('unknown' set to ROP=Y)**	76/554 (13.7)	74/525 (14.1)	0.96 (0.72, 1.28)	0.7599

Relative risks are adjusted for GA stratification, center and familial clustering.

Centers with fewer than 10 infants enrolled and those with an incidence of zero for the outcome in question were combined with the geographically closest site for RR calculation.

\* Majority rule: If 2 reviewers determined that the infant 'Probably never had ROP that met criteria for ROP intervention (laser/cryo) in either eye' then ROP=N; if 2 reviewers determined that 'There is no way to know if ROP criteria may have been met' then ROP=missing.

\*\* 'Unknown' set to ROP=Y: If 2 reviewers determined that the infant 'Probably never had ROP that met criteria for ROP intervention (laser/cryo) in either eye' then ROP=N; if 2 reviewers determined that 'There is no way to know if ROP criteria may have been met' then ROP=Y.

Stratification	CPAP (N=285)	Surfactant (N=280)	Relative Risk (95% CI)	Adjusted P-value
ROP/death without adjudication result	112/266 (42.1)	144/261 (55.2)	0.74 (0.62, 0.89)	0.0015
ROP among survivors without adjudication result	44/198 (22.2)	54/171 (31.6)	0.71 (0.5, 1)	0.0525
ROP/death with adjudication result (majority rule)*	112/281 (39.9)	144/275 (52.4)	0.75 (0.63, 0.91)	0.0031
ROP among survivors with adjudication result (majority rule)*	44/213 (20.7)	54/185 (29.2)	0.72 (0.51, 1.02)	0.0663
ROP/death with adjudication result ('unknown' set to ROP=Y)**	116/285 (40.7)	149/280 (53.2)	0.75 (0.63, 0.9)	0.0024
ROP among survivors with adjudication result ('unknown' set to ROP=Y)**	48/217 (22.1)	59/190 (31.1)	0.72 (0.52, 1)	0.0487

Relative risks are adjusted for GA stratification, center and familial clustering.

Centers with fewer than 10 infants enrolled and those with an incidence of zero for the outcome in question were combined with the geographically closest site for RR calculation.

\* Majority rule: If 2 reviewers determined that the infant 'Probably never had ROP that met criteria for ROP intervention (laser/cryo) in either eye' then ROP=N; if 2 reviewers determined that 'There is no way to know if ROP criteria may have been met' then ROP=missing.

\*\* 'Unknown' set to ROP=Y: If 2 reviewers determined that the infant 'Probably never had ROP that met criteria for ROP intervention (laser/cryo) in either eye' then ROP=N; if 2 reviewers determined that 'There is no way to know if ROP criteria may have been met' then ROP=Y.

Characteristic	CRAP (N=373)	Surfactant (N=373)	Relative Risk to CRAP vs Surfactant (95% CI)	Adjusted P-value
ROP/death without adjudication result	64/354 (18.1)	49/340 (14.4)	1.25 (0.88, 1.77)	0.2153
ROP among survivors without adjudication result	23/313 (7.3)	11/302 (3.6)	2.19 (1.06, 4.53)	0.0343
ROP/death with adjudication result (majority rule)*	64/373 (17.2)	49/369 (13.3)	1.29 (0.9, 1.83)	0.1616
ROP among survivors with adjudication result (majority rule)*	23/332 (6.9)	11/331 (3.3)	2.25 (1.09, 4.67)	0.0287
ROP/death with adjudication result ('unknown' set to ROP=Y)**	69/378 (18.3)	53/373 (14.2)	1.28 (0.91, 1.79)	0.1502
ROP among survivors with adjudication result ('unknown' set to ROP=Y)**	28/337 (8.3)	15/335 (4.5)	1.97 (1.06, 3.66)	0.0332

Relative risks are adjusted for GA stratification, center and familial clustering.

Centers with fewer than 10 infants enrolled and those with an incidence of zero for the outcome in question were combined with the geographically closest site for RR calculation.

\* Majority rule: If 2 reviewers determined that the infant 'Probably never had ROP that met criteria for ROP intervention (laser/cryo) in either eye' then ROP=N; if 2 reviewers determined that 'There is no way to know if ROP criteria may have been met' then ROP=missing.

\*\* 'Unknown' set to ROP=Y: If 2 reviewers determined that the infant 'Probably never had ROP that met criteria for ROP intervention (laser/cryo) in either eye' then ROP=N; if 2 reviewers determined that 'There is no way to know if ROP criteria may have been met' then ROP=Y.

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Dennis Wallace"  
**Subject:** FW: CONFIDENTIAL SUPPORT CPAP paper resubmission  
**Date:** Thursday, February 25, 2010 1:27:00 PM  
**Attachments:** NEJM CPAP Revision Clean Final for editor Feb 23 (2).doc

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Here is the most recent version of the CPAP paper that went back to NEJM on Tuesday

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Wednesday, February 24, 2010 12:18 PM  
**To:** 'vineet.bhandari@yale.edu'; (susie.buchter@oz.ped.emory.edu); 'Duara, Shahnaz'; 'Finer, Neil'; Gantz, Marie; Laroia, Nirupama; 'Brenda Morris'; nancy newman; 'Michael O`Shea'; 'Poole Kenneth (E-mail)'; Rich, Wade; bsood@med.wayne.edu; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Matthew Bizzarro; Michelle Walsh; Mickey Caplan; Oh William (E-mail); Pablo Sanchez; Roger Faix; Ronald Goldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; 'Zaterka-Baxter, Kristin'; 'Huitema, Carolyn Petrie'; 'Cunningham, Meg'  
**Subject:** CONFIDENTIAL SUPPORT CPAP paper resubmission

Hi,

NEJM asked for some minor clarifications on the CPAP paper. Attached is the most recent version which has gone back to the editors. I will keep everyone posted of any progress.

If you received an email regarding your ICJME form, please complete and return to Brendan Abel ASAP. IF you did not get a separate email, you do not need to do anything.

Thanks for all your help!!!

Rose

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network  
Pregnancy and Perinatology Branch  
Center for Developmental Biology and Perinatal Medicine  
Eunice Kennedy Shriver National Institute of Child Health and Human Development  
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Bethesda, MD 20892  
For overnight delivery use Rockville, MD 20852  
301-496-5575  
301-496-3790 (FAX)  
higginsr@mail.nih.gov



**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Dennis Wallace"  
**Subject:** FW: CONFIDENTIAL: New England Journal of Medicine 09-11781.R1  
**Date:** Thursday, February 25, 2010 1:27:00 PM  
**Attachments:** CarloSUPPORTwqgscomments rev 2- accepted changes.doc  
CarloSUPPORTwqgscomments rev 2 - tracked changes.doc

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Here is the saturation paper - Wally got some minor requests for revisions last night and is working on them today

Rose

-----Original Message-----

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Friday, February 19, 2010 5:12 PM  
**To:** Finer, Neil; Anthony Piazza (Anthony.Piazza@oz.ped.emory.edu); bsood@med.wayne.edu; nancy newman; Gantz, Marie; Laroia, Nirupama; 'Phelps, Dale'; 'Duara, Shahnaz'; 'Michael O'Shea'; Vivek Narendran; Rich, Wade; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Matthew Bizzarro; Michelle Walsh; Mickey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald Goldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa  
**Subject:** CONFIDENTIAL: New England Journal of Medicine 09-11781.R1

Hi all, Here is the revised saturation paper.

Thanks to Wally for his quick turnaround!!!

Rose

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Hale, Ellen"  
**Subject:** RE: SUPPORT FU  
**Date:** Thursday, February 25, 2010 1:20:00 PM

---

Enjoy the pancakes!!  
Rose

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**From:** Hale, Ellen [mailto:ehale@emory.edu]  
**Sent:** Thursday, February 25, 2010 1:13 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: SUPPORT FU

Rose,  
Child has been seen and I am awaiting NF05 from examiner.  
Exciting news. Have found another SUPPORT child who needs eye exam. Am going to IHOP now to try to find mother.  
Ellen

Ellen Hale, RN, BS, CCRC  
Neonatal Research Network  
Emory University School of Medicine  
Department of Pediatrics - Division of Neonatology  
Office: 404-778-1679  
Fax: 404-778-1467

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]  
**Sent:** Monday, February 22, 2010 10:10 AM  
**To:** Hale, Ellen; Barbara Stoll; Ira Adams-Chapman; Ellen Hale  
**Cc:** Gantz, Marie  
**Subject:** SUPPORT FU

Hi,

We are missing the following primary outcomes for the SUPPORT FU study. Let us know how you are doing.

Thanks for all the effort!!  
Rose

CENTER NETWORK FU\_message

9 (b) FU marked as complete (per NF10/SF10) but NF05 has not been completed.

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network  
Pregnancy and Perinatology Branch

This document is provided for reference purposes only. Persons with disabilities having difficulty accessing information in this document should e-mail NICHD FOIA Office at NICHDFOIARequest@mail.nih.gov for assistance.

Center for Developmental Biology and Perinatal Medicine

Eunice Kennedy Shriver National Institute of Child Health and Human Development

National Institutes of Health

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For overnight delivery use Rockville, MD 20852

301-496-5575

301-496-3790 (FAX)

[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

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**From:** Wally Carlo, M.D.  
**To:** Das, Abhik; Higgins, Rosemary (NIH/NICHD) [F]; Poole, W. Kenneth  
**Subject:** RE: SUPPORT DSMC Stopping recommendations document  
**Date:** Friday, February 25, 2005 12:59:39 PM

---

Ok, I get it. Thanks, the stats were beyond me. wally

-----Original Message-----

From: Das, Abhik [mailto:adas@rti.org]  
Sent: Friday, February 25, 2005 11:55 AM  
To: Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD); Poole, W. Kenneth  
Subject: RE: SUPPORT DSMC Stopping recommendations document

I don't think we are saying that. We will construct Pocock safety bounds for our outcomes, and if there is a difference at  $p = 0.001$  (or something like that, depending on the number of interim looks), then the DSMC may consider stopping (they may consider doing that without looking at any  $p$  values at all; it is up to them!). Note that the test statistic constructed for this purpose will use the standard error, not the standard deviation.

-----Original Message-----

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]  
Sent: Friday, February 25, 2005 12:48 PM  
To: Das, Abhik; Higgins, Rosemary (NIH/NICHD); Poole, W. Kenneth  
Subject: RE: SUPPORT DSMC Stopping recommendations document

Does that mean the IVH rate has to be 85% in the experimental group to stop? Wally

-----Original Message-----

From: Das, Abhik [mailto:adas@rti.org]  
Sent: Friday, February 25, 2005 11:46 AM  
To: Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD); Poole, W. Kenneth  
Subject: RE: SUPPORT DSMC Stopping recommendations document

I am not sure I understand your question. If you just want the value, it is  $2 * \text{square root of } (0.24 * (1 - 0.24)) = 0.85$ .

-----Original Message-----

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]  
Sent: Friday, February 25, 2005 12:39 PM  
To: Das, Abhik; Higgins, Rosemary (NIH/NICHD); Poole, W. Kenneth  
Subject: RE: SUPPORT DSMC Stopping recommendations document

Abhik: Could you us an idea of what the 2 SD for the 24% IVH rate would be? Wally

-----Original Message-----

From: Das, Abhik [mailto:adas@rti.org]  
Sent: Friday, February 25, 2005 11:34 AM  
To: Higgins, Rosemary (NIH/NICHD); Poole, W. Kenneth  
Cc: Wally Carlo, M.D.  
Subject: RE: SUPPORT DSMC Stopping recommendations document

SD for a proportion  $p$  is simply the square root of  $p*(1-p)$ , which lies

in the range (0,0.5]; so  $2*SD$  would range between (0,1]. It is higher for proportions closer to 0.5 and gets lower for more extreme prevalence rates (very high or very low). Since the rate for IVH is not very extreme in this population (around 24%), the associated  $2*SD$  would be high. As such, the standard error and specially the range across sites are the more appropriate/useful quantities to look at here.

Thanks

Abhik

-----Original Message-----

From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]  
Sent: Friday, February 25, 2005 11:43 AM  
To: Poole, W. Kenneth; Das, Abhik  
Cc: 'wcarlo@peds.uab.edu'  
Subject: Fw: SUPPORT DSMC Stopping recommendations document

Ken or Abhik

Can you answer this?

Thanks

Rose

-----  
Sent from my BlackBerry Wireless Handheld

-----Original Message-----

From: Wally Carlo, M.D. <WCarlo@peds.uab.edu>  
To: Higgins, Rosemary (NIH/NICHD) <higginsr@mail.nih.gov>;  
nfiner@ucsd.edu <nfiner@ucsd.edu>; wrich@ucsd.edu <wrich@ucsd.edu>;  
Everett, Ruth <REverett@med.miami.edu>; edward.donovan@chmcc.org  
<edward.donovan@chmcc.org>; Michele Walsh <mcw3@case.edu>;  
sduara@miami.edu <sduara@miami.edu>; Poole, W. Kenneth <poo@rti.org>;  
Das, Abhik <adas@rti.org>; Jobea0@chmcc.org <Jobea0@chmcc.org>  
CC: petrie@rti.org <petrie@rti.org>; bkh@rti.org <bkh@rti.org>  
Sent: Fri Feb 25 11:40:14 2005  
Subject: RE: SUPPORT DSMC Stopping recommendations document

Rose: Looks ok except I do not understand the  $2X$  SD data reaching such high proportions (e.g. 85% for grade 3-4 IVH) or is that 0.85 of 23.7%?  
Wally

-----  
From: Higgins, Rosemary (NIH/NICHD) [mailto:higginsr@mail.nih.gov]  
Sent: Tuesday, February 22, 2005 3:39 PM  
To: Wally Carlo, M.D.; nfiner@ucsd.edu; wrich@ucsd.edu; Everett, Ruth;  
edward.donovan@chmcc.org; Michele Walsh; sduara@miami.edu; Poole, W.  
Kenneth; Das, Abhik; Jobea0@chmcc.org  
Cc: petrie@rti.org; bkh@rti.org  
Subject: SUPPORT DSMC Stopping recommendations document

Hi SUPPORT Subcommittee,

Attached is a continuing draft of the DSMC rules for SUPPORT. I had received a few comments and have incorporated them. Please comment by Friday, February 25 so that we can send the document to the entire steering committee.

Also, we will need to have a plan for extra oximeters at a few selected sites which I am currently trying to put together.

Thanks

Rose

Rosemary D. Higgins, M.D.

Program Scientist for the Neonatal Research Network

Pregnancy and Perinatology Branch

Center for Developmental Biology and Perinatal Medicine

NICHD, NIH

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301-496-3790 (FAX)

[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

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Version: 6.0.857 / Virus Database: 584 - Release Date: 2/10/2005

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Dennis Wallace"  
**Subject:** FW: SUPPORT Oximeters used for Physio Challenge, 2009-11.xls  
**Date:** Thursday, February 25, 2010 12:48:00 PM  
**Attachments:** SUPPORT Oximeters used for Physio Challenge, 2009-11.xls

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Here is the site information

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Tuesday, February 23, 2010 4:46 PM  
**To:** Gantz, Marie  
**Cc:** 'Finer, Neil'; Wally Carlo, M.D.  
**Subject:** FW: SUPPORT Oximeters used for Physio Challenge, 2009-11.xls

Here it is

Rose

---

**From:** Archer, Stephanie (NIH/NICHD) [E]  
**Sent:** Tuesday, February 23, 2010 4:10 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** SUPPORT Oximeters used for Physio Challenge, 2009-11.xls

Here are the survey results.





**From:** Webb, Robin E.  
**To:** Webb, Robin E.; Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; Wally Carlo, M.D.; mcw3@case.edu; Bradley Yoder; Roger Faix; alaptook@WIHRI.org; kurt.schibler@cchmc.org; Das, Abhik; Wallace, Dennis; nancy\_newman; Rich, Wade; Gantz, Marie  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Cunningham, Meg; Huitema, Carolyn Petrie; Irene, Amanda; StWilliams@peds.uab.edu; fmartinez@ucsd.edu; Carolyn.Grier@UHhospitals.org; bvecchio@careNE.org  
**Subject:** SUPPORT Intermittent Hypoxia  
**Date:** Thursday, February 25, 2010 11:38:33 AM

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The call to review the secondary study has been scheduled for:

**Monday, 3/22**  
**2:00pm ET**

Dial:  
**Within the USA**  
866-675-(b) (6)  
or

**Outside the USA**  
1-203-310-(b) (6)

Then, enter Participant Passcode:  
(b) (6)

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Kristi Watterberg"; "goldb008@mc.duke.edu"; "matt\_laughon@med.unc.edu"; "Michelle Walsh"; "adas@rti.org"; "Dennis Wallace"; "Kathleen.A.Kennedy@uth.tmc.edu"; "richard.ehrenkranz@yale.edu"  
**Subject:** RE: RE: SUPPORT data  
**Date:** Thursday, February 25, 2010 10:55:00 AM  
**Attachments:** HC RCT 8-2009 revised KW 11-15.doc

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The advisory board approved the study as a two armed trial. I have attached the version of the protocol that was sent to the advisory board/outside reviewers.

Rose

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**From:** Kristi Watterberg [mailto:KWatterberg@salud.unm.edu]  
**Sent:** Wednesday, February 24, 2010 11:20 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; goldb008@mc.duke.edu; matt\_laughon@med.unc.edu; Michelle Walsh; adas@rti.org; Dennis Wallace; Kathleen.A.Kennedy@uth.tmc.edu; richard.ehrenkranz@yale.edu  
**Subject:** Fwd: RE: SUPPORT data

Hello, all. I am forwarding Marie's data regarding infants who remain on mechanical ventilation at 14 days and their BPD/death outcomes. As you will see, about 44% of the enrolled infants were on mechanical ventilation at that time (526). Of those, 30% survived without BPD, which is very close to the data provided by Abhik (24% of babies with at least 14 days of mechanical ventilation survived without BPD).

This is reassuring for our sample size estimation - if survival without BPD was 25%, as from Abhik's data, the total sample size to detect a 10% difference would be 658; if survival without BPD had improved to 35%, we would need 750. Because we cannot be sure of the baseline incidence at the time we start the study, we proposed a conservative sample size of 800. The SUPPORT data are between those two estimates, so the proposed sample size should be appropriate.

To make the best use of our conference call time on Monday, I would like to get a current poll of the subcommittee regarding inclusion of dexamethasone in the study before the call, so we can make a decision and go forward.

As I see it, a straight HC/placebo trial will give us a reasonable chance of enrolling an adequate sample size in less than 3 years within the network. We run the risk of futility - but if HC doesn't work to facilitate extubation and decrease BPD, that's a very important finding. A three-way trial will stretch the capability of the network to enroll, and still would not give us a large enough sample size to compare HC/Dex anyway for non-inferiority.

so I think we are better off running a straight HC/placebo trial to find out if it works. If it does, we have lots of evidence to say HC is better for neurodevelopmental outcomes, and this trial will add to the evidence available regarding outcome after HC Rx. If it doesn't, then we could proceed to a straight dex/placebo trial in a subsequent protocol. After all our e-mail discussion regarding a three-arm protocol comparing each drug to the same placebo group, I know Kathleen and Michelle favor a single drug (HC) trial. Rich, have you changed your position after all the back and forth? Others?

Rose, what is our position in responding to the outside reviewers in this regard?

Thanks, Kristi

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 401 – 1500 GRAMS BIRTH WEIGHT

Kristi Watterberg, University of New Mexico

Michele Walsh, Case Western Reserve University

Kathleen Kennedy, University of Texas, Houston

Ron Goldberg, Duke University

Matthew Laughon, University of North Carolina, Chapel Hill

Richard Ehrenkranz, Yale University

Dennis Wallace and Abhik Das, RTI

**ABSTRACT:** Bronchopulmonary dysplasia (BPD) remains a leading morbidity of the extremely preterm infant, and prolonged mechanical ventilation is associated with increased risk for BPD. Dexamethasone has been used previously to facilitate extubation and decrease the incidence of BPD; however, due to adverse effects on neurodevelopmental outcomes, the use of this drug has decreased. One cohort study has suggested that hydrocortisone (HC) also facilitates extubation. HC has thus far not been associated with adverse neurodevelopmental outcomes in either cohort studies or randomized controlled trials. A recent meta-analysis of postnatal corticosteroid therapy begun after the first week of life suggested that “late therapy may reduce neonatal mortality without significantly increasing the risk of adverse long-term neurodevelopmental outcomes,” although the methodological quality of some of the follow up was acknowledged to be limited. We propose a randomized controlled trial to study the efficacy and safety of a 10-day tapering course of hydrocortisone treatment for infants 401 – 1500 grams birth weight who remain intubated at 14 - 28 days postnatal age. Based on previous Network data, this defines a population with a risk of death or BPD at 36 weeks postmenstrual age of approximately 65 – 75%. The primary outcome for this study will incorporate both (1) survival without moderate to severe BPD by Network definition and (2) survival without major NDI at 18 – 22 months corrected age. Therefore, the results of this study will be reported only when follow up data are available. Secondary outcomes will include short term measures such as respiratory morbidities and growth at 36 weeks postmenstrual age, and long term measures including growth and other outcomes at 18 – 22 months corrected age.

## STATEMENT OF THE PROBLEM

Bronchopulmonary dysplasia remains a leading morbidity of the extremely preterm infant, resistant to therapeutic interventions and associated with adverse neurodevelopmental outcomes (1-3). Most studies indicate that its rate of occurrence has not decreased in recent years (4), and several reports suggest that the incidence and/or severity of the disease may be increasing as postnatal glucocorticoid use has decreased (5-7). Although dexamethasone can facilitate extubation and decrease the incidence of BPD (8, 9), such treatment can be associated with increased risk of short- and long-term complications including impaired growth and neurodevelopmental delay (10 – 12). However, because BPD also is associated with increased risk for death and adverse neurodevelopmental outcomes, meta-analyses have suggested that in populations at high risk for death or BPD, even dexamethasone therapy may be associated with net benefit (9, 12). Lower doses of dexamethasone may have equal pulmonary benefit with less toxicity (13 – 16); however, because it has a very long biologic half-life, suppresses endogenous cortisol production and disrupts the balance between mineralocorticoid and glucocorticoid in the brain (see below), dexamethasone may still be an inferior glucocorticoid choice for premature infants. Establishment of an alternative therapeutic agent to facilitate extubation may improve respiratory outcomes for these extremely preterm infants at very high risk for BPD, without the adverse effects previously seen with dexamethasone therapy.

## HYPOTHESIS

Compared to placebo, hydrocortisone treatment of preterm infants 401 – 1500 grams birth weight who remain on mechanical ventilation at 14 – 28 days postnatal age will significantly

improve the rate of survival without BPD and will be associated with improvement in survival without major neurodevelopmental impairment at 18 – 22 months corrected age.

### SPECIFIC AIMS

- To determine whether a 10 day course of hydrocortisone results in a significant increase in survival without BPD;
- To determine whether a 10 day course of hydrocortisone results in a significant increase in the number of infants successfully extubated during treatment;
- To determine whether this treatment affects other short-term outcomes including respiratory morbidities, growth and length of stay;
- To determine whether this treatment affects survival without major NDI at 18 – 22 months corrected age;
- To determine whether this treatment affects other outcomes, such as growth and pulmonary morbidity, at 18 – 22 months

### RATIONALE/JUSTIFICATION/PREVIOUS STUDIES

Glucocorticoid therapy to prevent or treat BPD began with high doses of dexamethasone, a powerful synthetic glucocorticoid with a myriad of predictable adverse effects on short and long term outcomes, including growth and neurodevelopment (8-12). Lower doses may have equal pulmonary benefit with less toxicity (13-16); however, because it has a very long biologic half-life, suppresses endogenous cortisol production and disrupts the balance between mineralocorticoid and glucocorticoid in the brain (see below), dexamethasone may still be an inferior glucocorticoid choice for premature infants. One cohort study has reported that

hydrocortisone was as efficacious as dexamethasone in facilitating extubation in preterm infants (17).

Data regarding the effect of neonatal hydrocortisone treatment on neurodevelopmental outcomes are encouraging. A meta-analysis of three RCTs evaluating 333 infants treated for the first two weeks of life with 1-2 mg/kg/day of hydrocortisone showed no difference at 18 – 22 months corrected age in the incidence of cerebral palsy (12% in each group) and a non-significant *increase* in survival without NDI (54% HC vs. 49% placebo) (18). The largest of the included studies (252 infants) showed suggestions of benefit, with a significantly lower incidence of Bayley-II MDI <70 and increased “awareness of object permanence”, an early measure of executive function and pre-frontal cortical development (19). At school age (7 – 8 years of age), outcome data from a cohort study comparing 62 infants treated with a 22 day course of hydrocortisone for BPD (median start 19d, initial dose 5mg/kg/day) to 164 non-treated infants who were larger, more mature and less sick showed no evidence of adverse functional or structural (MRI) effects (20). A recent RCT designed to evaluate the effects of hydrocortisone therapy for BPD on brain growth showed that hydrocortisone treatment (a tapering dose over 7 days, starting at 3mg/kg/day, total 17mg/kg) had no adverse effects on brain volumes on MRI at 38 weeks postmenstrual age (n=48, entry from 10 – 21 days postnatal age) (21).

Differences in the actions of dexamethasone and hydrocortisone in the brain may contribute to the observed differences in neurodevelopmental outcomes. Two types of corticosteroid receptors are found in the brain: mineralocorticoid and glucocorticoid. Under basal conditions, cortisol binds preferentially to mineralocorticoid receptors in the brain; at times of higher stress, cortisol also binds to glucocorticoid receptors (22, 23). Dexamethasone is a powerful synthetic glucocorticoid with no mineralocorticoid activity and a very long biologic



half-life. It suppresses endogenous cortisol production, leaving mineralocorticoid receptors unoccupied and thereby creating a “chemical adrenalectomy” (22, 23). A lack of cortisol binding to mineralocorticoid receptors has been shown in animal studies to result in neuronal apoptosis. This apoptosis occurs whether the lack of cortisol binding is the result of a cortisol deficiency produced by adrenalectomy or the result of dexamethasone administration (24, 25). Further, concurrent administration of corticosterone (the cortisol equivalent in rats) with dexamethasone has been shown to protect against dexamethasone-induced apoptosis (24, 25).

Corticosteroid receptors are found in high density in the hippocampus, an area of the brain critical for learning and memory (22, 25 – 27). Individuals born preterm have reductions in hippocampal volume compared to term (26 – 28), and hippocampal gray matter reduction has been associated with memory deficits in adolescents born prematurely (27). In small cohort studies, preterm infants treated with dexamethasone have been found to have decreased grey matter and/or hippocampal volume compared to untreated controls (29 – 31); however, those treated with hydrocortisone have shown no reduction in volume or increase in lesions vs. untreated controls (20, 21, 32).

Thus, there is both biologically plausible basis for preferring hydrocortisone over dexamethasone and clinical evidence in preterm infants that hydrocortisone does not impair long term neurodevelopmental outcomes whereas dexamethasone can do so. In addition, there is preliminary evidence from a small cohort study that hydrocortisone is equally efficacious as dexamethasone in facilitating extubation in preterm infants. Therefore, we propose a randomized, masked, placebo-controlled trial to study (1) the efficacy of hydrocortisone in facilitating extubation and thereby increasing survival without BPD and (2) the safety of HC for

this use, by assessing the effect of hydrocortisone on survival without major NDI at 18 – 22 months adjusted age.

## METHODS/PROCEDURES

(1) Study design: Randomized, masked placebo-controlled trial.

(2) Study population: Patients eligible for this study will be infants

- with birth weight 401 – 1500 grams, in 3 strata: 401-750g, 751-1000g 1001-1500g
- who have received  $\geq 7$  days of mechanical ventilation
- who remain on mechanical ventilation at 14 – 28 days

This will define a population at very high risk for death or moderate to severe BPD, based on previous NRN data (approximately 65 – 75%, see data below), and is a population for whom the most recent Cochrane review suggests it is reasonable to consider corticosteroid therapy (9). We will include infants who have failed extubation because of apnea, because they too are at risk for BPD from prolonged intubation. We will not open the study window for eligibility until DOL 14 to avoid the highest risk period for spontaneous gastrointestinal perforation (33).

Data provided by Dr. Das for the two year period 2006 – 2007, using the physiologic definition of moderate to severe BPD, i.e., supplemental oxygen and/or positive pressure ventilation at 36 weeks postmenstrual age showed that:

Of infants who received  $\geq 7$  days of mechanical ventilation in the first 14 days, the percentage surviving without BPD was:

401-999g BW: 368/1482 (24.83%)  
1000-1500 BW: 166/399 (41.80%)  
Total (401-1500 BW): 534/1881 (28.4%)

Of infants who received  $\geq 7$  days of ventilation in the first 28 days, the percentage surviving without BPD was:

401-999g BW: 457/1528 (29.91%)  
1000-1500 BW: 229/490 (46.73%)  
Total (401-1500 BW): 686/2018 (33.99%)

Of infants who received  $\geq 14$  days of ventilation in the first 28 days, the percentage surviving without BPD was:

401-999g BW: 292/1249 (23.38%)  
1000-1500 BW: 57/222 (25.68%)  
Total (401-1500 BW): 349/1471 (23.73%)

(3) Exclusions: Major congenital anomalies, a decision to limit support, previous corticosteroid treatment for BPD, and indomethacin/ibuprofen therapy within 48 hours. Previous treatment with hydrocortisone for hypotension will not be an exclusion; however, infants must have been off of hydrocortisone for at least one week prior to study enrollment, and infants who have received hydrocortisone treatment for  $>2$  weeks duration will be excluded.

(4) Study procedures

(a) Clinical management: Except as described below, all therapy will be directed by the clinical care team, including such medications as Vitamin A, caffeine, and inhaled nitric oxide. Stratification of the analysis by center should minimize the effect of center variation.

(b) Enrollment procedures: Beginning one to two days prior to the study window opening for an infant who meets study enrollment criteria, the clinical care team will be approached to ascertain their plans regarding extubation for the infant. If the attending neonatologist plans to extubate the infant within the next 48 hours, the parents will not be approached for consent at that time, and the reason noted on the study data form. If the attending neonatologist does not plan to extubate the baby within 48 hours (e.g., due to current ventilator settings or a recent failed extubation attempt), but would be willing to do so within the context of

the RCT, the parents will be approached for consent. Infants who are not approved for enrollment in the trial by the clinical care team at the opening of the window will be followed until enrollment is approved by the attending neonatologist, or until 28 postnatal days. The reason(s) for non-enrollment will be entered on the study data form.

(c) Therapeutic intervention: The infant will be randomized to saline placebo or hydrocortisone sodium succinate for intravenous administration (unpreserved, Solu-Cortef plain, Pfizer®), to be administered intravenously, or orally if no intravenous line is available, at the same dose, and tapered as follows:

4mg/kg/day ÷ q 6 hours x 2 days, then

2mg/kg/day ÷ q 6 hours x 3 days; then

1mg/kg/day ÷ q 12 hours x 3 days; then

0.5mg/kg/d as a single dose x 2 days

Rationale for dosing: This regimen begins with an anti-inflammatory dose, similar to the starting dose in the previously reported cohort study (5mg/kg/day) (17), and to the dose of dexamethasone given in the DART study (starting at 0.15mg/kg, or  $\cong$  4 – 6mg/kg/day hydrocortisone) (14). The length of therapy is shorter than the previous hydrocortisone cohort study (17), but equal to the DART study, consistent with an overall goal of giving lower doses of glucocorticoid for shorter periods of time (9).

The dose was also chosen using the following rationale and data. The serum cortisol concentration targeted for anti-inflammatory action is 40 – 50 mcg/dl, based on data showing that administration of a hydrocortisone infusion which mimicked the postoperative plasma cortisol concentrations of healthy adults (mean of 43mcg/dl) significantly suppressed postoperative interleukin-6 concentrations and increased intra-operative interleukin-10

concentrations; however, interleukin-6 was not further suppressed by doubling the infusion dose, suggesting a saturable anti-inflammatory effect (34).

Cortisol values were measured in 31 extremely low birth weight infants at DOL 5 – 7 as part of a randomized trial of early hydrocortisone therapy to prevent BPD (35). One value was obtained from each patient, and population data analyzed (36). Infants had received either placebo or  $\geq 5$  doses of 0.5mg/kg of hydrocortisone q12 hours. Serum values were highly variable; however, calculated median peak concentration in hydrocortisone-treated infants one hour post-dose was  $\sim 17$ mcg/dl greater than placebo, and calculated median trough value was  $\sim 6$ mcg/dl greater than placebo. With a 4 times higher dose, we can estimate achieving a median trough of  $\sim 24$ mcg/dl higher than placebo at steady state. We have previously reported that the median cortisol value in untreated ELBW infants at 3 weeks of age is  $\sim 12$  mcg/dl (37); therefore, the median value in the hydrocortisone-treated infants may be  $\sim 36$  mcg/dl. Even if this dose of hydrocortisone suppresses endogenous secretion, we should still achieve a serum concentration in the anti-inflammatory range ( $\sim 25 - 30$  mcg/dl).

(d) Extubation: Infants at this age may not have blood gases obtained regularly. Therefore, extubation criteria include information available without a blood gas, and were targeted toward the lower end of the criteria in the SUPPORT trial. Extubation must be attempted within 72 hours of starting study drug if the patient's FiO<sub>2</sub> 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, he/she will be reassessed every 24 hours during the intervention period and extubation will be attempted if/when those

criteria are met. If the infant is extubated and subsequently re-intubated, further attempts at extubation will be at the discretion of the clinical care team.

(e) Concurrent therapy with indomethacin/ibuprofen: As stated above, infants who have received indomethacin or ibuprofen within 48 hours are not eligible for the study. Spontaneous gastrointestinal perforation primarily occurs during the first 14 days of postnatal life (33). However, to minimize any possible remaining risk, if a patient in this study is determined by the clinical care team to have developed a PDA during the intervention period which must be treated with indomethacin/ibuprofen before study drug is completed, the study drug will be discontinued and PDA treated, after 48 hours if possible. If the infant is to be treated with surgical ligation, the study drug will be continued.

(5) Post-extubation respiratory care

(a) Respiratory support: Each center currently cares for these infants with techniques they feel appropriate, whether CPAP, CPAP with IMV, high-flow nasal cannula or other. This study will not prescribe the technique to be used. Because this is an RCT and because enrollment will be stratified by center and study treatment will be masked, the center-specific and attending-specific techniques should be balanced in both treatment groups equally over the course of the trial and therefore not introduce bias.

(b) Open-label glucocorticoid therapy

(i) Infants who remain successfully extubated are not to be treated with open-label glucocorticoids. This will be a protocol violation.

(ii) Infants who are not extubated during the study treatment period or who are subsequently reintubated may be treated with dexamethasone at the discretion of the clinical care team if their risk for BPD is considered to be >50% (likely for all infants who continue

to be ventilated, per NRN data previously shown, but can be confirmed with NRN calculator when available), using treatment similar to that described by Doyle (14). Further treatment with HC for prevention/treatment of BPD will be considered a protocol violation. The rationale for this is as follows: (1) HC has not been demonstrated in an RCT to be efficacious for extubation, whereas dexamethasone has (8, 9, 14); (2) this design will permit a true RCT of HC without open-label contamination of the placebo group. At the same time, we will not be denying treatment to the group of infants that meta-analysis suggests derive net benefit from treatment with dexamethasone (12).

(6) Definition of successful extubation: An infant who remains extubated for at least one week, including at least 3 days (72 hours) after the last dose of study medication, will be considered to be successfully extubated in response to this treatment.

(7) Laboratory specimens: none.

(8) Outcomes

(a) Primary outcome measure: The primary outcome for this study will include both a measure of efficacy (improvement in survival without BPD) and safety (survival without major NDI at 18 – 22 months corrected age). Because the primary study outcome will not be known until evaluation of the outcomes at 18 – 22 months corrected age, BPD outcome data will not be released until after this time.

We propose that if hydrocortisone treatment is efficacious in improving survival without BPD, this treatment will also result in an improvement in survival without NDI, since BPD is a risk factor for both mortality and adverse neurodevelopmental outcomes. Meta-analysis of early, low-dose hydrocortisone trials showed a non-significant 5% overall increase in survival without major NDI (18). The largest of those trials showed a significant improvement in the percentage

of infants with MDI <70 (27% vs. 37%) and a 4 percentage point improvement in survival without NDI (0.68 (0.41–1.10)), even in the absence of a significant effect on BPD (19). No previous RCT or cohort study of hydrocortisone using 5mg/kg/day or less has shown adverse neurodevelopmental effects associated with its use (17-21). Meta-regression has shown that even dexamethasone, with its numerous short and long term adverse effects, provided net benefit for the outcome of death or cerebral palsy for infants with an *a priori* risk of BPD or death of >50% (12).

(i) Power calculations and sample size:

((a) Efficacy: Considering a 10 percentage point difference in survival without BPD to be clinically significant, improving survival without BPD from approximately 25% in this population (historical NRN data, see Methods, section 2) to 35% with a power of 0.80 would require a sample size of 658 infants (Dennis Wallace, RTI). If the incidence of survival without BPD in the placebo group has improved over time to 35%, similar power to detect an increase to 45% would require a larger sample size, about 750. To assure adequate power to detect a 10 percentage point improvement in outcome regardless of the baseline incidence of survival without BPD going forward, we plan a sample size of 800.

((b) Safety: In view of the previous data suggesting possible benefit from hydrocortisone treatment, we anticipate that hydrocortisone treatment will be associated with improved survival without major neurodevelopmental impairment in this population. Meta-analysis of previous studies of early, low-dose hydrocortisone reported a non-significant increase in survival without NDI of 5% (18); we will postulate conservatively that hydrocortisone will provide a 3% improvement in survival without NDI. However,



we cannot anticipate demonstrating a statistically significant benefit of that magnitude within this sample size. Therefore, this safety outcome will be considered a success if either (1) the risk of death/NDI is lower on the hydrocortisone arm than on the control arm, or (2) there is an increase in risk for death or NDI in the hydrocortisone arm, but the lower limit of a one-sided 95% confidence interval for the ratio of increased benefit for BPD to increased risk for NDI is greater than 4. In other words, for every additional 4 infants surviving without BPD, we would have 95% confidence that no more than 1 additional infant would experience death or NDI. For example, if we achieve the successful outcome of an increase of 10% in survival without BPD, we would hypothesize also achieving an increase of 3% in survival without NDI, but would only define the treatment as a success if there were no more than a 2.5% increase in death or NDI in the treatment arm. Choosing an initial total sample size of 800, with an anticipated follow up rate of 90% of survivors, will yield an evaluable population of 720, or 360 per study arm. This sample size will have a power of  $>0.80$  to detect this outcome.

With the population available (below), this sample size should allow completion of enrollment in less than 3 years, will give a clear answer regarding the efficacy of hydrocortisone for improving survival without BPD, and will allow a reasonable assessment of safety and potential benefit at 18 – 22 months corrected age.

(b) Secondary outcomes: After analysis of unadjusted risk differences, other factors known to affect neurodevelopmental outcomes (such as gender, maternal education and dexamethasone exposure) will be entered into a multivariable analysis of outcome. Secondary

outcomes will include other standard NRN measures of morbidity and growth as collected for the GDB both at 36 weeks postmenstrual age and at 18 – 22 months corrected age, as well as successful extubation during the intervention period. We will incorporate the previous NRN data form regarding pulmonary outcomes at 18 – 22 months from the SUPPORT trial.

(c) Safety monitoring: Adverse events will be monitored, including those previously associated with glucocorticoid therapy, such as hyperglycemia, hypertension and gastrointestinal perforation (8, 9, 33). Any infant who develops new, sustained hyperglycemia (>180mg/dl on at least two determinations at least 6 hours apart) or new, sustained hypertension (mean arterial pressure >95<sup>th</sup> percentile for age on four serial determinations over at least 12 hours (38)) may have study drug held or discontinued if, in the opinion of the attending neonatologist, there is no plausible alternative explanation for these findings (such as new thrombus). Delaying the study window to 14 days and excluding infants receiving indomethacin/ibuprofen in the preceding 48 hours should minimize the possibility for spontaneous GI perforation (33). We will also specifically monitor for signs of adrenal insufficiency after study drug is discontinued, including hypotension and oliguria, as well as hyponatremia and hyperkalemia on clinically obtained electrolyte specimens. Previous studies of hydrocortisone at various doses have not reported these signs after discontinuation of a tapering course of the drug (17, 35, 39 and personal communication N. Parikh, study of 3mg/kg dose starting after day 7, tapering over 7 days). Patients who develop hypotension and oliguria significant enough in the judgment of the attending neonatologist to require support with volume and/or vasopressors should have a blood sample drawn for cortisol and may be restarted on hydrocortisone at the discretion of the clinical attending. A suggested dose based on limited experience is 1- 2 mg/kg initial dose with

observation for response; if an improvement in blood pressure is seen, continue at 0.5 – 1 mg/kg q 8 hours.

(9) Available population (based on GDB data, 06-07):

To create a conservative estimate of the population available for this study, we obtained from Dr. Das the number of babies 401 – 1500g birth weight who had received  $\geq 14$  days on mechanical ventilation during the 1<sup>st</sup> 28 days in the calendar years 2006 and 2007:

1242 (401 – 1000g), 214 (1001 – 1500g)	total = 1456, or 728/year
- If $\frac{3}{4}$ of those meet eligibility	= 546/year
- Consent rate at 60% (direct benefit study*)	= 328/year
- Total over a 3 year enrollment	= 983
- For a sample size of 800	= 30 months

(\*glutamine consent rate was 70%)

Competing studies: The primary outcome for inositol is ROP, rather than BPD.

Hydrocortisone treatment has not been shown to have effects on ROP. While inositol may have secondary effects on respiratory morbidities, these studies may be compatible. It appears from NRN conversations with the FDA that subjects may participate in more than one IND trial; therefore, this study would not conflict with probiotics.

RISKS, BENEFITS, POTENTIAL PROBLEMS

Risks: (1) Spontaneous gastrointestinal perforation is primarily observed before 14 days postnatal age, in infants receiving concurrent indomethacin/ibuprofen treatment who have high endogenous cortisol concentrations (35, 39). Remaining risk will be minimized by excluding infants who have received indomethacin/ibuprofen therapy within 48 hours prior to study entry.

(2) Short-term adverse effects of glucocorticoids, such as hyperglycemia, hypertension, growth failure. These effects have not been seen in RCTs of hydrocortisone vs. placebo (35, 39, 40); the plan for monitoring and addressing possible hyperglycemia and hypertension is outlined above (Methods).

(3) Adverse neurodevelopmental effects: This has not been reported as a consequence of hydrocortisone administration either in cohort studies or in RCTs. We will assess outcomes at 18 – 22 months corrected age and monitor for any such effects.

Benefits: If hydrocortisone proves effective in reducing time on mechanical ventilation, this therapy will benefit these individual patients by decreasing the ongoing noxious effects of an indwelling endotracheal tube, suctioning and positive pressure ventilation. If hydrocortisone proves effective in decreasing the incidence of BPD through its effect on decreasing mechanical ventilation and/or its anti-inflammatory effect, it will benefit these individual patients by decreasing oxygen exposure and decreasing BPD as a factor associated with adverse neurodevelopmental outcomes. Based on previous data, hydrocortisone treatment may be associated with improvement in neurodevelopmental outcomes (18, 19).

Possible problems: (1) Futility: hydrocortisone may not prove effective for extubation or reduction of BPD. To monitor this and to limit exposure to a futile therapy, interim monitoring will be done for both safety and effectiveness, with stopping rules developed and put into place for both, in consultation with RTI and the NRN DSMC.

(2) Slow patient enrollment: A timeline for enrollment is proposed, above, based on eligible patients anticipated at the NRN centers. This will be monitored, and if patient enrollment does not meet expected, the reasons for the problem will be analyzed and the potential for study

completion assessed. Study forms will be constructed to include reasons for lack of enrollment, to assist in this process.

BUDGET (not including RTI costs) based on 800 patients

Pharmacy cost (avg): \$2000/center set-up fee + \$500/year x 3 years =	\$ 56,000
Per patient (28 doses x \$20/dose) =	\$448,000*
Coordinator time: 10 hours/patient @ \$35/hr (\$350/pt)	\$280,000
Follow up (est. deaths 15%, followup rate 90% = 612):	
\$400 GDB babies, \$700/pt otherwise (est.2/3)	<u>\$367,200</u>
Estimated total:	\$1,151,200

(\*This may be lower, since all doses for each day can be prepared and dispensed at one time)

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**From:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**To:** ["Wally Carlo, M.D."](#)  
**Subject:** SUPPORT CPAP NEJM Feb 23 responses to editor Final  
**Date:** Thursday, February 25, 2010 10:32:00 AM  
**Attachments:** [SUPPORT CPAP NEJM Feb 23 responses to editor Final.doc](#)

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## Higgins, Rosemary (NIH/NICHD) [E]

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**From:** Finer, Neil <nfiner@ucsd.edu>  
**Sent:** Thursday, February 25, 2010 5:14 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** Fwd: Follow Up ON BPD and Oximeters

You wil never satisfy him Rose!  
Be well  
Neil

Sent from my iPhone

Begin forwarded message:

From: "Tyson, Jon E" <Jon.E.Tyson@uth.tmc.edu<mailto:Jon.E.Tyson@uth.tmc.edu>>  
Date: February 24, 2010 11:45:16 PM CST  
To: "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov<mailto:higginsr@mail.nih.gov>>, "Cunningham, Meg" <mcunningham@rti.org<mailto:mcunningham@rti.org>>, "[SCRN] Stoll, Barbara" <barbara\_stoll@oz.ped.emory.edu<mailto:barbara\_stoll@oz.ped.emory.edu>>, "alaptook@WIHRI.org<mailto:alaptook@WIHRI.org>" <alaptook@WIHRI.org<mailto:alaptook@WIHRI.org>>, "Bell, Edward" <edward-bell@uiowa.edu<mailto:edward-bell@uiowa.edu>>, "bpoindex@iupui.edu<mailto:bpoindex@iupui.edu>" <bpoindex@iupui.edu<mailto:bpoindex@iupui.edu>>, "Das, Abhik" <adas@rti.org<mailto:adas@rti.org>>, "goldb008@mc.duke.edu<mailto:goldb008@mc.duke.edu>" <goldb008@mc.duke.edu<mailto:goldb008@mc.duke.edu>>, "ifrantz@tuftsmedicalcenter.org<mailto:ifrantz@tuftsmedicalcenter.org>" <ifrantz@tuftsmedicalcenter.org<mailto:ifrantz@tuftsmedicalcenter.org>>, "Kennedy, Kathleen A" <Kathleen.A.Kennedy@uth.tmc.edu<mailto:Kathleen.A.Kennedy@uth.tmc.edu>>, "kurt.schibler@cchmc.org<mailto:kurt.schibler@cchmc.org>" <kurt.schibler@cchmc.org<mailto:kurt.schibler@cchmc.org>>, "kwatterberg@salud.unm.edu<mailto:kwatterberg@salud.unm.edu>" <kwatterberg@salud.unm.edu<mailto:kwatterberg@salud.unm.edu>>, "matthew.bizzarro@yale.edu<mailto:matthew.bizzarro@yale.edu>" <matthew.bizzarro@yale.edu<mailto:matthew.bizzarro@yale.edu>>, "mcw3@cwru.edu<mailto:mcw3@cwru.edu>" <mcw3@cwru.edu<mailto:mcw3@cwru.edu>>, "mcaplan@northshore.org<mailto:mcaplan@northshore.org>" <mcaplan@northshore.org<mailto:mcaplan@northshore.org>>, "Pablo.Sanchez@UTSouthwestern.edu<mailto:Pablo.Sanchez@UTSouthwestern.edu>" <Pablo.Sanchez@UTSouthwestern.edu<mailto:Pablo.Sanchez@UTSouthwestern.edu>>, "richard.ehrenkranz@yale.edu<mailto:richard.ehrenkranz@yale.edu>" <richard.ehrenkranz@yale.edu<mailto:richard.ehrenkranz@yale.edu>>, "Roger.Faix@hsc.utah.edu<mailto:Roger.Faix@hsc.utah.edu>" <Roger.Faix@hsc.utah.edu<mailto:Roger.Faix@hsc.utah.edu>>, "sshankar@med.wayne.edu<mailto:sshankar@med.wayne.edu>" <sshankar@med.wayne.edu<mailto:sshankar@med.wayne.edu>>, "vanmeurs@leland.stanford.edu<mailto:vanmeurs@leland.stanford.edu>" <vanmeurs@leland.stanford.edu<mailto:vanmeurs@leland.stanford.edu>>, "Wally Carlo, M.D." <WCarlo@peds.uab.edu<mailto:WCarlo@peds.uab.edu>>, "Wallace, Dennis" <dwallace@rti.org<mailto:dwallace@rti.org>>, "cotte010@mc.duke.edu<mailto:cotte010@mc.duke.edu>" <cotte010@mc.duke.edu<mailto:cotte010@mc.duke.edu>>, Bradley Yoder <Bradley.Yoder@hsc.utah.edu<mailto:Bradley.Yoder@hsc.utah.edu>>,</p></div>

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Subject: RE: Follow Up ON BPD and Oximeters

Rose, before we can understand and interpret this information noted in the mail, we really need to know more about what was done and answers to questions like those below:

1. Which trial result was addressed – whether the evaluation of BPD was biased in the analyses of CPAP/limited ventilation vs. surfactant/conventional ventilation arm (not the analysis for which there is concern) or the analyses of the high vs. low oxygen saturation goal.
2. Do we have reliable data to know whether individual infants were monitored on the study oximeter or on the clinical oximeter on the day the infant was 36 weeks and 0 and whether the oximeter was changed part way through that 24 hour period? What was done if the infant was switched on that day. As I understand it, the diagnosis of BPD was based on the entire 24 hours the day the infant was 36 weeks 0 days. Though the results of the survey weren't distributed, my impression from responses to my earlier e mails was that even the procedure usually followed in individual centers was not necessarily clear.
3. What variables in the model when the BPD oximeter was added? What variables were in the model when a BPD oximeter x study treatment group was added?
4. Do I understand Maria and you to conclude that because centers tended to be consistent in their oximeter use, controlling for center would prevent a biased assessment of the effect on BPD by oxygen administration?

This comment makes me wonder if the analysis was done for the wrong comparison, This conclusion would be correct for analyses of the effect of CPAP/limited ventilation vs. surfactant/ conventional ventilation on BPD by oxygen delivery (because each treatment arm would contain equal numbers of infants in the high and low sat groups). However, this isn't the comparison in question. This conclusion would certainly not be correct in analyzing the effect of high vs low sat goals on BPD. In this analysis, centers that used the study oximeter would be systematically more likely to administer oxygen to the high sat group than to the low sat group. The problem wouldn't go away by controlling for center, and the more centers that used the study oximeter, the more biased the result would be. How many centers were there that used the study oximeter?

5. What is the basis for believing that there would be anything near reasonable power to assess a oximeter x treatment group interaction?

I know that everyone is anxious to get this paper submitted. While I have an external advisory committee tomorrow, I will try to respond tomorrow night if the information requested above is sent tomorrow during the day.

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From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]  
Sent: Wednesday, February 24, 2010 7:53 AM  
To: Tyson, Jon E; 'Cunningham, Meg'; [SCRN] Stoll, Barbara; alaptook@WIHRI.org<mailto:alaptook@WIHRI.org>; Bell, Edward; bpoindex@iupui.edu<mailto:bpoindex@iupui.edu>; Das, Abhik; goldb008@mc.duke.edu<mailto:goldb008@mc.duke.edu>; ifrantz@tuftsmedicalcenter.org<mailto:ifrantz@tuftsmedicalcenter.org>; Kennedy, Kathleen A; kurt.schibler@cchmc.org<mailto:kurt.schibler@cchmc.org>; kwatterberg@salud.unm.edu<mailto:kwatterberg@salud.unm.edu>; matthew.bizzarro@yale.edu<mailto:matthew.bizzarro@yale.edu>; mcw3@cwru.edu<mailto:mcw3@cwru.edu>; mcaplan@northshore.org<mailto:mcaplan@northshore.org>; Pablo.Sanchez@UTSouthwestern.edu<mailto:Pablo.Sanchez@UTSouthwestern.edu>; richard.ehrenkranz@yale.edu<mailto:richard.ehrenkranz@yale.edu>; Roger.Faix@hsc.utah.edu<mailto:Roger.Faix@hsc.utah.edu>; sshankar@med.wayne.edu<mailto:sshankar@med.wayne.edu>; vanmeurs@leland.stanford.edu<mailto:vanmeurs@leland.stanford.edu>; Wally Carlo, M.D.; Wallace, Dennis; cotte010@mc.duke.edu<mailto:cotte010@mc.duke.edu>; Bradley Yoder; rohls@salud.unm.edu<mailto:rohls@salud.unm.edu>; Luc.Brion@utsouthwestern.edu<mailto:Luc.Brion@utsouthwestern.edu>; 'Stevenson David (E-mail)'; 'Finer, Neil'; Rich, Wade; Gantz, Marie  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Archer, Stephanie (NIH/NICHD) [E]  
Subject: Follow Up ON BPD and Oximeters

Hi all –

In Follow up to yesterday's discussion, Marie spent a great deal of time last evening running additional analyses to address (and now alleviate) Jon's concern as described:

We have looked into the question of whether the oximeter used to determine BPD impacted the BPD and death/BPD outcomes by adding a covariate for the BPD oximeter (study or clinical) to the statistical models. We found that the effect of the BPD oximeter was significant; however, the interaction between BPD oximeter and treatment oximeter (low or high SpO2 target range) was not significant in any model, indicating that, if there was a BPD oximeter effect, it was not different in the two treatment groups. In addition, it should be noted that BPD oximeter is confounded with center (centers tended to be consistent in their use of the study or clinical oximeters to determine BPD). Therefore, by including center in the original models, we have already accounted for the effect of the BPD oximeter the center chose to use. Finally, because center and BPD oximeter are confounded, we cannot know whether the significant BPD oximeter effect is due to the BPD oximeters themselves or other characteristics that differ between centers.

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From: Tyson, Jon E [mailto:Jon.E.Tyson@uth.tmc.edu]  
Sent: Tuesday, February 23, 2010 4:33 PM  
To: Higgins, Rosemary (NIH/NICHD) [E]; 'Cunningham, Meg'; [SCRN] Stoll, Barbara; alaptook@WIHRI.org<mailto:alaptook@WIHRI.org>; Bell, Edward; bpoindex@iupui.edu<mailto:bpoindex@iupui.edu>; Das, Abhik; goldb008@mc.duke.edu<mailto:goldb008@mc.duke.edu>; ifrantz@tuftsmedicalcenter.org<mailto:ifrantz@tuftsmedicalcenter.org>; Kennedy, Kathleen A; kurt.schibler@cchmc.org<mailto:kurt.schibler@cchmc.org>;

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Pablo.Sanchez@UTSouthwestern.edu<mailto:Pablo.Sanchez@UTSouthwestern.edu>;  
richard.ehrenkranz@yale.edu<mailto:richard.ehrenkranz@yale.edu>;  
Roger.Faix@hsc.utah.edu<mailto:Roger.Faix@hsc.utah.edu>;  
sshankar@med.wayne.edu<mailto:sshankar@med.wayne.edu>;  
vanmeurs@leland.stanford.edu<mailto:vanmeurs@leland.stanford.edu>; Wally Carlo, M.D.; Wallace, Dennis;  
cotte010@mc.duke.edu<mailto:cotte010@mc.duke.edu>; Bradley Yoder;  
rohls@salud.unm.edu<mailto:rohls@salud.unm.edu>;  
Luc.Brion@utsouthwestern.edu<mailto:Luc.Brion@utsouthwestern.edu>; <mailto:bbatton@siumed.edu>  
bbatton@siumed.edu<mailto:bbatton@siumed.edu>  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie;  
lmoore@med.wayne.edu<mailto:lmoore@med.wayne.edu>;  
pamela.neville@duke.edu<mailto:pamela.neville@duke.edu>;  
gonza025@mc.duke.edu<mailto:gonza025@mc.duke.edu>; Smith, Nancy M; Brenda Vecchio;  
msumner@peds.uab.edu<mailto:msumner@peds.uab.edu>; Archer, Stephanie (NIH/NICHD) [E]  
Subject: RE: Steering Committee Call Tomorrow

While it may seem that I am fixated on an unimportant issue regarding a not quite significant difference, I think we undermine the credibility of Network studies if we are not completely forthright about problems in measuring what everyone would agree is an important secondary outcome. Not reporting that the assessment of BPD by oxygen administration could be biased by continued use of the study oximeters would seem to be in the category of not reporting protocol deviations and not something that is in the Network's best interest. Why not just put a footnote under the table describing the problem?

Jon E. Tyson, MD, MPH  
Center for Clinical Research & Evidence-Based Medicine UT Medical School at Houston  
6431 Fannin St., MSB 2.106  
Houston, TX 77030  
voice 713-500-5651  
fax 713-500-0519

---

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
Sent: Tuesday, February 23, 2010 2:11 PM  
To: 'Cunningham, Meg'; [SCRN] Stoll, Barbara; alaptook@WIHRI.org<mailto:alaptook@WIHRI.org>; Bell, Edward;  
bpoindex@iupui.edu<mailto:bpoindex@iupui.edu>; Das, Abhik;  
goldb008@mc.duke.edu<mailto:goldb008@mc.duke.edu>;  
ifrantz@tuftsmedicalcenter.org<mailto:ifrantz@tuftsmedicalcenter.org>; Kennedy, Kathleen A;  
kurt.schibler@cchmc.org<mailto:kurt.schibler@cchmc.org>;  
kwatterberg@salud.unm.edu<mailto:kwatterberg@salud.unm.edu>;  
matthew.bizzarro@yale.edu<mailto:matthew.bizzarro@yale.edu>; mcw3@cwru.edu<mailto:mcw3@cwru.edu>;  
mcaplan@northshore.org<mailto:mcaplan@northshore.org>;  
Pablo.Sanchez@UTSouthwestern.edu<mailto:Pablo.Sanchez@UTSouthwestern.edu>;  
richard.ehrenkranz@yale.edu<mailto:richard.ehrenkranz@yale.edu>;  
Roger.Faix@hsc.utah.edu<mailto:Roger.Faix@hsc.utah.edu>;  
sshankar@med.wayne.edu<mailto:sshankar@med.wayne.edu>;  
vanmeurs@leland.stanford.edu<mailto:vanmeurs@leland.stanford.edu>; Wally Carlo, M.D.; Wallace, Dennis;  
cotte010@mc.duke.edu<mailto:cotte010@mc.duke.edu>; Tyson, Jon E; Bradley Yoder;  
rohls@salud.unm.edu<mailto:rohls@salud.unm.edu>;

Luc.Brion@utsouthwestern.edu<mailto:Luc.Brion@utsouthwestern.edu>; <mailto:bbatton@siumed.edu>  
bbatton@siumed.edu<mailto:bbatton@siumed.edu>  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie;  
lmoore@med.wayne.edu<mailto:lmoore@med.wayne.edu>;  
pamela.neville@duke.edu<mailto:pamela.neville@duke.edu>;  
gonza025@mc.duke.edu<mailto:gonza025@mc.duke.edu>; Smith, Nancy M; Brenda Vecchio;  
msumner@peds.uab.edu<mailto:msumner@peds.uab.edu>; Archer, Stephanie (NIH/NICHD) [E]  
Subject: RE: Steering Committee Call Tomorrow

If you joined the call already in progress, please send us an email so we can count your attendance.

Rose

---

From: Cunningham, Meg [mailto:mcunningham@rti.org]  
Sent: Monday, February 22, 2010 9:59 AM  
To: [SCRN] Stoll, Barbara; alaptook@WIHRI.org<mailto:alaptook@WIHRI.org>; Bell, Edward;  
bpoindex@iupui.edu<mailto:bpoindex@iupui.edu>; Das, Abhik;  
goldb008@mc.duke.edu<mailto:goldb008@mc.duke.edu>; Higgins, Rosemary (NIH/NICHD) [E];  
ifrantz@tuftsmedicalcenter.org<mailto:ifrantz@tuftsmedicalcenter.org>;  
Kathleen.A.Kennedy@uth.tmc.edu<mailto:Kathleen.A.Kennedy@uth.tmc.edu>;  
kurt.schibler@cchmc.org<mailto:kurt.schibler@cchmc.org>;  
kwatterberg@salud.unm.edu<mailto:kwatterberg@salud.unm.edu>;  
matthew.bizzarro@yale.edu<mailto:matthew.bizzarro@yale.edu>; mcw3@cwru.edu<mailto:mcw3@cwru.edu>;  
mcaplan@northshore.org<mailto:mcaplan@northshore.org>;  
Pablo.Sanchez@UTSouthwestern.edu<mailto:Pablo.Sanchez@UTSouthwestern.edu>;  
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Roger.Faix@hsc.utah.edu<mailto:Roger.Faix@hsc.utah.edu>;  
sshankar@med.wayne.edu<mailto:sshankar@med.wayne.edu>;  
vanmeurs@leland.stanford.edu<mailto:vanmeurs@leland.stanford.edu>; Wally Carlo, M.D.; Wallace, Dennis;  
cotte010@mc.duke.edu<mailto:cotte010@mc.duke.edu>; jon.e.tyson@uth.tmc.edu<mailto:jon.e.tyson@uth.tmc.edu>;  
Bradley Yoder; rohls@salud.unm.edu<mailto:rohls@salud.unm.edu>;  
Luc.Brion@utsouthwestern.edu<mailto:Luc.Brion@utsouthwestern.edu>; <mailto:bbatton@siumed.edu>  
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Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie;  
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Nancy.M.Smith@uth.tmc.edu<mailto:Nancy.M.Smith@uth.tmc.edu>; Brenda Vecchio;  
msumner@peds.uab.edu<mailto:msumner@peds.uab.edu>; Archer, Stephanie (NIH/NICHD) [E]  
Subject: Steering Committee Call Tomorrow

Dear All -

The next standing Steering Committee call is scheduled for tomorrow, Tuesday, February 23rd at 3:00pm ET.

Please Dial:

Outside the USA 1-203-310 (b)

or Within the USA 866-675 (b)

Then, enter Participant Passcode: (b) (6)

Steering Committee Conference Call Agenda 02/23/2010



1. Early BP discussion (attached are a brief description of the time limited data collection proposal and a draft of the form which would be used.)
2. SUPPORT manuscript discussion and update
3. New Business

Thanks,  
Meg

Meg Cunningham  
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Washington, DC 20005  
tel: 202-974-7837  
fax: 202-728-2095  
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**From:** Brenda Morris  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: SUPPORT copyright for CPAP Paper  
**Date:** Wednesday, February 24, 2010 6:34:23 PM

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Sending them again. I think I might have sent it to the NICHD fax number the first time.  
Brenda

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From: higginsr@mail.nih.gov  
To: edward.donovan@cchmc.org; (b) (6);  
Nirupama\_Laroia@URMC.Rochester.edu; bpoindex@iupui.edu  
CC: babel@nejm.org; archerst@mail.nih.gov  
Date: Wed, 24 Feb 2010 16:52:57 -0500  
Subject: SUPPORT copyright for CPAP Paper

Hi,  
NEJM is missing your copyright form for the CPAP surf paper. Please fill in the information and either fax it (781) 207.6529 or email a pdf with your signature to Brendan Abel. The information for the manuscript is as follows:

Manuscript number 09-11783  
Author - Neil Finer  
Title Early CPAP versus Surfactant in Extremely Preterm Infants

Thanks for your prompt attention

Rose

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network  
Pregnancy and Perinatology Branch  
Center for Developmental Biology and Perinatal Medicine  
Eunice Kennedy Shriver National Institute of Child Health and Human Development  
National Institutes of Health  
6100 Executive Blvd., Room 4B03  
MSC 7510  
Bethesda, MD 20892  
For overnight delivery use Rockville, MD 20852  
301-496-5575  
301-496-3790 (FAX)  
higginsr@mail.nih.gov

**From:** [Kennedy, Kathleen A](#)  
**To:** [Wallace, Dennis](#); [Kristi Watterberg](#); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [goldb008@mc.duke.edu](#); [matt\\_laughon@med.unc.edu](#); [Michelle Walsh](#); [Das, Abhik](#); [richard.ehrenkranz@yale.edu](#)  
**Subject:** RE: RE: RE: SUPPORT data  
**Date:** Wednesday, February 24, 2010 6:30:49 PM

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I think that Dennis is making very good points. If we end up wanting to compare dexamethasone to hydrocortisone, I think we could do a better job of planning that study after we have more information about the effect(s) of hydrocortisone. We probably need to consider plausible effect sizes and acceptable regions of indifference for both the BPD and neurodevelopmental outcomes and that would be virtually impossible to do with the information we now have.

Kathleen A. Kennedy, MD, MPH  
Richard W. Mithoff Professor of Pediatrics  
Director, Division of Neonatal-Perinatal Medicine  
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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**From:** Wallace, Dennis [mailto:[dwallace@rti.org](mailto:dwallace@rti.org)]  
**Sent:** Wednesday, February 24, 2010 5:08 PM  
**To:** [Kristi Watterberg](#); [Rosemary \(NIH/NICHD\) Higgins](#); [goldb008@mc.duke.edu](#); [matt\\_laughon@med.unc.edu](#); [Michelle Walsh](#); [Das, Abhik](#); [Kennedy, Kathleen A](#); [richard.ehrenkranz@yale.edu](#)  
**Subject:** RE: RE: RE: SUPPORT data

Kristi,

Thanks for forwarding these. As a consequence of (b) (6) I'm behind on getting the formal power calculations for a three-arm trial done. As I said in the earlier e-mail, I know that the sample size for 3 arms will be between 1200 and 1440 and probably about half way between. If we're seriously going to consider a 3-arm design, I'll go ahead with the programming for that, although it looks like it will take a bit more work than I originally thought. However, if we're not going to consider that design, then I'm not sure of the benefit of trying to refine these numbers. What are your thoughts? I'd also like to comment on Matt's suggestion regarding doing the 3-arm study with a plan to compare the HC and Dex arms while acknowledging that we haven't powered the study to do that. Assuming that the prevalence of an outcome of interest is in the 40% to 60% range, the half width of 95% confidence interval for the difference in prevalence of the outcomes is about 7%, which is 70% of the magnitude of the treatment effect that we're powering the study to find compared to placebo.

I really have concerns about planning to do an analysis that provides such imprecise information for comparing two active treatment arms, when an effect of that magnitude is clearly clinically significant. I'm concerned that taking such an approach will damage the scientific reputation of the Network. If we really want to compare two active treatments, we need to define a region of clinical indifference (whether that be 3%, 5%, or 7%) and then design the study to ensure that we have the power to demonstrate equivalence if the two treatments are really clinically equivalent.

Dennis

Dennis Wallace  
Senior Research Statistician  
Cox 241  
RTI International  
3040 Cornwallis Rd  
Research Triangle Park, NC 27709-2104  
Voice: 919-541-6271  
Fax: 919-541-6416

---

**From:** Kristi Watterberg [mailto:KWatterberg@salud.unm.edu]  
**Sent:** Wednesday, February 24, 2010 4:24 PM  
**To:** Rosemary (NIH/NICHD) Higgins; goldb008@mc.duke.edu; matt\_laughon@med.unc.edu; Michelle Walsh; Das, Abhik; Wallace, Dennis; Kathleen.A.Kennedy@uth.tmc.edu; richard.ehrenkranz@yale.edu  
**Subject:** Fwd: RE: RE: SUPPORT data

Matt's comments ~ Kristi

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**From:** [Kristi Watterberg](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [goldb008@mc.duke.edu](mailto:goldb008@mc.duke.edu); [matt\\_laughon@med.unc.edu](mailto:matt_laughon@med.unc.edu); [Michelle Walsh; adas@rti.org](#); [Dennis Wallace](#); [Kathleen.A.Kennedy@uth.tmc.edu](mailto:Kathleen.A.Kennedy@uth.tmc.edu); [richard.ehrenkranz@yale.edu](mailto:richard.ehrenkranz@yale.edu)  
**Subject:** Fwd: RE: RE: SUPPORT data  
**Date:** Wednesday, February 24, 2010 4:24:11 PM  
**Attachments:** [RE.RE.SUPPORT.data.msg](#)

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Matt's comments ~ Kristi

## **Blansfield, Earl (NIH/NICHD) [E]**

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**From:** Matt Laughon <matt\_laughon@med.unc.edu>  
**Sent:** Wednesday, February 24, 2010 2:22 PM  
**To:** 'Kristi Watterberg'  
**Cc:** 'Ronald N Goldberg'; 'Michael Cotten'  
**Subject:** RE: RE: SUPPORT data

Hi Kristi,

I think Ron is going out of town so he might not have time to respond for Duke before next week. I'm thinking, based on discussions with our faculty at UNC, the following options, in order of preference:

1. Three arm trial, with standard approach to sample size; would need more patients and centers
2. HC vs. placebo, Dex vs. placebo; planned a priori secondary examination of dex vs. HC, acknowledge that trial not powered to look at those groups
3. HC vs. placebo

It is my understanding that the late hypothermia study is adding centers; we are trying to add Charlotte (cools 20-30 babies/yr) to the trial. Thus, there is precedence for adding centers for an important trial that might not otherwise be performed, which might make option 1 possible.

It is going to be difficult to respond to the reviewers concerns about the issue of dexamethasone.

Thanks,  
Matt

Matthew M. Laughon, MD, MPH  
Division of Neonatal-Perinatal Medicine  
Department of Pediatrics  
The University of North Carolina at Chapel Hill  
Chapel Hill, NC 27599-7596  
Phone: (919) 966-5063  
Facsimile: (919) 966-3034

---

**From:** Kristi Watterberg [<mailto:KWatterberg@salud.unm.edu>]  
**Sent:** Wednesday, February 24, 2010 11:20 AM  
**To:** Rosemary (NIH/NICHD) Higgins; [goldb008@mc.duke.edu](mailto:goldb008@mc.duke.edu); [matt\\_laughon@med.unc.edu](mailto:matt_laughon@med.unc.edu); Michelle Walsh; [adas@rti.org](mailto:adas@rti.org); Dennis Wallace; [Kathleen.A.Kennedy@uth.tmc.edu](mailto:Kathleen.A.Kennedy@uth.tmc.edu); [richard.ehrenkranz@yale.edu](mailto:richard.ehrenkranz@yale.edu)  
**Subject:** Fwd: RE: SUPPORT data

Hello, all. I am forwarding Marie's data regarding infants who remain on mechanical ventilation at 14 days and their BPD/death outcomes. As you will see, about 44% of the enrolled infants were on mechanical ventilation at that time (526). Of those, 30% survived without BPD, which is very close to the data provided by Abhik (24% of babies with at least 14 days of mechanical ventilation survived without BPD).

This is reassuring for our sample size estimation - if survival without BPD was 25%, as from Abhik's data, the total sample size to detect a 10% difference would be 658; if survival without BPD had improved to 35%, we would need 750. Because we cannot be sure of the baseline incidence at the time we start the study, we proposed a conservative sample size of 800. The SUPPORT data are between those two estimates, so the proposed sample size should be appropriate.

To make the best use of our conference call time on Monday, I would like to get a current poll of the subcommittee regarding inclusion of dexamethasone in the study before the call, so we can make a decision and go forward.

As I see it, a straight HC/placebo trial will give us a reasonable chance of enrolling an adequate sample size in less than 3 years within the network. We run the risk of futility - but if HC doesn't work to facilitate extubation and decrease BPD, that's a very important finding. A three-way trial will stretch the capability of the network to enroll, and still would not give us a large enough sample size to compare HC/Dex anyway for non-inferiority.

so I think we are better off running a straight HC/placebo trial to find out if it works. If it does, we have lots of evidence to say HC is better for neurodevelopmental outcomes, and this trial will add to the evidence available regarding outcome after HC Rx. If it doesn't, then we could proceed to a straight dex/placebo trial in a subsequent protocol. After all our e-mail discussion regarding a three-arm protocol comparing each drug to the same placebo group, I know Kathleen and Michelle favor a single drug (HC) trial. Rich, have you changed your position after all the back and forth? Others?

Rose, what is our position in responding to the outside reviewers in this regard?

Thanks, Kristi

**From:** [Kristi Watterberg](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [goldb008@mc.duke.edu](mailto:goldb008@mc.duke.edu); [matt\\_laughon@med.unc.edu](mailto:matt_laughon@med.unc.edu); [Michelle Walsh](#); [adas@rti.org](mailto:adas@rti.org); [Dennis Wallace](#); [Kathleen.A.Kennedy@uth.tmc.edu](mailto:Kathleen.A.Kennedy@uth.tmc.edu); [richard.ehrenkranz@yale.edu](mailto:richard.ehrenkranz@yale.edu)  
**Subject:** Fwd: RE: RE: SUPPORT data  
**Date:** Wednesday, February 24, 2010 4:23:39 PM  
**Attachments:** RE\_RE SUPPORT data.msg

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I am forwarding Kathleen's comments. Will next forward Matt's. Kristi



## **Blansfield, Earl (NIH/NICHD) [E]**

---

**From:** Kennedy, Kathleen A <Kathleen.A.Kennedy@uth.tmc.edu>  
**Sent:** Wednesday, February 24, 2010 2:19 PM  
**To:** Kristi Watterberg  
**Subject:** RE: RE: SUPPORT data

As you implied, I think we should stick with a 2-arm trial and take our best shot at determining the safety and effectiveness of hydrocortisone vs placebo. If we have solid evidence that it's safe and effective, I don't think most people will care how it compares to dex. If it's not effective in reducing BPD, as you say, that's important to know. We may or may not decide to study dex later if that happens. I don't see how we gain much with a dex arm in this study. We already know that dex in relatively high doses reduces BPD and that it mostly likely causes neurologic impairment when used in infants who are at relatively low risk of BPD. A very large trial of low-dose dex would be great, but Lex Doyle couldn't pull that off as a stand-alone trial and I think we'll run the risk of having inconclusive results because of power problems if we try to study 3 arms.

As Michelle and I have said before, I think we need clear "failure" criteria for the use of dex (when and how). Then the study really becomes a comparison of relatively early hydrocortisone vs later, if needed dex (or hydrocortisone vs placebo with routine care including dex for more severe disease). As others have said, I think it would be hard to have a control arm where no steroids could be used, no matter what.

Kathleen A. Kennedy, MD, MPH  
Richard W. Mithoff Professor of Pediatrics  
Director, Division of Neonatal-Perinatal Medicine  
Director, MS in Clinical Research Degree Program  
UT-Houston Medical School  
6431 Fannin, Suite 2.106  
Houston, TX 77030  
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---

**From:** Kristi Watterberg [<mailto:KWatterberg@salud.unm.edu>]  
**Sent:** Wednesday, February 24, 2010 10:20 AM  
**To:** Rosemary (NIH/NICHD) Higgins; [goldb008@mc.duke.edu](mailto:goldb008@mc.duke.edu); [matt\\_laughon@med.unc.edu](mailto:matt_laughon@med.unc.edu); Michelle Walsh; [adas@rti.org](mailto:adas@rti.org); Dennis Wallace; Kennedy, Kathleen A; [richard.ehrenkranz@yale.edu](mailto:richard.ehrenkranz@yale.edu)  
**Subject:** Fwd: RE: SUPPORT data

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To make the best use of our conference call time on Monday, I would like to get a current poll of the subcommittee regarding inclusion of dexamethasone in the study before the call, so we can make a decision and go forward.

As I see it, a straight HC/placebo trial will give us a reasonable chance of enrolling an adequate sample size in less than 3 years within the network. We run the risk of futility - but if HC doesn't work to facilitate extubation and decrease BPD, that's a very important finding. A three-way trial will stretch the capability of the network to enroll, and still would not give us a large enough sample size to compare HC/Dex anyway for non-inferiority.

so I think we are better off running a straight HC/placebo trial to find out if it works. If it does, we have lots of evidence to say HC is better for neurodevelopmental outcomes, and this trial will add to the evidence available regarding outcome after HC Rx. If it doesn't, then we could proceed to a straight dex/placebo trial in a subsequent protocol. After all our e-mail discussion regarding a three-arm protocol comparing each drug to the same placebo group, I know Kathleen and Michelle favor a single drug (HC) trial. Rich, have you changed your position after all the back and forth? Others?

Rose, what is our position in responding to the outside reviewers in this regard?

Thanks, Kristi

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** FW: SUPPORT  
**Date:** Wednesday, February 24, 2010 4:16:00 PM

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**From:** Gail, Dorothy (NIH/NHLBI) [E]  
**Sent:** Friday, November 17, 2006 3:03 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: SUPPORT

Rose - Recruitment has to be the top priority. I agree that (b) (5)

Dorothy B. Gail, Ph.D  
Chief  
Lung Biology and Disease Branch  
Division of Lung Diseases, NHLBI  
(301) 435-0222 phone  
(301) 480-3557 fax  
gaild@mail.nih.gov

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Friday, November 17, 2006 1:28 PM  
**To:** Gail, Dorothy (NIH/NHLBI) [E]  
**Subject:** SUPPORT

Dorothy,

I received the update enrollment numbers for SUPPORT earlier this week. As of the end of October, we were up to 418 (out of approx 1300) infants. During the month of October, there were 19 children enrolled. We have 16 centers now approved for recruitment. I had discussed the possibility of adding back the (b) (5) site with you a few weeks ago. As you know, Neil Finer, the PI of the SUPPORT trial was not renewed in the NRN with the re-competition cycle. We do obtain steering committee approval (b) (5)

Let me know if this is OK with you. We can do a subcontract through our data coordinating center to fund (b) (5) on a per patient basis.

Thanks  
Rose

Rosemary D. Higgins, M.D.  
Program Scientist for the Neonatal Research Network

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301-496-3790 (FAX)  
[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "vineet.bhandari@yale.edu"; "(susie.buchter@oz.ped.emory.edu)"; "Duara, Shahnaz"; "Finer, Neil"; "Gantz, Marie"; "Laroia, Nirupama"; "Brenda Morris"; "nancy newman"; "Michael O`Shea"; "Poole Kenneth (E-mail)"; "Rich, Wade"; "bsood@med.wayne.edu"; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; "Abhik Das"; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); "Brenda Poindexter"; "Carlo Waldemar (E-mail)"; cotte010@mc.duke.edu; "Dennis Wallace"; "Ed Bell"; "Ed Donovan"; "Ehrenkranz Richard (E-mail)"; Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; "Kristi Watterberg"; Kurt Schibler (kurt.schibler@cchmc.org); "Matthew Bizzarro"; "Michelle Walsh"; "Mickey Caplan"; "Oh William (E-mail)"; "Pablo Sanchez"; "Roger Faix"; "Ronald GOLdbero"; "Seetha Shankaran"; "Stevenson David (E-mail)"; "Stoll Barbara (E-mail)"; "Tyson Jon (E-mail)"; VanMeurs, Krisa  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; "Zaterka-Baxter, Kristin"; "Huitema, Carolyn Petrie"; "Cunningham, Meg"  
**Subject:** CONFIDENTIAL SUPPORT CPAP paper resubmission  
**Date:** Wednesday, February 24, 2010 12:17:00 PM  
**Attachments:** NEJM CPAP Revision Clean Final for editor Feb 23 (2).doc

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Hi,

NEJM asked for some minor clarifications on the CPAP paper. Attached is the most recent version which has gone back to the editors. I will keep everyone posted of any progress.

If you received an email regarding your ICJME form, please complete and return to Brendan Abel ASAP. IF you did not get a separate email, you do not need to do anything.

Thanks for all your help!!!

Rose

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network  
Pregnancy and Perinatology Branch  
Center for Developmental Biology and Perinatal Medicine  
Eunice Kennedy Shriver National Institute of Child Health and Human Development  
National Institutes of Health  
6100 Executive Blvd., Room 4B03  
MSC 7510  
Bethesda, MD 20892  
For overnight delivery use Rockville, MD 20852  
301-496-5575  
301-496-3790 (FAX)  
higginsr@mail.nih.gov

**From:** Kristi Watterberg  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; goldb008@mc.duke.edu; matt\_laughon@med.unc.edu; Michelle Walsh; adas@rti.org; Dennis Wallace; Kathleen.A.Kennedy@uth.tmc.edu; richard.ehrenkranz@yale.edu  
**Subject:** Fwd: RE: SUPPORT data  
**Date:** Wednesday, February 24, 2010 11:20:31 AM  
**Attachments:** RE SUPPORT data.msg

---

Hello, all. I am forwarding Marie's data regarding infants who remain on mechanical ventilation at 14 days and their BPD/death outcomes. As you will see, about 44% of the enrolled infants were on mechanical ventilation at that time (526). Of those, 30% survived without BPD, which is very close to the data provided by Abhik (24% of babies with at least 14 days of mechanical ventilation survived without BPD).

This is reassuring for our sample size estimation - if survival without BPD was 25%, as from Abhik's data, the total sample size to detect a 10% difference would be 658; if survival without BPD had improved to 35%, we would need 750. Because we cannot be sure of the baseline incidence at the time we start the study, we proposed a conservative sample size of 800. The SUPPORT data are between those two estimates, so the proposed sample size should be appropriate.

To make the best use of our conference call time on Monday, I would like to get a current poll of the subcommittee regarding inclusion of dexamethasone in the study before the call, so we can make a decision and go forward.

As I see it, a straight HC/placebo trial will give us a reasonable chance of enrolling an adequate sample size in less than 3 years within the network. We run the risk of futility - but if HC doesn't work to facilitate extubation and decrease BPD, that's a very important finding. A three-way trial will stretch the capability of the network to enroll, and still would not give us a large enough sample size to compare HC/Dex anyway for non-inferiority.

so I think we are better off running a straight HC/placebo trial to find out if it works. If it does, we have lots of evidence to say HC is better for neurodevelopmental outcomes, and this trial will add to the evidence available regarding outcome after HC Rx. If it doesn't, then we could proceed to a straight dex/placebo trial in a subsequent protocol. After all our e-mail discussion regarding a three-arm protocol comparing each drug to the same placebo group, I know Kathleen and Michelle favor a single drug (HC) trial. Rich, have you changed your position after all the back and forth? Others?

Rose, what is our position in responding to the outside reviewers in this regard?

Thanks, Kristi

## Higgins, Rosemary (NIH/NICHD) [E]

---

**From:** Rich, Wade <wrich@ucsd.edu>  
**Sent:** Wednesday, February 24, 2010 10:42 AM  
**To:** Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie; Wally Carlo, M.D.  
**Subject:** FW: New England Journal of Medicine - 09-11783.R2

-----Original Message-----

**From:** onbehalfof+editorial+nejm.org@manuscriptcentral.com  
[mailto:onbehalfof+editorial+nejm.org@manuscriptcentral.com] On Behalf Of editorial@nejm.org  
**Sent:** Wednesday, February 24, 2010 7:38 AM  
**To:** Finer, Neil; wcarlo@peds.uab.edu; michele.walsh@cwru.edu; Rich, Wade; mgantz@rti.org; alaptook@wihri.org; Bradley.yoder@hsc.utah.edu; roger.faix@has.utah.edu; adas@rti.org; poo@rti.org; nambalavanan@peds.uab.edu; (b) (6) edward.donovan@cchmc.org; vivek.narendran@cchmc.org; nxs5@cwru.edu; ifrantz@tuftsmedicalcenter.org; Pablo.Sanchez@UTSouthwestern.edu; susie.buchter@oz.ped.emory.edu; (b) (6) nirupama\_laroia@urmc.rochester.edu; bpoindex@iupui.edu; cotte010@mc.duke.edu; vanmeurs@leland.stanford.edu; bsood@med.wayne.edu; sduara@med.miami.edu; moshea@wfubmc.edu; edward.bell@uiowa.edu; vineet.bhandari@yale.edu; kwatterberg@salud.unm.edu; higginsr@mail.nih.gov; (b) (6)  
**Subject:** New England Journal of Medicine - 09-11783.R2

Dear Dr. Finer and co-authors,

Thank you for submitting your revision, of "Early CPAP versus Surfactant in Extremely Preterm Infants: The SUPPORT Trial" to the New England Journal of Medicine.

Your submission will be forwarded to the editor, and may be sent out for review as necessary.

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

New England Journal of Medicine  
10 Shattuck Street  
Boston, MA 02115  
(617) 734-9800  
Fax: (617) 739-9864  
<http://www.nejm.org>

**Blansfield, Earl (NIH/NICHD) [E]**

---

**From:** Gantz, Marie <mgantz@rti.org>  
**Sent:** Wednesday, February 24, 2010 10:18 AM  
**To:** Kristi Watterberg  
**Subject:** RE: SUPPORT data  
**Attachments:** Kristi Watterberg request - 24FEB10.doc

Thanks, Kristi. The numbers are attached. Let me know if there is anything else you need. FYI, I will be out of town this afternoon through next Wednesday.

Marie

Marie Gantz, Ph.D.  
Research Statistician  
RTI International  
[mgantz@rti.org](mailto:mgantz@rti.org)  
828-254-6255

---

**From:** Kristi Watterberg [<mailto:KWatterberg@salud.unm.edu>]  
**Sent:** Wednesday, February 24, 2010 10:03 AM  
**To:** Gantz, Marie  
**Subject:** RE: SUPPORT data

Hi, Marie - it was just my attempt to make clear that we intend to only include those patients on mechanical ventilation through an endotracheal tube. Because the new modality of nasal intermittent positive pressure ventilation is becoming so prevalent, it would be helpful to us to know that number as well. Thanks ~ Kristi

>>> "Gantz, Marie" <[mgantz@rti.org](mailto:mgantz@rti.org)> 2/24/2010 7:39 AM >>>

Hi Kristi,

I have a couple of quick questions about your request.

- 1) I'm not sure what you mean by ETT. For ventilation I usually include HFV and CV, but please let me know if you intended to include any other form of support as well (such as nasal SIMV).
- 2) For IMV, I'm assuming you mean nasal SIMV, but please let me know if that is correct.

Thanks,

Marie

Marie Gantz, Ph.D.  
Research Statistician  
RTI International



[mgantz@rti.org](mailto:mgantz@rti.org)

828-254-6255

---

**From:** Kristi Watterberg [<mailto:KWatterberg@salud.unm.edu>]  
**Sent:** Wednesday, February 17, 2010 12:01 PM  
**To:** Das, Abhik  
**Cc:** Rosemary (NIH/NICHD) Higgins  
**Subject:** SUPPORT data

Hi, Abhik - I understand that the SUPPORT subcommittee OK'd giving the hydrocortisone protocol development group the data regarding the BPD/death outcomes for SUPPORT babies still on ETT/ventilation at 14 days. Can you also let me know the % of the SUPPORT babies who were still on IMV at 14 days? I'd like to have that information if possible before the next subcommittee meeting, scheduled for March 1.

thanks! Kristi

**Death or BPD (by physiologic definition or supplemental oxygen) at 36 weeks PMA  
for SUPPORT infants on HFV/CV at 14 days of life**

**The FREQ Procedure**

<b>BPD (physiologic definition) or death by 36 weeks PMA</b>				
<b>death/bpd</b>	<b>Frequency</b>	<b>Percent</b>	<b>Cumulative Frequency</b>	<b>Cumulative Percent</b>
<b>Y</b>	372	70.72	372	70.72
<b>N</b>	154	29.28	526	100.00

<b>BPD (supplemental O2) or death by 36 weeks PMA</b>				
<b>death/bpd</b>	<b>Frequency</b>	<b>Percent</b>	<b>Cumulative Frequency</b>	<b>Cumulative Percent</b>
<b>Y</b>	374	71.10	374	71.10
<b>N</b>	152	28.90	526	100.00

**The FREQ Procedure**

BPD (physiologic definition)				
bpd	Frequency	Percent	Cumulative Frequency	Cumulative Percent
Y	301	66.15	301	66.15
N	154	33.85	455	100.00

BPD (supplemental O2)				
bpd	Frequency	Percent	Cumulative Frequency	Cumulative Percent
Y	303	66.59	303	66.59
N	152	33.41	455	100.00

This document is provided for reference purposes only. Persons with disabilities having difficulty accessing information in this document should e-mail NICHD FOIA Office at NICHDFOIArequest@mail.nih.gov for assistance.

**SUPPORT infants on nasal SIMV at 14 days of life**  
**NOTE: 85 infants were on nasal SIMV and not HFV/CV at 14 days; 14 infants spent time on both**

**The FREQ Procedure**

simv14(On nasal SIMV at 14 days)	mv14(On HFV/CV at 14 days)	Y	Total
Y	85	14	99
Total	85	14	99

## Higgins, Rosemary (NIH/NICHD) [E]

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**From:** Finer, Neil <nfiner@ucsd.edu>  
**Sent:** Tuesday, February 23, 2010 10:53 PM  
**To:** Gantz, Marie; Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Rich, Wade  
**Subject:** RE: Steering Committee Call Tomorrow

Marie

Again many thanks

Your analyses has clearly shown that THE RANDOMIZED OXIMETER - HI VS LOW DID NOT EFFECT THE BPD DIAGNOSIS.

That was Jon's key point

He argued that infants randomized to the Hi arm would get more oxygen and have more BPD bet either diagnosis I think your analyses says that is not an issue The rest argues that centers are different - a persistent effect Be well - Now all of you need to go to bed!!!!

Sweet dreams kids!!!

Neil

-----Original Message-----

**From:** Gantz, Marie [mailto:mgantz@rti.org]  
**Sent:** Tuesday, February 23, 2010 6:59 PM  
**To:** Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; Das, Abhik; Rich, Wade  
**Subject:** RE: Steering Committee Call Tomorrow

Whether we group the centers by type of oximeter or not, the treatment effect is the same. This is because if we look at (a) center differences alone, or (b) BPD oximeter differences plus center differences within oximeter group, these are two different ways of specifying the same model. The treatment effect is the same either way.

Marie

Marie Gantz, Ph.D.  
Research Statistician  
RTI International  
mgantz@rti.org  
828-254-6255

-----Original Message-----

**From:** Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]  
**Sent:** Tuesday, February 23, 2010 9:43 PM  
**To:** Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu; wcarlo@peds.uab.edu; Das, Abhik; wrich@ucsd.edu  
**Subject:** RE: Steering Committee Call Tomorrow

Marie.

Is grouping of the centers by type of oximeter necessary to do the best analysis?

Sent from my Windows Mobile phone

-----Original Message-----

**From:** Gantz, Marie <mgantz@rti.org>

Sent: Tuesday, February 23, 2010 8:36 PM

To: Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov>; nfiner@ucsd.edu <nfiner@ucsd.edu>; wcarlo@peds.uab.edu <wcarlo@peds.uab.edu>; Das, Abhik <adas@rti.org>; wrich@ucsd.edu <wrich@ucsd.edu>  
Subject: RE: Steering Committee Call Tomorrow

Response: We have looked into the question of whether the oximeter used to determine BPD impacted the BPD and death/BPD outcomes by adding a covariate for the BPD oximeter (study or clinical) to the statistical models. We found that the effect of the BPD oximeter was significant; however, the interaction between BPD oximeter and treatment oximeter (low or high SpO2 target range) was not significant in any model, indicating that, if there was a BPD oximeter effect, it was not different in the two treatment groups. In addition, it should be noted that BPD oximeter is confounded with center (centers tended to be consistent in their use of the study or clinical oximeters to determine BPD). Therefore, by including center in the original models, we have already accounted for the effect of the BPD oximeter the center chose to use. Finally, because center and BPD oximeter are confounded, we cannot know whether the significant BPD oximeter effect is due to the BPD oximeters themselves or other characteristics that differ between centers.

Marie Gantz, Ph.D.

Research Statistician

RTI International

mgantz@rti.org

828-254-6255

---

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]

Sent: Tuesday, February 23, 2010 8:31 PM

To: Gantz, Marie; 'nfiner@ucsd.edu'; 'wcarlo@peds.uab.edu'; Das, Abhik; 'wrich@ucsd.edu'

Subject: Fw: Steering Committee Call Tomorrow

Marie (and Wade)

Here is the email sent shortly following the call.

Marie - can you craft a response that will address the concern?

Thanks (a million)

Rose

---

From: Tyson, Jon E <Jon.E.Tyson@uth.tmc.edu>

To: Higgins, Rosemary (NIH/NICHD) [E]; 'Cunningham, Meg'

<mcunningham@rti.org>; [SCRN] Stoll, Barbara <barbara\_stoll@oz.ped.emory.edu>; alaptook@WIHRI.org <alaptook@WIHRI.org>; Bell, Edward <edward-bell@uiowa.edu>; bpoindex@iupui.edu <bpoindex@iupui.edu>; Das, Abhik <adas@rti.org>; goldb008@mc.duke.edu <goldb008@mc.duke.edu>; ifrantz@tuftsmedicalcenter.org <ifrantz@tuftsmedicalcenter.org>; Kennedy, Kathleen A <Kathleen.A.Kennedy@uth.tmc.edu>; kurt.schibler@cchmc.org <kurt.schibler@cchmc.org>; kwatterberg@salud.unm.edu <kwatterberg@salud.unm.edu>; matthew.bizzarro@yale.edu <matthew.bizzarro@yale.edu>; mcw3@cwru.edu <mcw3@cwru.edu>; mcaplan@northshore.org <mcaplan@northshore.org>; Pablo.Sanchez@UTSouthwestern.edu <Pablo.Sanchez@UTSouthwestern.edu>; richard.ehrenkranz@yale.edu <richard.ehrenkranz@yale.edu>; Roger.Faix@hsc.utah.edu <Roger.Faix@hsc.utah.edu>; sshankar@med.wayne.edu <sshankar@med.wayne.edu>; vanmeurs@leland.stanford.edu <vanmeurs@leland.stanford.edu>; Wally Carlo, M.D. <WCarlo@peds.uab.edu>; Wallace, Dennis <dwallace@rti.org>; cotte010@mc.duke.edu <cotte010@mc.duke.edu>; Bradley Yoder <Bradley.Yoder@hsc.utah.edu>; rohls@salud.unm.edu <rohls@salud.unm.edu>; Luc.Brion@utsouthwestern.edu <Luc.Brion@utsouthwestern.edu>; bbatton@siumed.edu <bbatton@siumed.edu>  
Cc: Zaterka-Baxter, Kristin <kzaterka@rti.org>; Irene, Amanda <airene@rti.org>; Huitema, Carolyn Petrie <petrie@rti.org>; Newman, Jamie <newman@rti.org>; lmoore@med.wayne.edu <lmoore@med.wayne.edu>; pamelaneville@duke.edu <pamelaneville@duke.edu>; gonza025@mc.duke.edu <gonza025@mc.duke.edu>; Smith, Nancy M <Nancy.M.Smith@uth.tmc.edu>; Brenda Vecchio <BVecchio@WIHRI.org>; msumner@peds.uab.edu <msumner@peds.uab.edu>; Archer, Stephanie (NIH/NICHD) [E]  
Sent: Tue Feb 23 16:33:11 2010  
Subject: RE: Steering Committee Call Tomorrow

While it may seem that I am fixated on an unimportant issue regarding a not quite significant difference, I think we undermine the credibility of Network studies if we are not completely forthright about problems in measuring what everyone would agree is an important secondary outcome.

Not reporting that the assessment of BPD by oxygen administration could be biased by continued use of the study oximeters would seem to be in the category of not reporting protocol deviations and not something that is in the Network's best interest. Why not just put a footnote under the table describing the problem?

Jon E. Tyson, MD, MPH

Center for Clinical Research & Evidence-Based Medicine

UT Medical School at Houston

6431 Fannin St., MSB 2.106

Houston, TX 77030

voice 713-500-5651

fax 713-500-0519

---

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]

Sent: Tuesday, February 23, 2010 2:11 PM

To: 'Cunningham, Meg'; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org;

kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; Wallace, Dennis; cotte010@mc.duke.edu; Tyson, Jon E; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; bbatton@siumed.edu

Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Imoore@med.wayne.edu; pamela.neville@duke.edu; gonza025@mc.duke.edu; Smith, Nancy M; Brenda Vecchio; msumner@peds.uab.edu; Archer, Stephanie (NIH/NICHD) [E]

Subject: RE: Steering Committee Call Tomorrow

If you joined the call already in progress, please send us an email so we can count your attendance.

Rose

---

From: Cunningham, Meg [mailto:mcunningham@rti.org]  
Sent: Monday, February 22, 2010 9:59 AM  
To: [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; Higgins, Rosemary (NIH/NICHD) [E]; ifrantz@tuftsmedicalcenter.org; Kathleen.A.Kennedy@uth.tmc.edu; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; Wallace, Dennis; cotte010@mc.duke.edu; jon.e.tyson@uth.tmc.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; bbatton@siumed.edu  
Cc: Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Imoore@med.wayne.edu; pamela.neville@duke.edu; gonza025@mc.duke.edu; Nancy.M.Smith@uth.tmc.edu; Brenda Vecchio; msumner@peds.uab.edu; Archer, Stephanie (NIH/NICHD) [E]  
Subject: Steering Committee Call Tomorrow

Dear All -

The next standing Steering Committee call is scheduled for tomorrow, Tuesday, February 23rd at 3:00pm ET.

Please Dial:

Outside the USA 1-203-310-(b)

or Within the USA 866-675-(b)



Then, enter Participant Passcode: (b) (6) ■

Steering Committee Conference Call Agenda 02/23/2010

1. Early BP discussion (attached are a brief description of the time limited data collection proposal and a draft of the form which would be used.)
2. SUPPORT manuscript discussion and update
3. New Business

Thanks,

Meg

Meg Cunningham  
RTI International  
701 13th St. NW, Ste. 750  
Washington, DC 20005  
tel: 202-974-7837  
fax: 202-728-2095  
www.rti.org <<http://www.rti.org>>

## Higgins, Rosemary (NIH/NICHD) [E]

---

**From:** Finer, Neil <nfiner@ucsd.edu>  
**Sent:** Tuesday, February 23, 2010 10:45 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; 'wcarlo@peds.uab.edu'  
**Cc:** Rich, Wade  
**Subject:** RE: Steering Committee Call Tomorrow

Hi Rose

I would say it was a pleasure but exercising that much restraint is truly painful!!

God bless You, Wally, Marie, and Wade

Now I'm off to Ireland

Be well

Neil

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Tuesday, February 23, 2010 5:46 PM  
**To:** 'wcarlo@peds.uab.edu'; Finer, Neil  
**Subject:** Fw: Steering Committee Call Tomorrow

Hopefully this will put this to rest!!

Neil - thanks for joining the call today!!!

Rose

---

**From:** Gantz, Marie <mgantz@rti.org>  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu <nfiner@ucsd.edu>; wcarlo@peds.uab.edu <wcarlo@peds.uab.edu>; Das, Abhik <adas@rti.org>; wrich@ucsd.edu <wrich@ucsd.edu>  
**Sent:** Tue Feb 23 20:40:29 2010  
**Subject:** RE: Steering Committee Call Tomorrow

Rose, I will work on the response and send it back to you.

Marie

Marie Gantz, Ph.D.  
Research Statistician  
RTI International  
mgantz@rti.org  
828-254-6255

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Tuesday, February 23, 2010 8:31 PM  
**To:** Gantz, Marie; 'nfiner@ucsd.edu'; 'wcarlo@peds.uab.edu'; Das, Abhik; 'wrich@ucsd.edu'  
**Subject:** Fw: Steering Committee Call Tomorrow

Marie (and Wade)

Here is the email sent shortly following the call.

Marie - can you craft a response that will address the concern?

Thanks (a million)

Rose

---

**From:** Tyson, Jon E <Jon.E.Tyson@uth.tmc.edu>

**To:** Higgins, Rosemary (NIH/NICHD) [E]; 'Cunningham, Meg' <mcunningham@rti.org>; [SCRN] Stoll, Barbara <barbara\_stoll@oz.ped.emory.edu>; alaptook@WIHRI.org <alaptook@WIHRI.org>; Bell, Edward <edward-bell@uiowa.edu>; bpoindex@iupui.edu <bpoindex@iupui.edu>; Das, Abhik <adas@rti.org>; goldb008@mc.duke.edu <goldb008@mc.duke.edu>; ifrantz@tuftsmedicalcenter.org <ifrantz@tuftsmedicalcenter.org>; Kennedy, Kathleen A <Kathleen.A.Kennedy@uth.tmc.edu>; kurt.schibler@cchmc.org <kurt.schibler@cchmc.org>; kwatterberg@salud.unm.edu <kwatterberg@salud.unm.edu>; matthew.bizzarro@yale.edu <matthew.bizzarro@yale.edu>; mcw3@cwru.edu <mcw3@cwru.edu>; mcaplan@northshore.org <mcaplan@northshore.org>; Pablo.Sanchez@UTSouthwestern.edu <Pablo.Sanchez@UTSouthwestern.edu>; richard.ehrenkranz@yale.edu <richard.ehrenkranz@yale.edu>; Roger.Faix@hsc.utah.edu <Roger.Faix@hsc.utah.edu>; sshankar@med.wayne.edu <sshankar@med.wayne.edu>; vanmeurs@leland.stanford.edu <vanmeurs@leland.stanford.edu>; Wally Carlo, M.D. <WCarlo@peds.uab.edu>; Wallace, Dennis <dwallace@rti.org>; cotte010@mc.duke.edu <cotte010@mc.duke.edu>; Bradley Yoder <Bradley.Yoder@hsc.utah.edu>; rohls@salud.unm.edu <rohls@salud.unm.edu>; Luc.Brion@utsouthwestern.edu <Luc.Brion@utsouthwestern.edu>; bbatton@siumed.edu <bbatton@siumed.edu>

**Cc:** Zaterka-Baxter, Kristin <kzaterka@rti.org>; Irene, Amanda <airene@rti.org>; Huitema, Carolyn Petrie <petrie@rti.org>; Newman, Jamie <newman@rti.org>; Imoore@med.wayne.edu <Imoore@med.wayne.edu>; pamela.neville@duke.edu <pamela.neville@duke.edu>; gonza025@mc.duke.edu <gonza025@mc.duke.edu>; Smith, Nancy M <Nancy.M.Smith@uth.tmc.edu>; Brenda Vecchio <BVecchio@WIHRI.org>; msumner@peds.uab.edu <msumner@peds.uab.edu>; Archer, Stephanie (NIH/NICHD) [E]

**Sent:** Tue Feb 23 16:33:11 2010

**Subject:** RE: Steering Committee Call Tomorrow

While it may seem that I am fixated on an unimportant issue regarding a not quite significant difference, I think we undermine the credibility of Network studies if we are not completely forthright about problems in measuring what everyone would agree is an important secondary outcome. Not reporting that the assessment of BPD by oxygen administration could be biased by continued use of the study oximeters would seem to be in the category of not reporting protocol deviations and not something that is in the Network's best interest. Why not just put a footnote under the table describing the problem?

Jon E. Tyson, MD, MPH  
Center for Clinical Research & Evidence-Based Medicine  
UT Medical School at Houston  
6431 Fannin St., MSB 2.106  
Houston, TX 77030  
voice 713-500-5651  
fax 713-500-0519

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**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]

**Sent:** Tuesday, February 23, 2010 2:11 PM

**To:** 'Cunningham, Meg'; [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; Wallace, Dennis; cotte010@mc.duke.edu; Tyson, Jon E; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; bbatton@siumed.edu

**Cc:** Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Imoore@med.wayne.edu; pamela.neville@duke.edu; gonza025@mc.duke.edu; Smith, Nancy M; Brenda Vecchio; msumner@peds.uab.edu; Archer, Stephanie (NIH/NICHD) [E]

**Subject:** RE: Steering Committee Call Tomorrow

If you joined the call already in progress, please send us an email so we can count your attendance.

Rose

---

**From:** Cunningham, Meg [mailto:mcunningham@rti.org]  
**Sent:** Monday, February 22, 2010 9:59 AM  
**To:** [SCRN] Stoll, Barbara; alaptook@WIHRI.org; Bell, Edward; bpoindex@iupui.edu; Das, Abhik; goldb008@mc.duke.edu; Higgins, Rosemary (NIH/NICHD) [E]; ifrantz@tuftsmedicalcenter.org; Kathleen.A.Kennedy@uth.tmc.edu; kurt.schibler@cchmc.org; kwatterberg@salud.unm.edu; matthew.bizzarro@yale.edu; mcw3@cwru.edu; mcaplan@northshore.org; Pablo.Sanchez@UTSouthwestern.edu; richard.ehrenkranz@yale.edu; Roger.Faix@hsc.utah.edu; sshankar@med.wayne.edu; vanmeurs@leland.stanford.edu; Wally Carlo, M.D.; Wallace, Dennis; cotte010@mc.duke.edu; jon.e.tyson@uth.tmc.edu; Bradley Yoder; rohls@salud.unm.edu; Luc.Brion@utsouthwestern.edu; bbatton@siumed.edu  
**Cc:** Zaterka-Baxter, Kristin; Irene, Amanda; Huitema, Carolyn Petrie; Newman, Jamie; Imoore@med.wayne.edu; pamela.neville@duke.edu; gonza025@mc.duke.edu; Nancy.M.Smith@uth.tmc.edu; Brenda Vecchio; msumner@peds.uab.edu; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** Steering Committee Call Tomorrow

Dear All -

The next standing Steering Committee call is scheduled for tomorrow, Tuesday, February 23<sup>rd</sup> at 3:00pm ET.

**Please Dial:**

Outside the USA 1-203-310-(b)  
or Within the USA 866-675-(b)  
Then, enter Participant Passcode: (b) (6)

**Steering Committee Conference Call Agenda 02/23/2010**

1. Early BP discussion (attached are a brief description of the time limited data collection proposal and a draft of the form which would be used.)
2. SUPPORT manuscript discussion and update
3. New Business

Thanks,  
Meg

*Meg Cunningham  
RTI International  
701 13th St. NW, Ste. 750  
Washington, DC 20005  
tel: 202-974-7837  
fax: 202-728-2095  
www.rti.org*

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Gantz, Marie"  
**Cc:** "Finer, Neil"; "Wally Carlo, M.D."  
**Subject:** FW: SUPPORT Oximeters used for Physio Challenge, 2009-11.xls  
**Date:** Tuesday, February 23, 2010 4:46:00 PM  
**Attachments:** SUPPORT Oximeters used for Physio Challenge, 2009-11.xls

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Here it is

Rose

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**From:** Archer, Stephanie (NIH/NICHD) [E]  
**Sent:** Tuesday, February 23, 2010 4:10 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** SUPPORT Oximeters used for Physio Challenge, 2009-11.xls

Here are the survey results.

**Neonatal Research Network Steering Committee votes**

	03 Case	04 Dallas	05 Wayne	09 Emory	11 Cincinnati	12 Indiana	13 Yale	14 Brown	15 Stanford	16 Alabama	18 Houston	19 Duke	23 Tufts	24 Iowa	25 Utah	26 New Mexico	RTI	NICHD	Chairman	Total	Average rating	
<b>SUPPORT   Oximeters used for Physiologic Def. Challenge</b>																						
Voted	V	V	V	V	V	V	V	V	V	V	V	V	V		V	V					15	
For determination of eligibility for the challenge, did you determine eligibility using:																						
Study oximeter	1	1	1	1	1	1	1		1	1	1	1	1	see below	1	1					5	
Clinical oximeter															1						10	
Brown	Per FIO2 documentation in medical record at 36 weeks.																					
If a challenge occurred, did your site use:																						
Study Oximeter												1				1					3	
Clinical oximeter	1	1	1	1	1	1	1	1	1	1	1		1		1						13	
For BPD by oxygen definition, did you use:																						
Study oximeter	1	1	1	1	1	1	1	1	1	1	1	1	1		1	1					5	
Clinical oximeter																					11	
Utah	Our answer is mixed. Some of the kids moved up to the extension unit, where we weren't allowed to use the study oximeters (they didn't speak to the central alarm system). So, some were on the study ox and others on the clinical one. If you need me to send specifics, I can.																					
Indiana	We followed the manual guidelines for use of the study oximeters – so any baby on oxygen indeed was still on a study oximeter up until 36 weeks. We determined if babies were eligible for a challenge at 36 weeks – then notified the study RT that a challenge needed to be performed sometime in the next week. So, in general, all challenges would be performed on a clinical oximeters because the study oximeters was removed at 36 weeks and the challenge occurred in that next week after 36 weeks. What we don't know for sure is how efficient the RTs were in doing the challenge – in general, I think it is fair to say that babies would have all been on clinical oximeters – but could there have been a few babies here or there that the challenge was done on the same exact day that the baby hit 36 weeks and maybe the study oximeters was still on – possibly – but I really don't think we were that speedy in getting the challenges done exactly on the day the baby hit 36 weeks but we were efficient at removing the study oximeters on exactly that day. Clear as mud? I don't think any of the SUPPORT forms ask for the exact day the challenge was done, did they? Let us know if this doesn't make sense.																					
Alabama	At UAB, determination of eligibility by study pulse oximeter used on 36 week PCA day. If infant had challenge done, it was done with a clinical pulse oximeter. Study PO left on baby on day 36 week because 4 data points were required on that day. After the study PO was removed, the infant, if requiring challenge, had a 5 minute period of baseline on a clinical PO, and then the challenge was done.																					
Dallas	I looked at the completed PHY02BASE forms for our SUPPORT babies who had challenges. According to my records one of our infants was tested with a Masimo (not sure why or how it happened). All of the other infants had clinical oximeters used for eligibility, the challenge, and for BPD by oxygen definition. The infant, who had the Masimo in place, failed when the sats went to 68 so the outcome would have been the same with a clinical oximeter.																					

Date Request sent out

11/25/09

Deadline

Reply to:

Responses sent

UNM

In New Mexico the Study oximeter was kept on the patient until 36 weeks, death, transfer, or room air. Therefore, the study oximeter was used to determine eligibility for RA challenge, and to record the use of oxygen at 36 weeks. As you can see from the attached table, 16 subjects were alive at 36 weeks. Four of those were on clinical oximeters because they were in another hospital. One more was on a clinical oximeter because they were in room air. Of the 4 on whom the challenge was done, 3 were still on the study oximeter at the time of the challenge. One challenge was done on a clinical oximeter because it was done after the 36 weeks date, but the subject had been on the study oximeter at 36 weeks.

Emory

I went back through our SUPPORT folders and I think that only [REDACTED] (and (b) [REDACTED]) were evaluated for BPD using the study monitors. Both coded as not eligible for reduction because sats too low. I think these are the only ones.

Duke

The study oximeter was used to determine eligibility for the challenge (for those that were still on the study oximeter at 36 weeks) and was also used for the challenge.

Iowa

Our answer is mixed. Some of the kids moved up to the extension unit, where we weren't allowed to use the study oximeters (they didn't speak to the central alarm system). So, some were on the study ox and others on the clinical one. If you need me to send specifics, I can.

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Wally Carlo, M.D."; "Finer, Neil"  
**Subject:** FW: SUPPORT Oximeters used for Physio Challenge, 2009-11.xls  
**Date:** Tuesday, February 23, 2010 4:14:00 PM  
**Attachments:** SUPPORT Oximeters used for Physio Challenge, 2009-11.xls

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Here is the info

Rose

---

**From:** Archer, Stephanie (NIH/NICHD) [E]  
**Sent:** Tuesday, February 23, 2010 4:10 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** SUPPORT Oximeters used for Physio Challenge, 2009-11.xls

Here are the survey results.



**Neonatal Research Network Steering Committee votes**

	03 Case	04 Dallas	05 Wayne	09 Emory	11 Cincinnati	12 Indiana	13 Yale	14 Brown	15 Stanford	16 Alabama	18 Houston	19 Duke	23 Tufts	24 Iowa	25 Utah	26 New Mexico	RTI	NICHD	Chairman	Total	Average rating	
<b>SUPPORT   Oximeters used for Physiologic Def. Challenge</b>	V	V	V	V	V	V	V	V	V	V	V	V	V		V	V					15	
Voted	V	V	V	V	V	V	V	V	V	V	V	V	V		V	V					15	
For determination of eligibility for the challenge, did you determine eligibility using:																						
Study oximeter										1	1	1		see below	1	1					5	
Clinical oximeter	1	1	1	1	1	1	1		1						1						10	
Brown	Per FiO2 documentation in medical record at 36 weeks.																					
If a challenge occurred, did your site use:																						
Study Oximeter												1			1	1					3	
Clinical oximeter	1	1	1	1	1	1	1	1	1	1	1		1		1						13	
For BPD by oxygen definition, did you use:																						
Study oximeter															1	1					5	
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Date Request sent out: 11/25/09  
 Deadline:

Reply to:  
 Responses sent

UNM

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This document is provided for reference purposes only. Persons with disabilities having difficulty accessing information in this document should e-mail NICHD FOIA Office at NICHDFOIARequest@mail.nih.gov for assistance.

**From:** [Archer, Stephanie \(NIH/NICHD\) \[E\]](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Subject:** SUPPORT Oximeters used for Physio Challenge, 2009-11.xls  
**Date:** Tuesday, February 23, 2010 4:09:49 PM  
**Attachments:** [SUPPORT Oximeters used for Physio Challenge, 2009-11.xls](#)

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Here are the survey results.

Neonatal Research Network Steering Committee votes														Total	Average rating	Date Request sent out	Deadline		
	03 Case	04 Dallas	05 Wayne	09 Emory	11 Cincinnati	12 Indiana	13 Yale	14 Brown	15 Stanford	16 Alabama	18 Houston	19 Duke	23 Tufts	24 Iowa	25 Utah	26 New Mexico	RTI	NICHD	Chairman
<b>SUPPORT   Oximeters used for Physiologic Def. Challenge</b>	V	V	V	V	V	V	V	V	V	V	V	V	V		V	V			
Voted																			
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Clinical oximeter	1	1	1	1	1	1	1		1	1	1	1	1	1	1				
Brown	Per FIO2 documentation in medical record at 36 weeks.																		
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Study Oximeter																			
Clinical oximeter	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1			
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Reply to:

Responses sent

## Higgins, Rosemary (NIH/NICHD) [E]

---

**From:** Finer, Neil <nfiner@ucsd.edu>  
**Sent:** Tuesday, February 23, 2010 3:02 PM  
**To:** Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.; Das, Abhik  
**Cc:** Rich, Wade  
**Subject:** RE:

Thanks Marie  
I made this change  
Neil

---

**From:** Gantz, Marie [mailto:mgantz@rti.org]  
**Sent:** Tuesday, February 23, 2010 10:58 AM  
**To:** Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.; Das, Abhik  
**Cc:** Rich, Wade  
**Subject:** RE:

Just giving this one final look over, and had another comment on this sentence:

“We found no significant differences in rates of pneumothorax, intraventricular hemorrhage, or the need for chest compressions or epinephrine in the delivery room, when comparing the two groups or when comparing randomized infants to the previous NRN population from 2000 to 2004 of infants of similar gestational ages.”

We did not formally test the rates of these events in the SUPPORT population vs. the NRN population from 2000-2004. Thus, it might be more accurate to state the following (which uses the same number of words and avoids applying the word “significant” to the differences between support and NRN from 2000-2004):

“We found no significant differences in rates of pneumothorax, intraventricular hemorrhage, or the need for chest compressions or epinephrine in the delivery room, when comparing the two groups, and rates were comparable to those in the NRN population from 2000 to 2004 of infants of similar gestational ages.”

Marie Gantz, Ph.D.  
Research Statistician  
RTI International  
mgantz@rti.org  
828-254-6255

---

**From:** Finer, Neil [mailto:nfiner@ucsd.edu]  
**Sent:** Tuesday, February 23, 2010 11:41 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.; Gantz, Marie; Das, Abhik  
**Cc:** Rich, Wade  
**Subject:**

Hi Guys  
I have now further revised after talking with Marie  
Here are the last edits – saved for you to see  
We fit for words etc. I took out the sentence about the size of the small strata to underemphasize this.  
Please let me know your thoughts  
Neil

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Fuller, Martha"; "Finer, Neil"; "Rich, Wade"; "Vaucher, Yvonne"  
**Cc:** "Gantz, Marie"  
**Subject:** RE: SUPPORT FU  
**Date:** Tuesday, February 23, 2010 12:26:00 PM

---

Ok  
Thanks for looking into this

Rose

---

**From:** Fuller, Martha [mailto:mgfuller@ucsd.edu]  
**Sent:** Tuesday, February 23, 2010 12:26 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; Rich, Wade; Vaucher, Yvonne  
**Cc:** Gantz, Marie  
**Subject:** RE: SUPPORT FU

Child was seen 1/15/2010 (late).  
Pending data entry/transmission.  
Martha

Martha G. Fuller, RN, MSN  
Pediatric Nurse Practitioner  
UCSD Infant Special Care Follow-up Program  
(619) 543-3771 (office)  
(619) 543-3822 (direct line/voice mail)

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---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Monday, February 22, 2010 7:24 AM  
**To:** Finer, Neil; Rich, Wade; Fuller, Martha; Vaucher, Yvonne  
**Cc:** Gantz, Marie  
**Subject:** SUPPORT FU

Hi,  
We are missing the following primary outcomes for the SUPPORT FU study. Let us know how you are doing.

Thanks for all the effort!!

Rose

CENTER	NETWORK	FU_message
22	(b) (6)	FU window has closed but NF05 and NF09a have not been completed.

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network  
Pregnancy and Perinatology Branch  
Center for Developmental Biology and Perinatal Medicine  
Eunice Kennedy Shriver National Institute of Child Health and Human Development  
National Institutes of Health  
6100 Executive Blvd., Room 4B03  
MSC 7510  
Bethesda, MD 20892  
For overnight delivery use Rockville, MD 20852  
301-496-5575  
301-496-3790 (FAX)  
higginsr@mail.nih.gov

## **Higgins, Rosemary (NIH/NICHD) [E]**

---

**From:** Finer, Neil <nfiner@ucsd.edu>  
**Sent:** Tuesday, February 23, 2010 11:41 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.; 'Gantz, Marie'; adas@rti.org  
**Cc:** Rich, Wade  
**Attachments:** NEJM Feb 23 08-30 Gantz edits.doc

Hi Guys

I have now further revised after talking with Marie

Here are the last edits – saved for you to see

We fit for words etc. I took out the sentence about the size of the small strata to underemphasize this.

Please let me know your thoughts

Neil

## **Higgins, Rosemary (NIH/NICHD) [E]**

---

**From:** Finer, Neil <nfiner@ucsd.edu>  
**Sent:** Tuesday, February 23, 2010 10:49 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; 'Wally Carlo, M.D.'; 'Gantz, Marie'; adas@rti.org  
**Cc:** Rich, Wade  
**Subject:** RE:  
**Attachments:** NEJM Feb 22 Revision from Editor all edits shown.doc; NEJM Feb 23 07-30.doc

Hi Rose and Wally  
Thank you both for your comments  
I have attached a version with all changes.  
Rose I made your suggested additional changes

Wally- I hope the one with all the edits is readable – it is very difficult to follow the edits – for ease of doing this you may want to choose – Word –Preferences – click on track changes and you will get an option to see either balloons or you can select not to. We did the latter to make it easier to follow where the actual comments were inserted  
I hope this helps

I had placed the following sentence at the end of the paragraph in the discussion about death in the small strata – “This remains a post hoc observation, and thus needs further testing in this immature population.”

I thought this directly dealt with this issue

Have I missed something here??

I will look forward to your replies

Be well

Neil

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Tuesday, February 23, 2010 6:38 AM  
**To:** Finer, Neil; 'Wally Carlo, M.D.'; 'Gantz, Marie'; adas@rti.org  
**Cc:** Rich, Wade  
**Subject:** RE:  
**Importance:** High

Neil

Sorry for the delay. (b) (6)

First and foremost, a preliminary congratulations. Their suggestions are very minor in the big picture!!! Kudos to you!!!

I have added the ROP adjudication committee to your manuscript.



Comments:

(b) (4) [redacted] ?

S34 – we did not answer this one – we either need to say (b) (4) [redacted] of pre-specified gestational age strata” and point them to page 11 of 35 in the protocol stating:

(b) (4) [redacted]

We could also provide them with the background information for the DSMC showing them (b) (4) [redacted] (which was done).

I also did a few minor space edits.  
I am free until 3 PM ET today if you want to briefly discuss.

Rose

---

**From:** Finer, Neil [mailto:nfiner@ucsd.edu]  
**Sent:** Monday, February 22, 2010 7:22 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; 'Wally Carlo, M.D.'; 'Gantz, Marie'; adas@rti.org  
**Cc:** Rich, Wade  
**Subject:**

Hi Everyone

I have reviewed the editorial comments, and made all the changes that Wade and I can  
Marie and I have spoken and she will look at stating the range of differences in percent as requested – The manuscript already has the 95% CIs  
Otherwise I think we have answered all ( and there were many) comments  
Please review and let me know  
Thanks for your input – special thanks to Marie  
I think that the main message is still delivered appropriately.  
I am travelling Wednesday to the UK and I would like to complete this as much as we can and then you need to circulate/whatever following NRN procedure.  
Neil

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Finer, Nell"; "Wally Carlo, M.D."; "mcw3@case.edu"; "Bradley Yoder"; "Roger Faix"; "alaptook@WIHRI.org"; "Kurt Schibler [kurt.schibler@cchmc.org]"; "Abhik Das"; "Wallace, Dennis"; "nancy newman"; "Rich, Wade"; "Gantz, Marie"  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; "Zaterka-Baxter, Kristin"; "Cunningham, Meg"; "Carolyn Petrie"; "Webb, Robin E."  
**Subject:** SUPPORT Intermittent Hypoxia  
**Date:** Monday, February 22, 2010 11:15:00 AM  
**Attachments:** SUPPORT Intermittent Hypoxia.doc

---

Hi,  
Attached is a secondary study fro review.  
I will have Robin set up a call to discuss.

Thanks  
Rose

## Intermittent Hypoxia in Preterm Infants enrolled in the SUPPORT trial

### Secondary Study

Juliann Di Fiore, BSEE, Ryan Foglyano, BSBE, Richard Martin, MD,

Chris Wilson PhD, Michele Walsh, MD

[Case Western Reserve University School of Medicine, Cleveland, OH]

#### Abstract

Episodes of oxygen saturation are almost universal in very low birthweight infants. Neither their incidence, nor potential adverse effects on later neurodevelopmental outcome are known. The NICHD Neonatal Research Network, of which we are a participant, has completed a multicenter trial in which preterm infants of 24-28 weeks gestation were randomized to high versus low levels of baseline oxygen saturation. We have previously received approval from the NICHD Neonatal Research Network to perform a secondary study on a subcohort of the SUPPORT trial infants, entitled *INCIDENCE AND CONSEQUENCES OF EPISODIC DESATURATION IN PRETERM INFANTS ENROLLED IN THE NICHD NEONATAL NETWORK OXYGEN SATURATION [SUPPORT] STUDY*, to 1) characterize and compare the incidence and magnitude of episodic desaturation episodes in infants randomized to high versus low baseline oxygen saturation targets in the SUPPORT Trial 2) correlate the incidence and magnitude of such desaturation episodes over the first month of life with neurodevelopmental outcome at 18-22 months and 3) correlate the incidence of early intermittent hypoxia with a history of sleep disordered breathing (SDB) at 18-22 months.

Field Code Changed

To accurately detect the incidence of desaturation episodes, our current secondary study only includes infants from the San Diego and Cleveland sites where pulse oximetry data were acquired at high resolution (2 sec averaging time and 2 second sample). In contrast, the SUPPORT trial oximetry data at all other sites have been acquired at low resolution (16 second averaging time and 10 second sample rate). With the SUPPORT trial findings of increased mortality in the low baseline saturation group, there is interest in expanding the secondary study database to include a second cohort of infants with low resolution data as well. This may be problematic as the prolonged averaging times will smooth the SaO<sub>2</sub> waveform and may decrease the accuracy of detection of desaturation events. The low sample rate of 10 sec may further exacerbate this problem.

#### A. Specific Aim:

The aim of this study is to expand our current database of infants with high resolution pulse oximetry data to include the remaining low resolution pulse oximetry data SUPPORT infants. Using these two separate infant cohorts we aim to:

1. Assess the effect of data resolution (2/2sec, averaging time/sample rate versus 16/10sec, averaging time/sample rate) on the incidence, duration and magnitude of desaturation events between low and high baseline SaO<sub>2</sub> infant groups.
2. Assess the relationship between the incidence of desaturation events and the development of Retinopathy of Prematurity (ROP).
3. Analyze the correlation between the incidence of desaturation events and neurodevelopmental outcome.
4. Analyze the correlation between the incidence of desaturation events and mortality.

B. Hypothesis:

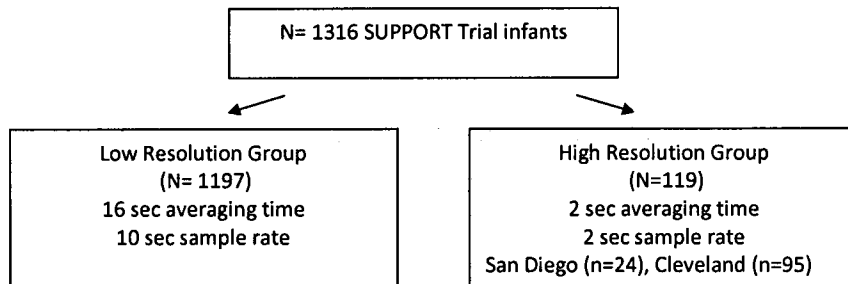
We hypothesize that:

1. Infants with low resolution oximetry data will have fewer desaturation events and of smaller magnitude than infants with high resolution data.
2. Infants with severe ROP requiring laser therapy will have a higher incidence of desaturation events.
3. A higher incidence of episodic desaturation in neonates is associated with greater neurodevelopmental handicap at 18-22 months.
4. A higher incidence of desaturation events is associated with an increase in infant mortality.

C. Rationale:

The SUPPORT Trial randomized infants to two ranges of SpO<sub>2</sub> in order to test the hypothesis that use of a lower SpO<sub>2</sub> range will result in an increase in survival of preterm infants without the occurrence of threshold retinopathy of prematurity [ROP] and/or the need for surgical intervention. However, the potential risk of a lower baseline SpO<sub>2</sub> range in increasing the incidence of episodic desaturation is unknown. In addition, prior studies in animal models have suggested that the neural effects of intermittent or episodic hypoxia may differ greatly than those of sustained hypoxia. Our previously approved secondary study represented a unique opportunity to acquire data to characterize the risk factors and consequences of episodic desaturation. Although we currently have 119 Infants in the high resolution cohort there are an additional 1316 infants enrolled in the SUPPORT trial in whom we may be able to extract additional desaturation data with low resolution. Although differences in monitor settings does not allow for combining the two infant cohorts, the larger sample size in the low resolution infant group may enable us to detect more subtle

associations between desaturation events and baseline saturation, ROP, mortality and detriments in neurodevelopmental outcome.



The low resolution group has a much larger sample size which increases the chances of finding a relationship between intermittent hypoxia and both morbidity and mortality. However, the low resolution of saturation data may limit the ability to accurately detect desaturation events in this cohort. Previous data (Ahmed) have suggested that application of a 16 sec averaging time window may result in an underestimation of short events (<30sec) and events of greater severity (<70%) and an overestimation of events of long duration (>300sec) when compared to application of a 2 sec averaging time window. If comparisons between low and high resolution groups reveal statistically significant differences in event detection parameters, interpretation of associations of desaturation events with baseline SaO<sub>2</sub> and morbidity may be limited to the infants in whom data were acquired with high resolution group (n=119). Due to the low incidence of infant mortality in the high resolution cohort we may not have the ability to assess the association between desaturation events and infant mortality.

If event parameters do not differ between low and high resolution groups the increased sample size of 1316 in the low resolution group may increase the ability to detect an association between these events and baseline SaO<sub>2</sub>, mortality, and neurodevelopmental outcome. Lastly, even if desaturation event detection is significantly compromised in the low resolution group, the low resolution may still be adequate to detect differences between the incidence of intermittent hypoxia and mortality/morbidity in this large infant cohort.

#### D. Methodologies:

##### Aim 1: Effect of data acquisition resolution and baseline SpO<sub>2</sub>

We request to be unblinded to the infant cohorts and have access to the saturation data corrected for the SUPPORT trial SpO<sub>2</sub> baseline randomization. None of the personnel involved in the saturation data analysis participate in developmental followup of the enrolled cohort and

thus cannot influence the outcome evaluations at CWRU, and thus are not a threat to the integrity of the main trial neurodevelopmental evaluations. To prevent inadvertent disclosure, all data files will be sequestered in the office of Ms. Juliann Di Fiore and will not be accessible to other members of the CWRU team. Further, data files will remain identified only by study number and not by the infant's name.

We will use currently developed software to document the occurrence, duration and magnitude of desaturation events  $\leq 80\%$  in the low resolution group. To comply with Nyquist sampling theorem limitations (2 x sample rate) and to distinguish intermittent hypoxia from prolonged changes in baseline SpO<sub>2</sub>, only events  $\geq 20$ sec and  $\leq 3$  min will be included in the analysis. Data will be analyzed for the first 8 weeks of life or shorter time periods for infants who completed the SUPPORT trial before 8 weeks post natal age. All desaturation events will be included regardless of the need for supplemental oxygen or ventilator support.

We will compare the occurrence, duration and magnitude of desaturation events for

1. Acquisition Resolution
  - a. High (2 sec average, 2 second sample rate) versus low (16 sec average and 10 sec sample rate) resolution in the low baseline SpO<sub>2</sub> infant groups
  - b. High versus low resolution in the high baseline SpO<sub>2</sub> infant groups
2. Baseline SpO<sub>2</sub>
  - a. Low versus High baseline SpO<sub>2</sub> in the low resolution group
  - b. Low versus High baseline SpO<sub>2</sub> in the high resolution group (previous secondary study)

#### Aim 2: Retinopathy of Prematurity

We will compare the incidence of desaturation events detected in Aim 1 between infants with and without severe retinopathy of prematurity (ROP). To minimize disparities in diagnosis of less severe forms of ROP, infants will be classified as 1) those requiring laser treatment for ROP or 2) those with either no ROP or ROP not severe enough to require laser therapy. The definitions used and reported in the SUPPORT main trial will be utilized for classifications of eye outcomes.

#### Aim 3: Neurodevelopmental Outcome

To analyze the correlation between the incidence of desaturation events and neurodevelopmental outcome we will include parameters acquired through the SUPPORT trial protocol including:

neurodevelopmental impairment at 18-22 months based on Bayley III using the accepted NRN definition

Death by discharge status  
BPD @36wks  
IVH  
PVL  
Cerebral palsy @ 18-22 months

#### Aim 4: Mortality

We will analyze the correlation between the incidence of desaturation events and mortality with and without the inclusion of baseline saturation randomization as a covariate.

#### Statistical Analyses

Statistical analyses will include a linear mixed model for repeated measures analysis to assess the time course of desaturation events for all infants and to identify the association between the number of events and ROP requiring laser treatment adjusting for baseline SpO<sub>2</sub> randomization group, gestational age, race, gender, and multiple births. Based on previous work [Di Fiore] the square root of the number of desaturation events will be used to better meet normality assumptions of the mixed model. A linear regression model will be used to assess the univariate relationship between continuous variables such as the number of desaturation events and mental and motor scores at 18-22 months. To compare the number of desaturation events between the low and high baseline SpO<sub>2</sub> groups, and mortality, we will use a two way ANOVA with repeated measures.

#### E. Discussion of Anticipated Results

We anticipate that a lower number of desaturation events will be detected in the low versus high resolution group. Previous work has suggested that the 16 second average time used in the SUPPORT trial may result in an underestimation of events <30 seconds and events of greater severity (<70%) and an overestimation of events of long duration (>300sec)[Ahmed]. This study will focus on desaturation events of  $\leq 80\%$  for  $\geq 20$  sec and  $\leq 3$ min in duration. Thus, we do anticipate a significant difference between low and high resolutions due to events of greater severity or of long duration as proposed by Ahmed et al. However, the prolonged average time in the low resolution group may inhibit our ability to detect desaturation events between 20 and 30seconds in duration. We may have a further compromise in event detection due to the low sample rate of 10 seconds versus 2 seconds in the low and high resolution infant groups, respectively. Although a higher incidence of desaturation events has been shown to be associated with severe ROP [Di Fiore], it is currently unknown whether the characteristics of the desaturation event, in terms of duration and severity, are additional risk factors. Therefore, if short desaturation events are not as detrimental to the development of ROP, even with a compromise in detection of all desaturation events in the low resolution group we may still be able to detect differences in the number of events in the low and high baseline SpO<sub>2</sub> groups and in infants with and without severe ROP.

We speculate that if a higher incidence or desaturation events is found in the low baseline SpO<sub>2</sub> group, this will be associated with both infant mortality and lower neurodevelopmental outcome scores at 18-22 months of age.

If there is no difference in event detection in the high versus low resolution group, and no difference in the number of desaturation events between the low and high baseline SpO<sub>2</sub> infant groups we will conclude that keeping the infants in the low saturation target range does not put them at risk for episodic desaturation. If a difference in event detection is found between low and high resolution groups our conclusions between the low and high baseline saturation ranges will be limited by the ability to compare severe events and events of shorter duration.

#### F. Budget

##### Equipment:

We have previously acquired and analyzed desaturation data in 79 preterm infants with high resolution over a time period of comparable duration as the infants enrolled in the SUPPORT trial [Di Fiore]. Based on these infants, we estimate that the raw and processed data files for the 1316 SUPPORT trial infants will take approximately 400 gigabytes of storage space. For data safety/quality assurance concerns, we would like to purchase a password protected server dedicated to storage of this dataset. We estimate that the server with RAID 0 mirroring of the data will cost approximately \$1000. Only investigators working on this project will have access to the server. Additionally, we will maintain a backup of our datasets. Currently, a 1000 gigabyte hard drive costs \$200 through local computer stores. The server will be equipped with a writable DVD drive to maintain additional backups as needed. We currently use automated software to perform data backups once per week. Both the backup hard drive and DVDs will be stored in a locked cabinet in the locked office of Juliann Di Fiore and only she will have access to these backup devices. These files will be de-identified for patient confidentiality.

##### Salary Support and Project Duration:

Under Dr. Chris Wilson as PI, Juliann Di Fiore and Ryan Foglyano will currently be receiving grant funding to develop software to automate additional analyses of saturation data on the infants enrolled in the currently approved secondary study, INCIDENCE AND CONSEQUENCES OF EPISODIC DESATURATION IN PRETERM INFANTS ENROLLED IN THE NICHD NEONATAL NETWORK OXYGEN SATURATION [SUPPORT] STUDY. This infant cohort includes SUPPORT infants enrolled at the Cleveland and San Diego sites with high resolution, and 79 additional preterm infants at the Cleveland site that were not enrolled in the SUPPORT trial. The purpose of this grant is to develop a suite of linear and non-linear analysis algorithms to quantify patterns of intermittent hypoxia (IH), and to evaluate the relationship between IH patterns and severe ROP requiring laser surgery. The initial phase of this grant will require development of automated software code to identify desaturation events from the infant data files. Once developed, we plan to use this software for analysis of the additional 1197 SUPPORT trial infants.



Based on previous data analysis of desaturation events in 79 preterm infants with high resolution analyzed over a time period of comparable duration as the infants enrolled in the SUPPORT trial, we are currently able to analyze 5-7 infants per day. We anticipate an increase in the number of infants analyzed per day with automation of the software. Based on our previous experience and additional time needed for summary data analysis, we anticipate 10 months of time will be needed to complete this protocol.

Salary support will include 50% for Juliann Di Fiore 33% for Ryan Foglyano and, as it is difficult to estimate, support for a biostatistician to be determined. (Table).

Travel:

We anticipate travel to RTI for statistical analysis (\$1500.00) and the steering committee meeting (\$1500.00) to present the results. (Table)

References:

1. Ahmed SJ, Rich W, Finer NN. The effect of averaging time on oximetry values in the premature infant. *Pediatrics* 2010:e115-e121.
2. Di Fiore JM, Bloom JN, Orge F, Schutt A, Schluchter M, Cheruvu VK, Walsh M, Finer N, Martin RJ. A higher incidence of intermittent hypoxemic episodes is associated with severe retinopathy of prematurity. *J of Peds* ( In press).

Program Director/Principal Investigator (Last, First, Middle):

<b>DETAILED BUDGET FOR INITIAL BUDGET PERIOD DIRECT COSTS ONLY</b>	FROM	THROUGH
--	------	---------

List PERSONNEL (Applicant organization only)  
Use Cal, Acad, or Summer to Enter Months Devoted to Project  
Enter Dollar Amounts Requested (omit cents) for Salary Requested and Fringe Benefits

NAME	ROLE ON PROJECT	Cal. Mths	Acad. Mths	Summer Mths	INST.BASE SALARY	SALARY REQUESTED	FRINGE BENEFITS	TOTAL
Michele Walsh	PD/PI							
Juliann Di Fiore		1			(b)	38,425	8,838	47,263
Ryan Foglyano		(b)			(b)	15,557	3,578	19,135
<b>SUBTOTALS</b> →						<b>53,982</b>	<b>12,416</b>	<b>66,398</b>

<b>CONSULTANT COSTS</b>		
Statistical Analysis- Biostatistician from RTI cost TBD		
<b>EQUIPMENT (Itemize)</b>		
Hard drive \$200		
RAID 0 [protected server] \$1000		1,200
<b>SUPPLIES (Itemize by category)</b>		
<b>TRAVEL</b>		
Travel to RTI (\$1500) and steering committee meeting (\$1500)		3,000
<b>INPATIENT CARE COSTS</b>		
<b>OUTPATIENT CARE COSTS</b>		
<b>ALTERATIONS AND RENOVATIONS (Itemize by category)</b>		
<b>OTHER EXPENSES (Itemize by category)</b>		

CONSORTIUM/CONTRACTUAL COSTS	DIRECT COSTS	
<b>SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD (Item 7a, Face Page)</b>		<b>\$ 70,598</b>
CONSORTIUM/CONTRACTUAL COSTS	FACILITIES AND ADMINISTRATIVE COSTS	38,531
<b>TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD</b>		<b>\$ 109,129</b>

**From:** Auman, Jeanette O.  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Johnson, Karen; Bell, Edward; Acarregui, Michael; Eastman, Diane  
**Cc:** Gantz, Marie; Auman, Jeanette O.  
**Subject:** RE: SUPPORT FU  
**Date:** Monday, February 22, 2010 11:03:28 AM

---

(b) has been assigned the follow-up ID of (b) based on the NF00 record for this patient, but I don't see any NF05 or NF09A forms keyed as of yet. I checked the most recent unprocessed text files received here at RTI from the center's NRN computer dated 2/16/2010 and neither the NF05 nor the NF09A are showing up in there.

Karen, take a look at the data management system for Follow-up. If you see them keyed in the system, please transmit again and let me know so I can double check that we've received the records for this week's data processing.

Thanks,

Jenny

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Monday, February 22, 2010 10:53 AM  
**To:** 'Johnson, Karen'; Bell, Edward; Acarregui, Michael; Eastman, Diane; Auman, Jeanette O.  
**Cc:** Gantz, Marie  
**Subject:** RE: SUPPORT FU

Jenny-  
Can you check on this one?  
Thanks  
Rose

---

**From:** Johnson, Karen [mailto:karen-johnson@uiowa.edu]  
**Sent:** Monday, February 22, 2010 10:52 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Bell, Edward; Acarregui, Michael; Eastman, Diane  
**Cc:** Gantz, Marie  
**Subject:** RE: SUPPORT FU

(b) (6) will be seen on 3/1.  
(b) These forms were entered into the DMS on 2/10. Can someone at RTI check on why they are not showing up as completed?

Thanks,  
Karen

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Monday, February 22, 2010 9:25 AM  
**To:** Bell, Edward; Acarregui, Michael; Johnson, Karen; Eastman, Diane  
**Cc:** Gantz, Marie  
**Subject:** SUPPORT FU

Hi,  
We are missing the following primary outcomes for the SUPPORT FU study. Let us know how you are doing.

Thanks for all the effort!!

Rose

CENTER	NETWORK	FU_message
24	(b)	FU window has closed but NF05 and NF09a have not been completed.
24	(6)	FU window has closed but NF05 and NF09a have not been completed.
24		FU marked as complete (per NF10/SF10) but NF05 and NF09a have not been completed.

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network  
Pregnancy and Perinatology Branch

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Center for Developmental Biology and Perinatal Medicine  
Eunice Kennedy Shriver National Institute of Child Health and Human Development  
National Institutes of Health  
6100 Executive Blvd., Room 4B03  
MSC 7510  
Bethesda, MD 20892  
For overnight delivery use Rockville, MD 20852  
301-496-5575  
301-496-3790 (FAX)  
higginsr@mail.nih.gov

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Hamer, Faithe Angeline"; "Poindexter, Brenda B."; "Dusick, Anna M."; "Wilson, Leslie Dawn"  
**Cc:** "Gantz, Marie"  
**Subject:** RE: SUPPORT FU  
**Date:** Monday, February 22, 2010 11:03:00 AM

---

Great!  
Thanks  
Rose

---

**From:** Hamer, Faithe Angeline [mailto:fahamer@iupui.edu]  
**Sent:** Monday, February 22, 2010 10:56 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Poindexter, Brenda B; Dusick, Anna M.; Wilson, Leslie Dawn  
**Cc:** Gantz, Marie  
**Subject:** RE: SUPPORT FU

Please see below.

Kind Regards,

*Faithe Hamer, MD*

Riley Hospital for Children  
NICHD Follow Up Coordinator  
[fahamer@iupui.edu](mailto:fahamer@iupui.edu) (email)  
278-7364 (phone)  
278-7856 (fax)  
312-(b) (pager)

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Monday, February 22, 2010 10:17 AM  
**To:** Poindexter, Brenda B; Dusick, Anna M.; Hamer, Faithe Angeline; Wilson, Leslie Dawn  
**Cc:** Gantz, Marie  
**Subject:** SUPPORT FU

Hi,  
We are missing the following primary outcomes for the SUPPORT FU study. Let us know how you are doing.

Thanks for all the effort!!  
Rose

CENTER	NETWORK	FU_message
12	(b)	FU window has closed but NF05 and NF09a have not been completed. - visit completed - forms being completed this week.
12	(b)	FU window has closed but NF09a has not been completed. -patient is scheduled tomorrow for the NF09A- form will be entered as soon as possible.

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network  
Pregnancy and Perinatology Branch  
Center for Developmental Biology and Perinatal Medicine  
Eunice Kennedy Shriver National Institute of Child Health and Human Development  
National Institutes of Health  
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Bethesda, MD 20892  
For overnight delivery use Rockville, MD 20852

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301-496-5575  
301-496-3790 (FAX)  
higginsr@mail.nih.gov

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Bell, Edward"; "Acarregui, Michael"; "Johnson, Karen"; "Eastman, Diane"  
**Cc:** "Gantz, Marie"  
**Subject:** SUPPORT FU  
**Date:** Monday, February 22, 2010 10:25:00 AM

---

Hi,

We are missing the following primary outcomes for the SUPPORT FU study. Let us know how you are doing.

Thanks for all the effort!!

Rose

CENTER	NETWORK	FU_message
24	(b)	FU window has closed but NF05 and NF09a have not been completed.
24	(6)	FU window has closed but NF05 and NF09a have not been completed.
24		FU marked as complete (per NF10/SF10) but NF05 and NF09a have not been completed.

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network  
Pregnancy and Perinatology Branch  
Center for Developmental Biology and Perinatal Medicine  
Eunice Kennedy Shriver National Institute of Child Health and Human Development  
National Institutes of Health  
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Bethesda, MD 20892  
For overnight delivery use Rockville, MD 20852  
301-496-5575  
301-496-3790 (FAX)  
higginsr@mail.nih.gov



**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Finer, Neil; Rich, Wade; "mfuller@ucsd.edu"; Vaucher, Yvonne  
**Cc:** Gantz, Marie  
**Subject:** SUPPORT FU  
**Date:** Monday, February 22, 2010 10:24:00 AM

---

Hi,

We are missing the following primary outcomes for the SUPPORT FU study. Let us know how you are doing.

Thanks for all the effort!!

Rose

CENTER	NETWORK	FU_message
22	(b)	FU window has closed but NF05 and NF09a have not been completed.

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network  
Pregnancy and Perinatology Branch  
Center for Developmental Biology and Perinatal Medicine  
Eunice Kennedy Shriver National Institute of Child Health and Human Development  
National Institutes of Health  
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MSC 7510  
Bethesda, MD 20892  
For overnight delivery use Rockville, MD 20852  
301-496-5575  
301-496-3790 (FAX)  
higginsr@mail.nih.gov

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Kennedy, Kathleen A"; "Evans, Patricia W"; "Georgia.E.McDavid@uth.tmc.edu"  
**Cc:** "Gantz, Marie"  
**Subject:** SUPPORT FU  
**Date:** Monday, February 22, 2010 10:23:00 AM  
**Importance:** High

---

Hi,

We are missing the following primary outcomes for the SUPPORT FU study. Let us know how you are doing.

Thanks for all the effort!!

Rose

CENTER	NETWORK	FU_message
18	(b)	FU window has closed but NF05 and NF09a have not been completed.
18	(b)	FU window has closed but NF05 and NF09a have not been completed.

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network  
Pregnancy and Perinatology Branch  
Center for Developmental Biology and Perinatal Medicine  
Eunice Kennedy Shriver National Institute of Child Health and Human Development  
National Institutes of Health  
6100 Executive Blvd., Room 4B03  
MSC 7510  
Bethesda, MD 20892  
For overnight delivery use Rockville, MD 20852  
301-496-5575  
301-496-3790 (FAX)  
higginsr@mail.nih.gov

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Wally Carlo, M.D."; "Myriam Peralta, M.D."; "scosby@peds.uab.edu"; "Vivien Phillips"; "mcollins@peds.uab.edu"  
**Cc:** "Gantz, Marie"  
**Subject:** SUPPORT FU  
**Date:** Monday, February 22, 2010 10:22:00 AM

---

Hi,

We are missing the following primary outcomes for the SUPPORT FU study. Let us know how you are doing.

Thanks for all the effort!! This is terrific given your high recruitment into this trial!!

Rose

CENTER	NETWORK	FU_message
16	(b)	FU window has closed but NF05 and NF09a have not been completed.
16	(6)	FU window has closed but NF05 and NF09a have not been completed.
16		FU window has closed but NF05 and NF09a have not been completed.

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network  
Pregnancy and Perinatology Branch  
Center for Developmental Biology and Perinatal Medicine  
Eunice Kennedy Shriver National Institute of Child Health and Human Development  
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Bethesda, MD 20892  
For overnight delivery use Rockville, MD 20852  
301-496-5575  
301-496-3790 (FAX)  
higginsr@mail.nih.gov

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "alaptok@WIHRI.org"; "Vohr, Betty"; "Hensman, Angelita"; "sventura@wihri.org"  
**Cc:** "Gantz, Marie"  
**Subject:** SUPPORT FU  
**Date:** Monday, February 22, 2010 10:18:00 AM

---

Hi,

We are missing the following primary outcomes for the SUPPORT FU study. Let us know how you are doing.

Thanks for all the effort!! This is terrific given your high recruitment into this trial!!

Rose

CENTER	NETWORK	FU_message
14	(b)	FU window has closed but NF05 and NF09a have not been completed.

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network  
Pregnancy and Perinatology Branch  
Center for Developmental Biology and Perinatal Medicine  
Eunice Kennedy Shriver National Institute of Child Health and Human Development  
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MSC 7510  
Bethesda, MD 20892  
For overnight delivery use Rockville, MD 20852  
301-496-5575  
301-496-3790 (FAX)  
higginsr@mail.nih.gov

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Brenda Poindexter"; "Dusick, Anna M."; "fahamer@iupui.edu"; "ldw@iupui.edu"  
**Cc:** "Gantz, Marie"  
**Subject:** SUPPORT FU  
**Date:** Monday, February 22, 2010 10:17:00 AM

---

Hi,

We are missing the following primary outcomes for the SUPPORT FU study. Let us know how you are doing.

Thanks for all the effort!!

Rose

CENTER	NETWORK	FU_message
12	(b)	FU window has closed but NF05 and NF09a have not been completed.
12	(b)	FU window has closed but NF09a has not been completed.

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network  
Pregnancy and Perinatology Branch  
Center for Developmental Biology and Perinatal Medicine  
Eunice Kennedy Shriver National Institute of Child Health and Human Development  
National Institutes of Health  
6100 Executive Blvd., Room 4B03  
MSC 7510  
Bethesda, MD 20892  
For overnight delivery use Rockville, MD 20852  
301-496-5575  
301-496-3790 (FAX)  
higginsr@mail.nih.gov

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Kurt Schibler [kurt.schibler@cchmc.org]"; "Kimberly Yolton@cchmc.org"; "steichji@email.uc.edu"; "Teresa.Gratton@uc.edu"; "Grisby, Cathy (grisbyca)"  
**Cc:** "Gantz, Marie"  
**Subject:** SUPPORT FU  
**Date:** Monday, February 22, 2010 10:13:00 AM

---

Hi,

We are missing the following primary outcomes for the SUPPORT FU study. Let us know how you are doing.

Thanks for all the effort!!

Rose

CENTER	NETWORK	FU_message
11	(b)	FU window has closed but NF05 and NF09a have not been completed.

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network  
Pregnancy and Perinatology Branch  
Center for Developmental Biology and Perinatal Medicine  
Eunice Kennedy Shriver National Institute of Child Health and Human Development  
National Institutes of Health  
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MSC 7510  
Bethesda, MD 20892  
For overnight delivery use Rockville, MD 20852  
301-496-5575  
301-496-3790 (FAX)  
higginsr@mail.nih.gov

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Barbara Stoll"; "Ira Adams-Chapman"; "ellen\_hale@oz.ced.emory.edu"  
**Cc:** "Gantz, Marie"  
**Subject:** SUPPORT FU  
**Date:** Monday, February 22, 2010 10:09:00 AM

---

Hi,

We are missing the following primary outcomes for the SUPPORT FU study. Let us know how you are doing.

Thanks for all the effort!!

Rose

CENTER	NETWORK	FU_message
9	(b)	FU marked as complete (per NF10/SF10) but NF05 has not been completed.

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network  
Pregnancy and Perinatology Branch  
Center for Developmental Biology and Perinatal Medicine  
Eunice Kennedy Shriver National Institute of Child Health and Human Development  
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Bethesda, MD 20892  
For overnight delivery use Rockville, MD 20852  
301-496-5575  
301-496-3790 (FAX)  
higginsr@mail.nih.gov

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Shankaran, Seetha"; "Pappas, Athina"; "rbara@med.wayne.edu"  
**Cc:** "Gantz, Marie"  
**Subject:** SUPPORT FU  
**Date:** Monday, February 22, 2010 10:06:00 AM  
**Importance:** High

---

Hi,

We are missing the following primary outcomes for the SUPPORT FU study. Let us know how you are doing.

Thanks for all the effort!!

Rose

CENTER	NETWORK	FU_message
5	(b)	FU window has closed but NF05 and NF09a have not been completed.
5	(6)	FU window has closed but NF09a has not been completed.
5		FU window has closed but NF05 and NF09a have not been completed.
5		FU window has closed but NF05 and NF09a have not been completed.
5		FU window has closed but NF05 and NF09a have not been completed.

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network  
Pregnancy and Perinatology Branch  
Center for Developmental Biology and Perinatal Medicine  
Eunice Kennedy Shriver National Institute of Child Health and Human Development  
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301-496-5575  
301-496-3790 (FAX)  
higginsr@mail.nih.gov



## **Higgins, Rosemary (NIH/NICHD) [E]**

---

**From:** Finer, Neil <nfiner@ucsd.edu>  
**Sent:** Sunday, February 21, 2010 5:05 PM  
**To:** Susan Hintz; Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: another draft

Hi Susan

This looks very good

Thanks for comparing the CUS readings between your readers and the sites. I think this information is very useful I think it reads very well so I will not micromanage.

Great stuff

Hope things are OK at home

Be well

Neil

-----Original Message-----

From: Susan Hintz [mailto:srhintz@stanford.edu]

Sent: Sunday, February 21, 2010 12:21 PM

To: Rosemary Higgins

Cc: Finer, Neil

Subject: another draft

Hi Rose and Neil

I am still waiting for some additional analysis today, but I am trying to re-work the abstract as much as possible in real time.

Please see the attached and provide feedback if you have a chance.

Note:

- 1) Focus has been shifted to descriptive only without any mention of SUPPORT randomized groups, except to say we are working on analyses in the "justification" for why this research could not make the normal PAS abstract deadline.
- 2) As it stands, it is exactly at 100% space filled.
- 3) I think this now reads as a descriptive CUS rates, and a reliability and accuracy analysis. I have tried to say some interesting things about progression of findings, but see if you think it sounds interesting enough
- 4) I have 95% CI for the kappas, but if I put them in the table I get to about 109%. I don't think most people will be too put out if I leave them off.
- 5) I have done my best to try to whip up some interest in this subcohort - and hopefully it will be seen as a promise of things to come. I remain concerned that this will not meet the bar for acceptance to Late breaker, but such is life. See if you can make it sound more interesting
- 6) I will likely make a few more "tweaks" as I get a few more bits of analysis later this afternoon and tonight.

Thanks again

Susan

--

Susan R. Hintz, M.D., M.S. Epi

Associate Professor of Pediatrics

Division of Neonatal and Developmental Medicine Stanford University School of Medicine 750 Welch Road, Suite 315

Palo Alto, CA 94304

ph: 650-723-5711

fax: 650-725-8351

**From:** Ronald N Goldberg  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** Fw: Breathing Outcomes - prelim data request  
**Date:** Sunday, February 21, 2010 1:44:32 PM

---

Hi Rose,  
I agree with wally.  
Ron

Ronald N. Goldberg, M.D.  
Shaad-McBryde Professor of Pediatrics  
Chief, Neonatal-Perinatal Medicine  
Box 2739  
Duke University Medical Center  
Durham, NC 27710  
Phone: 919-681-6037  
Fax: 919-681-6065  
email: goldb008@mc.duke.edu

----- Forwarded by Ronald N Goldberg/Pediatrics/mc/Duke on 02/21/2010 01:41 PM -----

"Wally Carlo, M.D." <WCarlo@peds.uab.edu>

02/17/2010 10:07 AM

To "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>, "Finer, Neil" <nfiner@ucsd.edu>, <Luc.Brion@UTSouthwestern.edu>, <rohls@unm.edu>, <aaf2@po.cwru.edu>, "Abhik Das" <adas@rti.org>, <alaptook@WIHRI.org>, <ambal@uab.edu>, <Bradley.yoder@hsc.utah.edu>, "Brenda Poindexter" <bpoindex@iupui.edu>, <cotte010@mc.duke.edu>, "Dennis Wallace" <dwallace@rti.org>, "Ed Bell" <Edward-bell@uiowa.edu>, "Ed Donovan" <edward.donovan@cchmc.org>, "Ehrenkranz Richard (E-mail)" <richard.ehrenkranz@yale.edu>, <ifrantz@tuftsmedicalcenter.org>, "Kennedy, Kathleen A" <Kathleen.A.Kennedy@uth.tmc.edu>, "Kristi Watterberg" <kwatterberg@salud.unm.edu>, <kurt.schibler@cchmc.org>, "Matthew Bizzarro" <matthew.bizzarro@yale.edu>, "Michelle Walsh" <mcw3@po.cwru.edu>, "Mickey Caplan" <mcaplan@northshore.org>, "Oh William (E-mail)" <william\_oh@brown.edu>, "Pablo Sanchez" <Pablo.Sanchez@UTSouthwestern.edu>, "Poole Kenneth (E-mail)" <poo@rti.org>, "Roger Faix" <Roger.Faix@hsc.utah.edu>, "Ronald Goldberg" <goldb008@mc.duke.edu>, "Seetha Shankaran" <sshankar@med.wayne.edu>, "Stevenson David (E-mail)" <dstevenson@stanford.edu>, "Stoll Barbara (E-mail)" <barbara\_stoll@oz.ped.emory.edu>, "Tyson Jon (E-mail)" <Jon.E.Tyson@uth.tmc.edu>, "VanMeurs, Krisa" <vanmeurs@leland.stanford.edu>

cc "Archer, Stephanie (NIH/NICHD) [E]" <archerst@mail.nih.gov>, "Zaterka-Baxter, Kristin" <kzaterka@rti.org>, "Newman, Jamie" <newman@rti.org>

Subject RE: Breathing Outcomes - prelim data request

I would think that some unmasked data evaluation not analyzed by treatment group may be ok. Any analysis by treatment group should wait until the data collection are completed.

Wally

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Wed 2/17/2010 9:02 AM

**To:** Higgins, Rosemary (NIH/NICHD) [E]; 'Finer, Neil'; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; 'Abhik Das'; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); 'Brenda Poindexter'; Wally Carlo, M.D.; cotte010@mc.duke.edu; 'Dennis Wallace'; 'Ed Bell'; 'Ed Donovan'; 'Ehrenkranz Richard (E-mail)'; Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; 'Kristi Watterberg'; Kurt Schibler [kurt.schibler@cchmc.org]; 'Matthew Bizzarro'; 'Michelle Walsh'; 'MIckey Caplan'; 'Oh William (E-mail)'; 'Pablo Sanchez'; 'Poole Kenneth (E-mail)'; 'Roger Faix'; 'Ronald GOLdberg'; 'Seetha Shankaran'; 'Stevenson David (E-mail)'; 'Stoll Barbara (E-mail)'; 'Tyson Jon (E-mail)'; VanMeurs, Krisa  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; 'Zaterka-Baxter, Kristin'; 'Newman, Jamie'  
**Subject:** RE: Breathing Outcomes - prelim data request

Tim had sent the following as a basis for his request:

**One of the criticisms of the School Age Breathing Outcomes Proposal is the lack of preliminary data from Breathing Outcomes that supports longer term follow up. To address this concern Richard and I thought it would be helpful to have preliminary analyses of a few questions from Breathing Outcomes.**

The concept was approved by the steering committee and the protocol has been reviewed by protocol review subcommittee with a request for revisions. The data requested is to provide support for longer term FU (at school age). I hope this clarifies the subject.

Thanks  
Rose

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Tuesday, February 16, 2010 4:44 PM  
**To:** Finer, Neil; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Matthew Bizzarro; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOLdberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; 'Zaterka-Baxter, Kristin'; Newman, Jamie  
**Subject:** Breathing Outcomes - prelim data request

Hi,  
Tim Stevens is preparing a revision to his school age breathing outcomes study protocol and would like the following information from the school age SUPPORT trial for the 6 and 12 month visits.

Pease let me know by February 23 if the data can be given at this time. Some of the infants have not yet completed the 12 month assessment.

Thanks  
Rose

**From:** Gantz, Marie  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** Missing FU for SUPPORT  
**Date:** Friday, February 19, 2010 5:17:45 PM  
**Attachments:** Infants with missing FU outcomes 19FEB10.xls

---

Rose,

Here is the list of SUPPORT infants missing FU data this month.

Marie

Marie Gantz, Ph.D.  
Research Statistician  
RTI International  
mgantz@rti.org  
828-254-6255

CENTER	NETWORK	FU_message
5	(b) (6)	FU window has closed but NF05 and NF09a have not been completed.
5		FU window has closed but NF09a has not been completed.
5		FU window has closed but NF05 and NF09a have not been completed.
5		FU window has closed but NF05 and NF09a have not been completed.
5		FU window has closed but NF05 and NF09a have not been completed.
9		FU marked as complete (per NF10/SF10) but NF05 has not been completed.
11		FU window has closed but NF05 and NF09a have not been completed.
12		FU window has closed but NF05 and NF09a have not been completed.
12		FU window has closed but NF09a has not been completed.
14		FU window has closed but NF05 and NF09a have not been completed.
16		FU window has closed but NF05 and NF09a have not been completed.
16		FU window has closed but NF05 and NF09a have not been completed.
16		FU window has closed but NF05 and NF09a have not been completed.
18		FU window has closed but NF05 and NF09a have not been completed.
18		FU window has closed but NF05 and NF09a have not been completed.
22		FU window has closed but NF05 and NF09a have not been completed.
24		FU window has closed but NF05 and NF09a have not been completed.
24		FU window has closed but NF05 and NF09a have not been completed.
24		FU marked as complete (per NF10/SF10) but NF05 and NF09a have not been completed.

**From:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**To:** [Archer, Stephanie \(NIH/NICHD\) \[E\]](#)  
**Subject:** RE: Disclosure for CPAP Support  
**Date:** Friday, February 19, 2010 5:12:00 PM

---

She needed to send both – I sent them to Brendan already

Rose

---

**From:** Archer, Stephanie (NIH/NICHD) [E]  
**Sent:** Friday, February 19, 2010 5:11 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** FW: Disclosure for CPAP Support

This version is for Neil's paper, not Wally's.

---

**From:** Brenda Morris [mailto:[\(b\) \(6\)](#)]  
**Sent:** Friday, February 19, 2010 3:57 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** Disclosure for CPAP Support

Rose, See attachment for disclosure for Neil's manuscript. I still think they should have changed it to CPAP vs Early Intubation. Wasn't that the main issue??? If you intubate, then you are going to give surfactant so giving surfactant isn't really the issue.... it is when to intubate. Oh, well. The results are the same. Have a good weekend. Brenda

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Finer, Neil"; "Anthony Piazza (Anthony.Piazza@oz.ped.emory.edu)"; "bsood@med.wayne.edu"; "nancy newman"; "Gantz, Marie"; "Laroia, Nirupama"; "Phelps, Dale"; "Duara, Shahnaz"; "Michael O' Shea"; "Vivek Narendran"; "Rich. Wade"; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwrn.edu; "Abhik Das"; alaptook@WIHLI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); "Brenda Poindexter"; "Carlo Waldemar (E-mail)"; cotte010@mc.duke.edu; "Dennis Wallace"; "Ed Bell"; "Ed Donovan"; "Fhrenkranz Richard (E-mail)"; Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; "Kristi Watterberg"; Kurt Schibler (kurt.schibler@cchmc.org); "Matthew Bizzarro"; "Michelle Walsh"; "Mickey Caplan"; "Oh William (E-mail)"; "Pablo Sanchez"; "Poole Kenneth (E-mail)"; "Roger Faix"; "Ronald Goldberg"; "Seetha Shankaran"; "Stevenson David (E-mail)"; "Stoll Barbara (E-mail)"; "Tyson Jon (E-mail)"; VanMeurs, Krisa  
**Bcc:** Archer, Stephanie (NIH/NICHD) [E]; "Zaterka-Baxter, Kristin"; "Cunningham, Meg"  
**Subject:** CONFIDENTIAL: New England Journal of Medicine 09-11781.R1  
**Date:** Friday, February 19, 2010 5:12:00 PM  
**Attachments:** CarloSUPPORTwcgscomments rev 2- accepted changes.doc  
CarloSUPPORTwcgscomments rev 2 - tracked changes.doc

---

Hi all, Here is the revised saturation paper.

Thanks to Wally for his quick turnaround!!!  
Rose



**From:** [Archer, Stephanie \(NIH/NICHD\) \[E\]](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Subject:** FW: Disclosure for CPAP Support  
**Date:** Friday, February 19, 2010 5:10:35 PM  
**Attachments:** [ICMJE-Disclosure-Form-102309.cpapsupport.morris.pdf](#)

---

This version is for Neil's paper, not Wally's.

---

**From:** Brenda Morris [mailto:[\(b\) \(6\)](#)]  
**Sent:** Friday, February 19, 2010 3:57 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** Disclosure for CPAP Support

Rose, See attachment for disclosure for Neil's manuscript. I still think they should have changed it to CPAP vs Early Intubation. Wasn't that the main issue??? If you intubate, then you are going to give surfactant so giving surfactant isn't really the issue.... it is when to intubate. Oh, well. The results are the same. Have a good weekend. Brenda



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### **INSTRUCTIONS:**

The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. The form has five parts.

#### **1. Identifying information.**

Each author should submit a separate form. Provide complete information and double-check the manuscript number. If you are NOT the corresponding author please insert his or her name.

#### **2. The work under consideration for publication.**

Please provide information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The idea is to provide for the reader information about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. If you check the "No" box it means that you did the work without receiving any financial support from any third party -- that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds to pay you. If you or your institution did receive funds from a third party to support the work, check "Yes" along with the appropriate boxes to indicate the type of support and whether you or your institution received it.

#### **3. Relevant financial activities outside the submitted work.**

Please report all sources of revenue relevant to the submitted work that accrued either directly to you or were paid to your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. If there is any question, it is usually better to disclose a relationship than not to do so. Please note that your interactions with the work's sponsor outside the submitted work should be listed here. For each category list each entity on a separate line. Use as many lines as necessary to provide complete information. In addition, please disclose relationships that fall outside the 36-month window that readers may want to know about and could reasonably criticize you for not disclosing (for example, long-term financial relationships that are now ended).

The goal of this section is to provide information for our reviewers and readers about your interactions with entities in the biomedical arena that could be perceived to influence, or that give the appearance of potentially influencing, what you wrote in the submitted work. You should disclose interactions with ANY entity that could be considered broadly relevant to the work. For example, if your article is about testing an epidermal growth factor receptor (EGFR) antagonist in lung cancer, you should report all associations with entities pursuing diagnostic or therapeutic strategies in cancer in general, not just in the area of EGFR or lung cancer. For grants you have received for work outside the submitted work, you should disclose support ONLY from entities that could be perceived to benefit financially from the published work, such as drug companies, or foundations supported by entities that could be perceived to have a financial stake in the outcome. Public funding sources, such as the NIH or the MRC, need not be disclosed. For example, if the NIH sponsored a piece of work you have been involved in but drugs were provided by a pharmaceutical company, you need only list the pharmaceutical company.

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If monies from the types of relationships listed in Section 3 were paid to your spouse or partner or dependent children, please list the type of activity and source of the money.

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Given Name:  
(or first)

Brenda

Surname:  
(or last)

Morris

Effective Date:

04-February-2010

Format example: 07-August-2008

Are you the corresponding author?  Yes  No

Manuscript Title:

Early CPAP versus Surfactant in Extremely Preterm Infants: The SUPPORT Trial

Manuscript Identifying Number (if you know it):

09-11783

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Did you or your institution at any time receive payment or support in kind for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc...)?

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							Add +
Consulting fee or honorarium	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del x
							Add +
Support for travel to meetings for the study or otherwise	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	NICHD/UT Houston	Expenses for travel	Del x
							Add +
Fees for participation in review activities such as data monitoring boards, statistical analysis, end point committees, and the like	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del x
							Add +
Payment for writing or reviewing the manuscript	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del x
							Add +



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## ICMJE Uniform Disclosure Form for Potential Conflicts of Interest

Type	Money Paid to You*		Money to Your Institution		Name of Entity	Comments**	
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			
Support in kind such as writing, provision of medicines or equipment, or administrative support	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del X
							Add +
Other	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del X
							Add +

\*\*Use this section to provide any needed explanation

### Section 3. Information about relevant financial relationships outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with any entities that have an interest related to the submitted work. Use one line for each entity; add as many lines as you need. Use the comments column to indicate any additional information that you think a reader or editor would want to know about the compensation. Report relationships that were present during the 36 months prior to submission. In addition please disclose relationships that fall outside the 36-month window that readers may want to know about and could reasonably criticize you for not disclosing (for example, long-term financial relationships that are now ended).

If you have more than one relationship, click "Add +" to add a row. Click "Del X" to delete an extra row.

Type of Relationship (In alphabetical order)	No	Money Paid to You	Money to Your institution	Entity	Comments	
Board membership	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del X
						Add +
Consultancy	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del X
						Add +
Employment	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del X
						Add +
Expert testimony	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del X
						Add +
Gifts	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del X
						Add +
Grants/grants pending	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del X
						Add +



# ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

## ICMJE Uniform Disclosure Form for Potential Conflicts of Interest

Type of Relationship (in alphabetical order)	No	Money Paid to You	Money to Your institution	Entity	Comments	
Honoraria	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del X
						Add +
Payment for manuscript preparation	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del X
						Add +
Patents (planned, pending or issued)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del X
						Add +
Royalties	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del X
						Add +
Payment for development of educational presentations including service on speakers' bureaus	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del X
						Add +
Stock/stock options	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del X
						Add +
Travel/accommodations expenses covered or reimbursed	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del X
						Add +
Other (err on the side of full disclosure)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del X
						Add +

### Section 4. Information about financial relationships involving your spouse or partner or your children (under 18 years of age).

Do your children or your spouse or partner have financial relationships with entities that have an interest in the content of the submitted work?

- No other relationships/conditions/circumstances that present potential conflict of interest
- Yes, the following relationships/conditions/circumstances are present (explain below):



## ICMJE Uniform Disclosure Form for Potential Conflicts of Interest

### Section 5. Information about relevant nonfinancial associations.

Do you have any relevant nonfinancial associations or interests (personal, professional, political, institutional, religious, or other) that a reasonable reader would want to know about in relation to the submitted work?

- No relevant nonfinancial relationships/conditions/circumstances to report.
- Yes, the following relevant nonfinancial relationships/conditions/circumstances are present (explain below):

At the time of manuscript acceptance, journals will ask authors to confirm and, if necessary, update their disclosure statements. On occasion, journals may ask authors to disclose further information about reported relationships.



**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Zaterka-Baxter, Kristin"; "Gantz, Marie"  
**Cc:** "Wally Carlo, M.D."; "Finer, Neil"; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: New England Journal of Medicine 09-11781.R1  
**Date:** Friday, February 19, 2010 4:51:00 PM

---

Please add a section to the boilerplate for both papers

ROP Adjudication Committee

Gary David Markowitz, M.D., University of Rochester  
Amy K. Hutchinson, MD, Emory University  
David K. Wallace, MD, MPH, Duke University  
Sharon F. Freedman, MD, Duke University

---

**From:** Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]  
**Sent:** Friday, February 19, 2010 3:33 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie  
**Cc:** Wally Carlo, M.D.; Finer, Neil; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: New England Journal of Medicine 09-11781.R1

Pulled from their respective university profiles; please note the "K" in Dr. Hutchinson's name and Dr. Markowitz middle name.

**Gary David Markowitz, M.D.**  
**Amy K. Hutchinson, MD**  
**David K. Wallace, MD, MPH**  
**Sharon F. Freedman, MD**

Thanks,  
Kris

---

-----Original Message-----

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Friday, February 19, 2010 3:01 PM  
**To:** Zaterka-Baxter, Kristin; Gantz, Marie  
**Cc:** 'Wally Carlo, M.D.'; Finer, Neil; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** FW: New England Journal of Medicine 09-11781.R1

Kris and Marie

Can you verify that I have the 4 ophthalmologists' names spelled correctly?

we are planning on including them in the SUPPORT boilerplate:

Sharon F. Freedman, M.D. Duke University  
David K. Wallace, MD, Duke University  
Amy Hutchinson, MD, Emory University  
Gary Markowitz, MD University of Rochester

Thanks  
Rose

-----Original Message-----

**From:** Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]  
**Sent:** Friday, February 19, 2010 2:57 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; Gantz, Marie;  
das@rti.org; Rich, Wade  
**Subject:** RE: New England Journal of Medicine 09-11781.R1

Ok.

Wally Carlo, M.D.  
Edwin M. Dixon Professor of Pediatrics  
University of Alabama at Birmingham  
Director, Division of Neonatology  
Director, Newborn Nurseries  
619 South 20th Street  
525 New Hillman Building  
Birmingham, AL 35233-7335  
Phone: 205 934 4680  
FAX: 205 934 3100  
Cell: 205 266 (b)

-----Original Message-----

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
Sent: Friday, February 19, 2010 1:56 PM  
To: Wally Carlo, M.D.; Finer, Neil; Gantz, Marie; das@rti.org; Rich, Wade  
Subject: RE: New England Journal of Medicine 09-11781.R1

We don't need to add it to the paper (or even the letter - We can just add the ophthalmologists in the acknowledgements.

I will get the list and send it

Rose

-----Original Message-----

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]  
Sent: Friday, February 19, 2010 2:54 PM  
To: Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; Gantz, Marie; das@rti.org; Rich, Wade  
Subject: RE: New England Journal of Medicine 09-11781.R1

Ok. I will drop Avastin.

If we add the adjudication to the methods we should add it to the results.

Maybe we should add Caron also what would be best.

I am worried that we may delay the paper.

Wally

Wally Carlo, M.D.  
Edwin M. Dixon Professor of Pediatrics  
University of Alabama at Birmingham  
Director, Division of Neonatology  
Director, Newborn Nurseries  
619 South 20th Street  
525 New Hillman Building  
Birmingham, AL 35233-7335  
Phone: 205 934 4680  
FAX: 205 934 3100  
Cell: 205 266 (b)

-----Original Message-----

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
Sent: Friday, February 19, 2010 1:48 PM  
To: Wally Carlo, M.D.; Finer, Neil; Gantz, Marie; das@rti.org; Rich, Wade  
Subject: RE: New England Journal of Medicine 09-11781.R1

I would just delete it and tell her in the cover letter that we checked and they both had threshold disease as described in the protocol.

One more thing - do we want to add a sentence in the letter stating the ROP adjudication process and include the ophthalmologists in the boiler plates? We had told the ophthalmologists that they would be acknowledged. I don't think we need to add anything to the paper (or even the letter if you don't want to ) but we should update the boilerplate with their names.

Let me know

-----Original Message-----



From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]  
Sent: Friday, February 19, 2010 2:46 PM  
To: Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]; Gantz, Marie; das@rti.org; Rich, Wade  
Subject: RE: New England Journal of Medicine 09-11781.R1

Ok. So if both met criteria for ROP, dropping Avastin would not change results.

I agree it is ok. How should we handle with NEJM? Is it not better to say that the two babies who got Avastin also met ROP criteria?

Wally

Wally Carlo, M.D.  
Edwin M. Dixon Professor of Pediatrics  
University of Alabama at Birmingham  
Director, Division of Neonatology  
Director, Newborn Nurseries  
619 South 20th Street  
525 New Hillman Building  
Birmingham, AL 35233-7335  
Phone: 205 934 4680  
FAX: 205 934 3100  
Cell: 205 266 (b)

-----Original Message-----

From: Finer, Neil [mailto:nfiner@ucsd.edu]  
Sent: Friday, February 19, 2010 1:40 PM  
To: Higgins, Rosemary (NIH/NICHD) [E]; 'Gantz, Marie'; Wally Carlo, M.D.; das@rti.org; Rich, Wade  
Subject: RE: New England Journal of Medicine 09-11781.R1

I would agree to delete avastin - its use was not a protocol driven intervention  
Neil

-----Original Message-----

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
Sent: Friday, February 19, 2010 11:19 AM  
To: 'Gantz, Marie'; Wally Carlo, M.D.; das@rti.org; Finer, Neil; Rich, Wade  
Subject: RE: New England Journal of Medicine 09-11781.R1

Ok

So both met criteria - I would recommend deleting avastin from the paper.  
In the meantime, perhaps we should go back and affirm that there was in fact plus disease from the original ophthalmology record.

What do you guys think??

Rose

-----Original Message-----

From: Gantz, Marie [mailto:mgantz@rti.org]  
Sent: Friday, February 19, 2010 2:17 PM  
To: Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.; das@rti.org; nfiner@ucsd.edu; wrich@ucsd.edu  
Subject: RE: New England Journal of Medicine 09-11781.R1

Two infants received Avastin without having laser or cryo. One definitely also met criteria for threshold ROP at the exam prior to Avastin treatment (stage 3 ROP and plus disease in zone II). The other infant (who was at UAB) is coded on the SUPP10 as having threshold ROP on the day of Avastin treatment (the threshold variable is marked "Y"), although there is a missing value in the plus disease field for both eyes (with zone=2, stage=2) and no comment to explain the missing value.

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: Friday, February 19, 2010 1:37 PM  
To: 'Wally Carlo, M.D.'; das@rti.org; Gantz, Marie; nfiner@ucsd.edu; wrich@ucsd.edu  
Subject: RE: New England Journal of Medicine 09-11781.R1

Did we have any children that received Avastin that did not get laser or cryo??

For query 10:  
Threshold retinopathy of prematurity (New Type 1 threshold per Early Treatment of Retinopathy Cooperative Group [ref 20]) was coded if retinal exam had zone I ROP of any stage with plus disease, Zone I ROP of stage 3 without plus disease, or zone II ROP of stage 2 or 3 with plus disease.  
You may also wish to consider referencing the screening guidelines published in 2006 (but those post-dated the protocol).

For # 11 - I have searched the manual and the protocol and find no mention of bevacizumab or avastin. Should this be in the methods. How many infants received avastin and did not receive surgery?? If the answer is 0, we are in good shape to delete it.

My read of what she is asking for #16 is to give a response such as "Despite defined saturations targets, maintenance of narrow target range occurred \_\_\_% of the time and there was overlap between the two groups. Previous studies (STOP ROP and BOOST) showed similar results with targeting oxygen saturations in a narrow range."  
She is asking for a sentence or two regarding the difficulties of staying in target range in a closely monitored trial.

We have almost all of the copyright/ICMJE documents (still missing a few but moving in the right direction). I will keep sending reminders.

THANKS FOR ALL THE HARD WORK AND EFFORT!!!  
Rose

-----Original Message-----

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]  
Sent: Thursday, February 18, 2010 9:30 PM  
To: Higgins, Rosemary (NIH/NICHD) [E]; das@rti.org; Gantz, Marie; nfiner@ucsd.edu; wrich@ucsd.edu  
Cc: Wally Carlo, M.D.  
Subject: FW: New England Journal of Medicine 09-11781.R1

Enclosed is the revised 02 sat draft. The comments are trivial. They accepted the 95% CI and all the changes we made.

I have a few requests:

Rose:

Comment #10 Can you verify that the ROP wording is as clear as it can be?  
Comment #11 Would you say treatment for pre-threshold ROP?  
Comment #16 See if you like the change I made

Abhik:

Comments #13 and 14 Can you help with the response and change?

Marie:

Comments #24, 25, and 27. Please verify/comment.  
Comment #26 Can you provide wording for Physiologic definition we used (should I use what is in the MOO?)

Thanks for all your help.

Wally

Wally Carlo, M.D.  
Edwin M. Dixon Professor of Pediatrics  
University of Alabama at Birmingham  
Director, Division of Neonatology  
Director, Newborn Nurseries

619 South 20th Street  
525 New Hillman Building  
Birmingham, AL 35233-7335  
Phone: 205 934 4680  
FAX: 205 934 3100  
Cell: 205 266 (b)

-----Original Message-----

From: onbehalfof+editorial+nejm.org@manuscriptcentral.com  
[mailto:onbehalfof+editorial+nejm.org@manuscriptcentral.com] On Behalf  
Of editorial@nejm.org  
Sent: Thursday, February 18, 2010 2:52 PM  
To: Wally Carlo, M.D.  
Subject: New England Journal of Medicine 09-11781.R1

Dear Wally:

I am writing again about your manuscript, "Oxygen Saturation Targets in Extremely Preterm Infants: The SUPPORT Trial." Your revision has been evaluated by the editors and addresses the key concerns raised previously. However, we do need to ask for some additional changes before it is accepted for publication.

At this point I am attaching a partially edited version of your manuscript in which I have inserted editorial comments and queries. (These comments are most easily viewed in Word by viewing in "reading layout" or "print layout.") In general, the changes I have suggested should be incorporated, unless there are places where I have inadvertently changed your meaning.

When you send in your revised manuscript, it is not necessary to provide a letter with responses to the inserted editorial comments, but please note anywhere that you did not make suggested changes (and why); it is fine to insert any responses in the associated comment box. Please return two copies of the revision: one in which the changes you have made are highlighted, and the other a clean copy.

Please include a word count for the text. As you know, the word count for text should not exceed 2700 words, and there should be no more than 5 tables or figures in the print version of the manuscript, though it is fine to include additional "web only" appendix tables.

Any changes in authorship must be made in writing, signed by all authors.

To revise your manuscript, log into <http://mc.manuscriptcentral.com/nejm> and enter For Authors, where you will find a button to "Submit a Revision."

Journal policy dictates that we must have on file a signed Copyright Transfer Agreement from each author before a manuscript can be accepted. If not already done, please ask all authors to sign and fax back the enclosed form as soon as possible to (781) 207-6529. This will eliminate unnecessary delays in the event that your manuscript is accepted.

The Universal Disclosure form is also attached. Each author must complete it. After you have filled in the appropriate information in the spaces provided, you may either e-mail your completed form to Brendan Abel at [babel@nejm.org](mailto:babel@nejm.org) or upload it to your Author Dashboard of ScholarOne Manuscripts. It is essential that you return the forms as soon as possible, because we cannot process your manuscript without them.

Please recall that the Journal requires that neither an article under consideration nor any part of its essential substance, tables, or figures has been or will be published or submitted elsewhere before appearing in the Journal.

We look forward to receiving your revised manuscript and will plan a prompt evaluation when it arrives. Please do not hesitate to contact me if you have questions.

Thank you again for your work.

Sincerely,

Caren Solomon

Caren G. Solomon, MD  
Deputy Editor

New England Journal of Medicine  
10 Shattuck Street  
Boston, MA 02115  
(617) 734-9800  
Fax: (617) 739-9864  
<http://www.nejm.org>

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Brenda Morris"  
**Subject:** RE: Request for forms for saturation SUPPORT paper  
**Date:** Friday, February 19, 2010 4:34:00 PM

---

As far as the early intubation is concerned, Colin Morley did that in the COIN trial. We were testing surfactant specifically (not required by the COIN trial).

(b) (6)

Take care

Thanks

Rose

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**From:** Brenda Morris [mailto:(b) (6)]  
**Sent:** Friday, February 19, 2010 3:51 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Request for forms for saturation SUPPORT paper

Rose, All are doing well. I need to send an updated picture, but it isn't on this computer. It is hard to keep up with all the activities. (b) (6)

(b) (6). I sure miss y'all and the Network. Maybe we can get together at the SPR. Of course, you have tons of people trying to talk to you there. Hope you are well. (b) (6)  
Brenda

---

**From:** higginsr@mail.nih.gov  
**To:** (b) (6)  
**Date:** Fri, 19 Feb 2010 15:42:37 -0500  
**Subject:** Re: Request for forms for saturation SUPPORT paper

Yes, (b) (6)

---

**From:** Brenda Morris <(b) (6)>  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Fri Feb 19 15:37:19 2010  
**Subject:** RE: Request for forms for saturation SUPPORT paper

Sorry, I should have said.... Do you need them for Neil's manuscript??? Brenda

---

**From:** higginsr@mail.nih.gov  
**To:** adas@rti.org; bsood@med.wayne.edu; bpointindex@iupui.edu; (b) (6); ifrantz@tuftsmedicalcenter.org; mgantz@rti.org; Nirupama\_Laroya@URMC.Rochester.edu; moshea@wfubmc.edu; poo@rti.org; wrich@ucsd.edu  
**CC:** archerst@mail.nih.gov; wacarlo@uab.edu  
**Date:** Fri, 19 Feb 2010 08:52:04 -0500

Subject: Request for forms for saturation SUPPORT paper

Hi,

**We are missing forms for the saturation paper from you.**

**Please fill out the attached copyright and disclosure form.**

**You may either submit them on line or fax them to us (301-496-3790). Please do this *TODAY!!!!***

**Let me know if there are any questions.**

**The title of the paper is:**

**Oxygen Saturation Targets in Extremely Preterm Infants:  
The SUPPORT Trial**

**The manuscript number is 09-11781**

**Waldemar A. Carlo is the corresponding author**

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network  
Pregnancy and Perinatology Branch  
Center for Developmental Biology and Perinatal Medicine  
Eunice Kennedy Shriver National Institute of Child Health and Human Development  
National Institutes of Health  
6100 Executive Blvd., Room 4B03  
MSC 7510  
Bethesda, MD 20892  
For overnight delivery use Rockville, MD 20852  
301-496-5575  
301-496-3790 (FAX)  
higginsr@mail.nih.gov

**From:** [Brenda Morris](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Archer, Stephanie \(NIH/NICHD\) \[E\]](#)  
**Subject:** Disclosure for CPAP Support  
**Date:** Friday, February 19, 2010 3:57:47 PM  
**Attachments:** [ICMJE-Disclosure-Form-102309.cpapsupport.morris.pdf](#)

---

Rose, See attachment for disclosure for Neil's manuscript. I still think they should have changed it to CPAP vs Early Intubation. Wasn't that the main issue??? If you intubate, then you are going to give surfactant so giving surfactant isn't really the issue.... it is when to intubate. Oh, well. The results are the same. Have a good weekend. Brenda



# ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

## **ICMJE Uniform Disclosure Form for Potential Conflicts of Interest**

### **INSTRUCTIONS:**

The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. The form has five parts.

#### **1. Identifying information.**

Each author should submit a separate form. Provide complete information and double-check the manuscript number. If you are NOT the corresponding author please insert his or her name.

#### **2. The work under consideration for publication.**

Please provide information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The idea is to provide for the reader information about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. If you check the "No" box it means that you did the work without receiving any financial support from any third party -- that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds to pay you. If you or your institution did receive funds from a third party to support the work, check "Yes" along with the appropriate boxes to indicate the type of support and whether you or your institution received it.

#### **3. Relevant financial activities outside the submitted work.**

Please report all sources of revenue relevant to the submitted work that accrued either directly to you or were paid to your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. If there is any question, it is usually better to disclose a relationship than not to do so. Please note that your interactions with the work's sponsor outside the submitted work should be listed here. For each category list each entity on a separate line. Use as many lines as necessary to provide complete information. In addition, please disclose relationships that fall outside the 36-month window that readers may want to know about and could reasonably criticize you for not disclosing (for example, long-term financial relationships that are now ended).

The goal of this section is to provide information for our reviewers and readers about your interactions with entities in the biomedical arena that could be perceived to influence, or that give the appearance of potentially influencing, what you wrote in the submitted work. You should disclose interactions with ANY entity that could be considered broadly relevant to the work. For example, if your article is about testing an epidermal growth factor receptor (EGFR) antagonist in lung cancer, you should report all associations with entities pursuing diagnostic or therapeutic strategies in cancer in general, not just in the area of EGFR or lung cancer. For grants you have received for work outside the submitted work, you should disclose support ONLY from entities that could be perceived to benefit financially from the published work, such as drug companies, or foundations supported by entities that could be perceived to have a financial stake in the outcome. Public funding sources, such as the NIH or the MRC, need not be disclosed. For example, if the NIH sponsored a piece of work you have been involved in but drugs were provided by a pharmaceutical company, you need only list the pharmaceutical company.

#### **4. Financial relationships involving your spouse or partner or your children (under 18 years of age).**

If monies from the types of relationships listed in Section 3 were paid to your spouse or partner or dependent children, please list the type of activity and source of the money.

#### **5. Nonfinancial associations.**

Please report any personal, professional, political, institutional, religious, or other associations that a reasonable reader would want to know about in relation to the submitted work.





# ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

## ICMJE Uniform Disclosure Form for Potential Conflicts of Interest

### Section 1. Identifying Information.

Given Name:  
(or first)

Brenda

Surname:  
(or last)

Morris

Effective Date:

04-February-2010

Format example: 07-August-2008

Are you the corresponding author?  Yes  No

Manuscript Title:

Early CPAP versus Surfactant in Extremely Preterm Infants: The SUPPORT Trial

Manuscript Identifying Number (if you know it):

09-11783

### Section 2. Information about the support of the work under consideration for publication.

Did you or your institution at any time receive payment or support in kind for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc...)?

No

Yes, specify nature of compensation

If you have more than one relationship, click "Add +" to add a row. Click "Del x" to delete an extra row.

Type	Money Paid to You*		Money to Your Institution		Name of Entity	Comments**	
	No	Yes	No	Yes			
Grant	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	NICHD	Funded trial	Del x
							Add +
Consulting fee or honorarium	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del x
							Add +
Support for travel to meetings for the study or otherwise	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	NICHD/UT Houston	Expenses for travel	Del x
							Add +
Fees for participation in review activities such as data monitoring boards, statistical analysis, end point committees, and the like	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del x
							Add +
Payment for writing or reviewing the manuscript	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del x
							Add +



# ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

## ICMJE Uniform Disclosure Form for Potential Conflicts of Interest

Type	Money Paid to You*		Money to Your Institution		Name of Entity	Comments**	
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			
Support in kind such as writing, provision of medicines or equipment, or administrative support	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del X
							Add +
Other	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del X
							Add +

\*\*Use this section to provide any needed explanation

### Section 3. Information about relevant financial relationships outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with any entities that have an interest related to the submitted work. Use one line for each entity; add as many lines as you need. Use the comments column to indicate any additional information that you think a reader or editor would want to know about the compensation. Report relationships that were present during the 36 months prior to submission. In addition please disclose relationships that fall outside the 36-month window that readers may want to know about and could reasonably criticize you for not disclosing (for example, long-term financial relationships that are now ended).

If you have more than one relationship, click "Add +" to add a row. Click "Del x" to delete an extra row.

Type of Relationship (in alphabetical order)	No	Money Paid to You	Money to Your Institution	Entity	Comments	
Board membership	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del X
						Add +
Consultancy	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del X
						Add +
Employment	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del X
						Add +
Expert testimony	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del X
						Add +
Gifts	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del X
						Add +
Grants/grants pending	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del X
						Add +



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Type of Relationship (in alphabetical order)	No	Money Paid to You	Money to Your institution	Entity	Comments	
Honoraria	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del X
						Add +
Payment for manuscript preparation	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del X
						Add +
Patents (planned, pending or issued)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del X
						Add +
Royalties	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del X
						Add +
Payment for development of educational presentations including service on speakers' bureaus	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del X
						Add +
Stock/stock options	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del X
						Add +
Travel/accommodations expenses covered or reimbursed	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del X
						Add +
Other (err on the side of full disclosure)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del X
						Add +

### Section 4. Information about financial relationships involving your spouse or partner or your children (under 18 years of age).

Do your children or your spouse or partner have financial relationships with entities that have an interest in the content of the submitted work?

- No other relationships/conditions/circumstances that present potential conflict of interest
- Yes, the following relationships/conditions/circumstances are present (explain below):



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## ICMJE Uniform Disclosure Form for Potential Conflicts of Interest

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Do you have any relevant nonfinancial associations or interests (personal, professional, political, institutional, religious, or other) that a reasonable reader would want to know about in relation to the submitted work?

- No relevant nonfinancial relationships/conditions/circumstances to report.
- Yes, the following relevant nonfinancial relationships/conditions/circumstances are present (explain below):

At the time of manuscript acceptance, journals will ask authors to confirm and, if necessary, update their disclosure statements. On occasion, journals may ask authors to disclose further information about reported relationships.

Save Form

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** (b) (6)  
**Subject:** Re: Request for forms for saturation SUPPORT paper  
**Date:** Friday, February 19, 2010 3:42:22 PM

---

Yes, Neil's paper  
Thanks  
Rose

---

**From:** Brenda Morris (b) (6)  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Fri Feb 19 15:35:45 2010  
**Subject:** RE: Request for forms for saturation SUPPORT paper

See attachment for the disclosure form. I will fax the Copyright form. Do you need the form for Wally's paper as well??? Brenda

---

**From:** higginsr@mail.nih.gov  
**To:** adas@rti.org; bsood@med.wayne.edu; bpoindex@iupui.edu; (b) (6); ifrantz@tuftsmedicalcenter.org; mgantz@rti.org; Nirupama\_Laroia@URMC.Rochester.edu; moshea@wfubmc.edu; poo@rti.org; wrich@ucsd.edu  
**CC:** archerst@mail.nih.gov; wacarlo@uab.edu  
**Date:** Fri, 19 Feb 2010 08:52:04 -0500  
**Subject:** Request for forms for saturation SUPPORT paper

Hi,

**We are missing forms for the saturation paper from you.  
Please fill out the attached copyright and disclosure form.  
You may either submit them on line or fax them to us (301-496-3790). Please do this *TODAY!!!!***

**Let me know if there are any questions.**

**The title of the paper is:**

**Oxygen Saturation Targets in Extremely Preterm Infants:  
The SUPPORT Trial**

**The manuscript number is 09-11781**

**Waldemar A. Carlo is the corresponding author**

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network  
Pregnancy and Perinatology Branch  
Center for Developmental Biology and Perinatal Medicine  
Eunice Kennedy Shriver National Institute of Child Health and Human Development  
National Institutes of Health  
6100 Executive Blvd., Room 4B03

**MSC 7510**

**Bethesda, MD 20892**

**For overnight delivery use Rockville, MD 20852**

**301-496-5575**

**301-496-3790 (FAX)**

**[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)**

**From:** Brenda Morris  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Request for forms for saturation SUPPORT paper  
**Date:** Friday, February 19, 2010 3:35:56 PM  
**Attachments:** ICMJE-Disclosure-Form-102309.support.morris.pdf

---

See attachment for the disclosure form. I will fax the Copyright form. Do you need the form for Wally's paper as well??? Brenda

---

From: higginsr@mail.nih.gov  
To: adas@rti.org; bsood@med.wayne.edu; bpoindex@iupui.edu; (b) (6); ifrantz@tuftsmedicalcenter.org; mgantz@rti.org; Nirupama\_Laroia@URMC.Rochester.edu; moshea@wfubmc.edu; poo@rti.org; wrich@ucsd.edu  
CC: archerst@mail.nih.gov; wacarlo@uab.edu  
Date: Fri, 19 Feb 2010 08:52:04 -0500  
Subject: Request for forms for saturation SUPPORT paper

**Hi,**  
**We are missing forms for the saturation paper from you.**  
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Rosemary D. Higgins, MD  
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### INSTRUCTIONS:

The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. The form has five parts.

#### 1. Identifying information.

Each author should submit a separate form. Provide complete information and double-check the manuscript number. If you are NOT the corresponding author please insert his or her name.

#### 2. The work under consideration for publication.

Please provide information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The idea is to provide for the reader information about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. If you check the "No" box it means that you did the work without receiving any financial support from any third party -- that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds to pay you. If you or your institution did receive funds from a third party to support the work, check "Yes" along with the appropriate boxes to indicate the type of support and whether you or your institution received it.

#### 3. Relevant financial activities outside the submitted work.

Please report all sources of revenue relevant to the submitted work that accrued either directly to you or were paid to your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. If there is any question, it is usually better to disclose a relationship than not to do so. Please note that your interactions with the work's sponsor outside the submitted work should be listed here. For each category list each entity on a separate line. Use as many lines as necessary to provide complete information. In addition, please disclose relationships that fall outside the 36-month window that readers may want to know about and could reasonably criticize you for not disclosing (for example, long-term financial relationships that are now ended).

The goal of this section is to provide information for our reviewers and readers about your interactions with entities in the biomedical arena that could be perceived to influence, or that give the appearance of potentially influencing, what you wrote in the submitted work. You should disclose interactions with ANY entity that could be considered broadly relevant to the work. For example, if your article is about testing an epidermal growth factor receptor (EGFR) antagonist in lung cancer, you should report all associations with entities pursuing diagnostic or therapeutic strategies in cancer in general, not just in the area of EGFR or lung cancer. For grants you have received for work outside the submitted work, you should disclose support ONLY from entities that could be perceived to benefit financially from the published work, such as drug companies, or foundations supported by entities that could be perceived to have a financial stake in the outcome. Public funding sources, such as the NIH or the MRC, need not be disclosed. For example, if the NIH sponsored a piece of work you have been involved in but drugs were provided by a pharmaceutical company, you need only list the pharmaceutical company.

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If monies from the types of relationships listed in Section 3 were paid to your spouse or partner or dependent children, please list the type of activity and source of the money.

#### 5. Nonfinancial associations.

Please report any personal, professional, political, institutional, religious, or other associations that a reasonable reader would want to know about in relation to the submitted work.





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### Section 1. Identifying Information.

Given Name:  
(or first)

Brenda

Surname:  
(or last)

Morris

Effective Date:

04-February-2010

Format example: 07-August-2008

Are you the corresponding author?  Yes  No

Manuscript Title:

Oxygen Saturation Targets in Extremely Preterm Infants: The SUPPORT Trial

Manuscript Identifying Number (if you know it):

09-11781

### Section 2. Information about the support of the work under consideration for publication.

Did you or your institution at any time receive payment or support in kind for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc...)?

No

Yes, specify nature of compensation

If you have more than one relationship, click "Add +" to add a row. Click "Del x" to delete an extra row.

Type	Money Paid to You*		Money to Your Institution		Name of Entity	Comments**	
	No	Yes	No	Yes			
Grant	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	NICHD	Funded trial	Del x
							Add +
Consulting fee or honorarium	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del x
							Add +
Support for travel to meetings for the study or otherwise	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	NICHD/UT Houston	Expenses for travel	Del x
							Add +
Fees for participation in review activities such as data monitoring boards, statistical analysis, end point committees, and the like	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del x
							Add +
Payment for writing or reviewing the manuscript	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del x
							Add +



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	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			
Support in kind such as writing, provision of medicines or equipment, or administrative support	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del X
							Add +
Other	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del X
							Add +

\*\*Use this section to provide any needed explanation

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If you have more than one relationship, click "Add +" to add a row. Click "Del x" to delete an extra row.

Type of Relationship (in alphabetical order)	No	Money Paid to You	Money to Your Institution	Entity	Comments	
Board membership	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del X
						Add +
Consultancy	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del X
						Add +
Employment	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del X
						Add +
Expert testimony	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del X
						Add +
Gifts	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del X
						Add +
Grants/grants pending	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del X
						Add +



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						Add +
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Patents (planned, pending or issued)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del X
						Add +
Royalties	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del X
						Add +
Payment for development of educational presentations including service on speakers' bureaus	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del X
						Add +
Stock/stock options	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del X
						Add +
Travel/accommodations expenses covered or reimbursed	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del X
						Add +
Other (err on the side of full disclosure)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del X
						Add +

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## **Higgins, Rosemary (NIH/NICHD) [E]**

---

**From:** Finer, Neil <nfiner@ucsd.edu>  
**Sent:** Friday, February 19, 2010 2:41 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; 'Wally Carlo, M.D.'  
**Subject:** RE: Steering committee update

This is fine  
Neil

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Friday, February 19, 2010 11:24 AM  
**To:** 'Wally Carlo, M.D.'; Finer, Neil  
**Subject:** Steering committee update  
**Importance:** High

Wally and Neil

I have a steering committee update to send later today.  
I would like to include the following (it will help get the last of the copyrights and ICMJE forms):

*As you know, the SUPPORT papers were resubmitted to NEJM on 2/12. Wally received a request from Dr. Solomon yesterday stating the following:*

*I am writing again about your manuscript, "Oxygen Saturation Targets in Extremely Preterm Infants: The SUPPORT Trial." Your revision has been evaluated by the editors and addresses the key concerns raised previously. However, we do need to ask for some additional changes before it is accepted for publication.*

*Neil received the following request:*

*Please send a copy of the revision in a Word (.doc) version to me via email at your soonest convenience.*

Let me know if you are ok with this

Rose

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network  
Pregnancy and Perinatology Branch  
Center for Developmental Biology and Perinatal Medicine  
Eunice Kennedy Shriver National Institute of Child Health and Human Development  
National Institutes of Health  
6100 Executive Blvd., Room 4B03  
MSC 7510  
Bethesda, MD 20892  
For overnight delivery use Rockville, MD 20852  
301-496-5575  
301-496-3790 (FAX)  
higginsr@mail.nih.gov

## Higgins, Rosemary (NIH/NICHD) [E]

---

**From:** Finer, Neil <nfiner@ucsd.edu>  
**Sent:** Friday, February 19, 2010 2:39 PM  
**To:** Susan Hintz; Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** hcheng@rti.org; wcarlo@peds.uab.edu; Rich, Wade; Dorothy Bulas; Tom Slovis; adas@rti.org; Krisa Van Meurs  
**Subject:** RE: CUS analysis revisions

Many thanks Susan  
I hope all is well with you and family  
Neil

---

**From:** Susan Hintz [mailto:srhintz@stanford.edu]  
**Sent:** Friday, February 19, 2010 10:30 AM  
**To:** Rosemary Higgins  
**Cc:** hcheng@rti.org; Finer, Neil; wcarlo@peds.uab.edu; Rich, Wade; Dorothy Bulas; Tom Slovis; adas@rti.org; Krisa Van Meurs  
**Subject:** CUS analysis revisions

Hi all,

Due to significant and reasonable concerns regarding potential misinterpretation of the implications of our findings with respect to late CUS findings between SUPPORT randomized groups, **I will be re-working the abstract as a descriptive analysis ONLY**. In other words, at this point I will be revising the abstract only to describe early and late CUS findings for the NEURO subcohort overall, and describe progression of findings from early to late CUS for the NEURO subcohort overall.

First and foremost we want to make sure that the important and central messages of the main trial are heard. The NEURO subcohort is, after all, a **secondary** and a **small** subgroup of the main trial. In the future, we will undertake additional investigations before reports of randomized group comparisons are made.

I will be asking for some additional analyses from RTI now - **again, only with respect to findings OVERALL**. I am hoping that this can be done ASAP so that I can work on revisions to the abstract over the next day or 2 and get another revision out by Monday early AM. Recall that the deadline for submission for Late Breakers is the evening of 2/24.

Thank you for your input and support,

Susan

--

Susan R. Hintz, M.D., M.S. Epi  
Associate Professor of Pediatrics  
Division of Neonatal and Developmental Medicine  
Stanford University School of Medicine  
750 Welch Road, Suite 315  
Palo Alto, CA 94304

ph: 650-723-5711  
fax: 650-725-8351

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** FW: Breathing Outcomes - prelim data request  
**Date:** Friday, February 19, 2010 8:54:00 AM

---

---

**From:** Roger Faix [mailto:Roger.Faix@hsc.utah.edu]  
**Sent:** Thursday, February 18, 2010 6:17 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Breathing Outcomes - prelim data request

Hi Rose!

The concerns raised by Neil et al are quite legitimate in my opinion. Any analysis that requires unmasking should be deferred.

Roger

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]  
**Sent:** Tuesday, February 16, 2010 2:43 PM  
**To:** Finer, Neil; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Bradley Yoder; Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Matthew Bizzarro; Michelle Walsh; Mickey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOLdberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; 'Zaterka-Baxter, Kristin'; Newman, Jamie  
**Subject:** Breathing Outcomes - prelim data request

Hi,

Tim Stevens is preparing a revision to his school age breathing outcomes study protocol and would like the following information from the school age SUPPORT trial for the 6 and 12 month visits.

Please let me know by February 23 if the data can be given at this time. Some of the infants have not yet completed the 12 month assessment.

Thanks  
Rose



**From:** Susan Hintz  
**To:** Finer, Neil  
**Cc:** wcarlo@peds.uab.edu; Higgins, Rosemary (NIH/NICHD) [E]; Dorothy Bulas; Tom Slovis; wrich@ucsd.edu; adas@rti.org; hcheng@rti.org  
**Subject:** RE: Abstract preview - CUS results of SUPPORT NEURO secondary  
**Date:** Friday, February 19, 2010 12:48:42 AM  
**Attachments:** Table1a\_1b\_16feb1.doc

---

Hi Neil,

The central readers read only the Neuroimaging cohort CUS. They did NOT read all the other early CUS in the main trial.

The information about % of 24-25 weekers in this subcohort is on Table 1a, which I thought I attached a few emails ago, but I may be crazy - so I am attaching it to this email too.

Remember, this secondary cohort is composed of patients that survived to have both the early and late CUS. So it is not surprising that the proportion of extraordinarily preterm infants is slightly less than the main trial.

Also, let me reiterate what we said in the abstract - there were NO significant differences between CPAP vs. Surfactant, or High vs. Low on the Early CUS - specifically, there were no differences in Grade 3 or 4. From the questions that have come up I feel I may not have been clear enough in the abstract on this point. It is true that the *rate* of Grade 3 or 4 on Early CUS was lower in this secondary cohort than in the main trial, but again, I believe that gets back to the point that this secondary cohort is by definition made up of patients that had both early and late CUS meaning that they had to survive to get the late CUS at 34+ weeks. So, many patients with severe IVH would have died before they could make it to be included in the secondary cohort. For this secondary cohort, both central readers found slightly higher grade 3/4 for CPAP vs Surf (9%vs 5% and 11% vs. 8%) BUT THIS WAS NOT significant on unadjusted or adjusted analyses.

I completely agree that this analysis should not appear to contradict the strength and superior power of the main trial - but I do not think that is the case. As far as Early CUS findings go, this analysis does not in any way contradict or appear to diminish the SUPPORT results.

So I have a few questions -

- 1) Do you think it would be helpful (and make it clearer) for me to say in the abstract something very specific like "There were no differences between CPAP vs. surfactant or High vs. Low oxygenation on any major Early CUS outcome, including grade 3 or 4 IVH"
- 2) Do you think it would be helpful if I found a way to even more clearly state that this is a "convenience" subcohort of the main trial? or to underscore that the patients included in this analysis had to have survived to get the 34+ week CUS?

Thanks again and let me know what you think

Susan

Hi Susan

I would like to see how the readers interpretation from your study compared with the CUS from the main trial - this would be the first CUS - did your reviewers look at these?

Next I am concerned as is Wally regarding stating any outcomes from the secondary that are also reported in the primary - like IVH Gr 3-4 as we are reporting from all the infants where we have the data. I also note that you have lesser of the more immature infants - what proportion of your study patients are in the 24-25 weeks strata?

Thanks for listening

Be well

Neil

**From:** Susan Hintz [mailto:srhintz@stanford.edu]

**Sent:** Thursday, February 18, 2010 8:16 PM

**To:** Finer, Neil

**Cc:** Rosemary Higgins; hcheng@rti.org; Dorothy Bulas; Tom Slovis; adas@rti.org; Rich, Wade; Wally Carlo, M.D.

**Subject:** Re: Abstract preview - CUS results of SUPPORT NEURO secondary

Hi Neil,

I completely agree that we should not overplay the findings - which is why we stated in the abstract that the findings may not represent the overall cohort, and also why we said that MRI and follow-up would further inform data. We also deliberately chose NOT to frame the results regarding the treatment groups as a finding in the table - rather, we highlighted the overall low rates of adverse CUS outcomes.

As I said before, even though we tried to underscore that this was a secondary study and not necessarily representative of the trial cohort, we can certainly find a way to make it even clearer that this subcohort is basically a convenience cohort within the trial cohort. Clearly, there are only 574 patients here, so obviously this is a subgroup of the # that survived to 36 weeks in the main trial cohort.

I want to make sure we look at the issues you want to address, but I am not sure I

understand what you mean by "seeing how the CUS in the overall study compared with those read by the 2 central readers". Since the main trial did not require "late" CUS and did not report late CUS findings, are you asking about the main trial "early" CUS findings? Are you asking for sensitivity and specificity analysis for early CUS (i.e, local reader compared with central readers as gold standards)? Or are you asking how many infants with CUS in the main trial survived?

Thanks again,

Susan

Sent from my iPhone

On Feb 18, 2010, at 7:14 PM, "Finer, Neil" <[nfiner@ucsd.edu](mailto:nfiner@ucsd.edu)> wrote:

Hi Susan

There was no separate randomization for the CUS study. As such we need to be careful how we frame these results. This did require consent and we have already learned that families not consenting may not be the same as those that do.

I would like to see how the CUS in the overall study compared in diagnosis to those that were reviewed by the 2 reviewers. What were the differences etc?

I look forward to hearing more about this. I am concerned that until we know more including the longer term follow-up we do not overplay the differences between the groups

Neil

**From:** Susan Hintz [<mailto:srhintz@stanford.edu>]  
**Sent:** Thursday, February 18, 2010 4:19 PM  
**To:** Finer, Neil  
**Cc:** Rosemary Higgins; [hcheng@rti.org](mailto:hcheng@rti.org); Dorothy Bulas; Tom Slovis; [adas@rti.org](mailto:adas@rti.org)  
**Subject:** RE: Abstract preview - CUS results of SUPPORT NEURO secondary

Hi Neil

Thanks for your input and for your support.

While it is true that the overall study did not find this, it is also true that the only difference we found between randomized groups was in LATE CUS findings, which the main trial did not look for specifically.

As for the lower % with ADVERSE early CUS outcomes in this group compared with the main trial - I think we all expected that because of course this subcohort represents a group that MADE it to at least around 34 weeks, so we would expect that some of the patients reported with Grade 3 or 4 in the main trial would have died before getting into this group.

We tried to emphasize more the *overall* findings of this cohort, and put those overall CUS outcomes (and progression from early to late CUS) on the front line.

As for looking at the 2 strata - as you know we adjusted for EGA strata in the regression analysis. But, I had also asked Helen Cheng to look JUST at the group with the adverse Late CUS findings, and parse those patients out by EGA strata. I am attaching that output (SHintz\_05febRequest\_16feb.xls). As you can see, the numbers are very small once you start slicing and dicing. But bottom line, she did look at randomized group by EGA strata (by Fisher's Exact because the numbers were so small) and did not find anything significant. You may look at it and say there seems to be a "trend", but again the numbers are very very small once the slicing and dicing begins.

The pre-randomization data tables for this subcohort show the groups to be well matched (see attached Table 1a). Formal comparisons were run on a number of these to make sure they really were similar. Also of note, the neonatal morbidities/interventions table (Table 1b) show - not surprisingly - findings that are consistent with the main trial (i.e., postnatal steroids in CPAP vs. surf, Severe ROP as defined by SUPPORT in High vs. Low)

We tried to be very clear - both in emphasizing that this is a *subcohort* and in our statements in the conclusions - that these findings may not represent the entire cohort. I hope you think that was emphasized enough in the abstract. Please let me know if you have ideas to re-word.

Thanks again

Susan

Hi Susan

Very nice and provocative

We obviously did not find this in the overall study. We will need to discuss the implications because of the selection bias and other issues

We did find more Gr 3-4 IVH in the CPAP infants but this was not significant -

CPAP 14.3% (92/642)

Surf 11.5% (72/628)

1.26 (0.94, 1.68)

0.12

Susan have you looked at the 2 strata?

Neil

-----Original Message-----

From: Susan Hintz [mailto:srhintz@stanford.edu]

Sent: Thursday, February 18, 2010 1:04 PM

To: Rosemary Higgins

Cc: [hcheng@rti.org](mailto:hcheng@rti.org); [adas@rti.org](mailto:adas@rti.org); Dorothy Bulas; Tom Slovis; Finer, Neil

Subject: Abstract preview - CUS results of SUPPORT  
NEURO secondary

Hello all,

Attached is a draft of the Late Breaker abstract for the SUPPORT Neuroimaging and Outcomes secondary (now dubbed the "NEURO" cohort).

Obviously these are very selected results due to space constraints.

As it stands we are at 98.5%.

Please let me know your comments, edits, etc. Also, please pay particular attention to the paragraph I have highlighted in red - it is a required explanation for why this analysis did not meet the original abstract deadline. Comments and edits there are welcome as well -

Thank you all for your hard work on this - and continued hard work.

Susan

--

Susan R. Hintz, M.D., M.S. Epi

Associate Professor of Pediatrics

Division of Neonatal and Developmental Medicine  
Stanford University School of Medicine 750 Welch  
Road, Suite 315 Palo Alto, CA 94304

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--

Susan R. Hintz, M.D., M.S. Epi  
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Palo Alto, CA 94304  
ph: 650-723-5711  
fax: 650-725-8351

**Table 1a: Demographic and perinatal clinical characteristics of CUS cohort by ventilation and oxygenation randomized groups.**

	VENTILATION STRATEGY		OXYGENATION STRATEGY	
	CPAP	Surfactant	High sat	Low sat
N	282/572 (49%)	290/572 (51%)	302/572 (53%)	270/572 (47%)
BW (grams) (mean (SD))	851 (186)	845 (193)	838 (194)	859 (185)
EGA (weeks) (mean (SD))	25.9 (1.03)	25.8 (1.02)	25.9 (1.03)	25.8 (1.01)
% 24 -25 weeks	107/282 (38%)	113/290 (39%)	120/302 (40%)	100/270 (37%)
Multiple gestation	64/282 (23%)	70/290 (24%)	73/302 (24%)	61/270 (23%)
Race				
Non-hispanic Black	86/282 (30%)	88/289 (30%)	77/301 (26%)	97/270 (36%)
Non-hispanic White	122/282 (43%)	122/289 (42%)	136/301 (45%)	108/270 (40%)
Hispanic	63/282 (22%)	65/289 (22%)	73/301 (24%)	55/270 (20%)
Other	11/282 (4%)	14/289 (5%)	15/301 (5%)	10/270 (4%)
Male	149/282 (53%)	170/290 (59%)	174/302 (58%)	145/270 (54%)
Any antenatal steroids	273/282 (97%)	273/290 (94%)	286/302 (95%)	260/270 (96%)
Maternal hypertension	68/282 (24%)	76/290 (26%)	75/302 (25%)	69/270 (26%)
ROM >18 hours	107/282 (38%)	95/290 (33%)	110/302 (36%)	92/270 (34%)
Cesarean section	187/282 (66%)	205/290 (71%)	207/302 (69%)	185/270 (69%)
Apgar <3 at 5 minutes	8/282 (3%)	9/290 (3%)	11/302 (4%)	6/270 (2%)
Epinephrine or chest compressions in DR	15/282 (5%)	19/290 (7%)	19/302 (6%)	15/270 (6%)



**Table 1b: In hospital morbidities and characteristics of CUS cohort by ventilation and oxygenation randomized groups**

	VENTILATION STRATEGY		OXYGENATION STRATEGY	
	CPAP	Surfactant	High sat	Low sat
N	282/572 (49%)	290/572 (51%)	302/572 (53%)	270/572 (47%)
On ANY ventilator at any time	234/280 (84%)	289/289 (100%)	279/301 (93%)	244/268 (91%)
On high-frequency ventilation at any time	93/282 (33%)	115/290 (40%)	120/302 (40%)	88/270 (33%)
Surfactant treatment	195/282 (69%)	285/290 (98%)	257/302 (85%)	223/270 (83%)
PDA diagnosed	139/282 (49%)	150/290 (52%)	158/302 (52%)	131/270 (49%)
Surgery for PDA	36/282 (13%)	34/290 (12%)	35/302 (12%)	35/270 (13%)
Sepsis - Early	9/282 (3%)	10/290 (3%)	11/302 (4%)	8/270 (3%)
Sepsis - Late	89/282 (32%)	102/290 (35%)	107/302 (35%)	84/270 (31%)
NEC (definite) diagnosed	27/282 (10%)	18/290 (6%)	23/302 (8%)	22/270 (8%)
Surgery for NEC (lap OR drain)	11/282 (4%)	8/290 (3%)	11/302 (4%)	8/270 (3%)
ROP stage 3 or greater with plus	20/281 (7%)	21/285 (7%)	33/298 (11%)	8/268 (3%)
Severe ROP as defined by SUPPORT (Marie G)	32/262 (12%)	36/265 (14%)	49/276 (18%)	19/251 (8%)
Surgery for PDA or NEC or ROP	55/282 (20%)	60/290 (21%)	67/302 (22%)	48/270 (18%)
Postnatal steroids	20/282 (7%)	34/290 (12%)	29/302 (10%)	25/270 (9%)
BPD (physiologic) (Marie G)	105/282 (37%)	112/290 (39%)	122/302 (40%)	95/270 (35%)

## Higgins, Rosemary (NIH/NICHD) [E]

---

**From:** Finer, Neil <nfiner@ucsd.edu>  
**Sent:** Thursday, February 18, 2010 10:16 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Abstract preview - CUS results of SUPPORT NEURO secondary

Rose

I could do a call preferably at 11:00 or 12:00 PT Neil

-----Original Message-----

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Thursday, February 18, 2010 6:15 PM  
**To:** 'tslovis@med.wayne.edu'; 'srhintz@stanford.edu'  
**Cc:** 'hcheng@rti.org'; 'adas@rti.org'; 'dbulas@cnmc.org'; Finer, Neil  
**Subject:** Re: Abstract preview - CUS results of SUPPORT NEURO secondary

If you would like, we could potentially schedule a brief call between 12-3 pm ET.  
Let me know

Thanks  
Rose

----- Original Message -----

**From:** Slovis, Thomas <tslovis@med.wayne.edu>  
**To:** Susan Hintz <srhintz@stanford.edu>; Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** hcheng@rti.org <hcheng@rti.org>; adas@rti.org <adas@rti.org>; Dorothy Bulas <dbulas@cnmc.org>; Neil Finer <nfiner@ucsd.edu>  
**Sent:** Thu Feb 18 19:09:25 2010  
**Subject:** RE: Abstract preview - CUS results of SUPPORT NEURO secondary

Hi, I see some good news in that Dorothy and I were quite consistent. The difference in CPAP and surfactant also appears real if the sample size was big enough. After all have replied, perhaps Susan can talk to Dorothy and as I am sure we are missing some important things that the neonatologists are deriving from the study. Good work. Tom

---

**From:** Susan Hintz [srhintz@stanford.edu]  
**Sent:** Thursday, February 18, 2010 4:03 PM  
**To:** Rosemary Higgins  
**Cc:** hcheng@rti.org; adas@rti.org; Dorothy Bulas; Slovis, Thomas; Neil Finer  
**Subject:** Abstract preview - CUS results of SUPPORT NEURO secondary

Hello all,

Attached is a draft of the Late Breaker abstract for the SUPPORT Neuroimaging and Outcomes secondary (now dubbed the "NEURO" cohort).

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Please let me know your comments, edits, etc. Also, please pay particular attention to the paragraph I have highlighted in red - it is a required explanation for why this analysis did not meet the original abstract deadline. Comments and edits there are welcome as well -

Thank you all for you hard work on this - and continued hard work.

Susan

--

Susan R. Hintz, M.D., M.S. Epi  
Associate Professor of Pediatrics  
Division of Neonatal and Developmental Medicine Stanford University School of Medicine  
750 Welch Road, Suite 315  
Palo Alto, CA 94304  
ph: 650-723-5711  
fax: 650-725-8351

## Higgins, Rosemary (NIH/NICHD) [E]

---

**From:** Finer, Neil <nfiner@ucsd.edu>  
**Sent:** Thursday, February 18, 2010 10:09 PM  
**To:** Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; das@rti.org; Gantz, Marie; Rich, Wade  
**Subject:** RE: New England Journal of Medicine 09-11781.R1

This looks good Wally

I would use the (b) (4) for consistency The issue of (b) (4) is tricky - there is no solid evidence for any indication, (b) (4)

This is the most recent review of its use that I can find:

(b) (4)

Neil

-----Original Message-----

**From:** Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]  
**Sent:** Thursday, February 18, 2010 6:30 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; das@rti.org; Gantz, Marie; Finer, Neil; Rich, Wade  
**Cc:** Wally Carlo, M.D.  
**Subject:** FW: New England Journal of Medicine 09-11781.R1

Enclosed is the revised O2 sat draft. The comments are trivial. They accepted the (b) (4) and all the changes we made.

I have a few requests:

Rose:

Comment #10 Can you verify that the (b) (4)?

Comment #11 Would you say (b) (4)?

Comment #16 See if you like the change I made

Abhik:

Comments #13 and 14 Can you help with the response and change?

Marie:

Comments #24, 25, and 27. Please verify/comment.

Comment #26 Can you provide wording for (b) (4)

Thanks for all your help.

Wally

Wally Carlo, M.D.  
Edwin M. Dixon Professor of Pediatrics  
University of Alabama at Birmingham  
Director, Division of Neonatology  
Director, Newborn Nurseries  
619 South 20th Street  
525 New Hillman Building  
Birmingham, AL 35233-7335  
Phone: 205 934 4680  
FAX: 205 934 3100  
Cell: 205 266 (b)

-----Original Message-----

From: onbehalfof+editorial+nejm.org@manuscriptcentral.com  
[mailto:onbehalfof+editorial+nejm.org@manuscriptcentral.com] On Behalf Of editorial@nejm.org  
Sent: Thursday, February 18, 2010 2:52 PM  
To: Wally Carlo, M.D.  
Subject: New England Journal of Medicine 09-11781.R1

Dear Wally:

I am writing again about your manuscript, "Oxygen Saturation Targets in Extremely Preterm Infants: The SUPPORT Trial." Your revision has been evaluated by the editors and addresses the key concerns raised previously. However, we do need to ask for some additional changes before it is accepted for publication.

At this point I am attaching a partially edited version of your manuscript in which I have inserted editorial comments and queries.

(These comments are most easily viewed in Word by viewing in "reading layout" or "print layout.") In general, the changes I have suggested should be incorporated, unless there are places where I have inadvertently changed your meaning.

When you send in your revised manuscript, it is not necessary to provide a letter with responses to the inserted editorial comments, but please note anywhere that you did not make suggested changes (and why); it is fine to insert any responses in the associated comment box. Please return two copies of the revision: one in which the changes you have made are highlighted, and the other a clean copy.

Please include a word count for the text. As you know, the word count for text should not exceed 2700 words, and there should be no more than

5 tables or figures in the print version of the manuscript, though it is fine to include additional "web only" appendix tables.

Any changes in authorship must be made in writing, signed by all authors.

To revise your manuscript, log into <http://mc.manuscriptcentral.com/nejm> and enter For Authors, where you will find a button to "Submit a Revision."

Journal policy dictates that we must have on file a signed Copyright Transfer Agreement from each author before a manuscript can be accepted.

If not already done, please ask all authors to sign and fax back the enclosed form as soon as possible to (781) 207-6529. This will eliminate unnecessary delays in the event that your manuscript is accepted.

The Universal Disclosure form is also attached. Each author must complete it. After you have filled in the appropriate information in the spaces provided, you may either e-mail your completed form to Brendan Abel at [babel@nejm.org](mailto:babel@nejm.org) or upload it to your Author Dashboard of ScholarOne Manuscripts. It is essential that you return the forms as soon as possible, because we cannot process your manuscript without them.

Please recall that the Journal requires that neither an article under consideration nor any part of its essential substance, tables, or figures has been or will be published or submitted elsewhere before appearing in the Journal.

We look forward to receiving your revised manuscript and will plan a prompt evaluation when it arrives. Please do not hesitate to contact me if you have questions.

Thank you again for your work.

Sincerely,

Caren Solomon

Caren G. Solomon, MD  
Deputy Editor

New England Journal of Medicine  
10 Shattuck Street  
Boston, MA 02115  
(617) 734-9800  
Fax: (617) 739-9864  
<http://www.nejm.org>

**From:** Slovis, Thomas  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Abstract preview - CUS results of SUPPORT NEURO secondary  
**Date:** Thursday, February 18, 2010 9:25:44 PM

---

Hi, actually I am in Colorado soon to be Montana. Maybe we can do it the first week of March. I haven't spoken to Dorothy yet but if she agrees we should do it. Tom

---

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]  
Sent: Thursday, February 18, 2010 9:14 PM  
To: Slovis, Thomas; 'srhintz@stanford.edu'  
Cc: 'hcheng@rti.org'; 'adas@rti.org'; 'dbulas@cnmc.org'; 'nfiner@ucsd.edu'  
Subject: Re: Abstract preview - CUS results of SUPPORT NEURO secondary

If you would like, we could potentially schedule a brief call between 12-3 pm ET.  
Let me know

Thanks  
Rose

----- Original Message -----

From: Slovis, Thomas <tslovis@med.wayne.edu>  
To: Susan Hintz <srhintz@stanford.edu>; Higgins, Rosemary (NIH/NICHD) [E]  
Cc: hcheng@rti.org <hcheng@rti.org>; adas@rti.org <adas@rti.org>; Dorothy Bulas <dbulas@cnmc.org>; Neil Finer <nfiner@ucsd.edu>  
Sent: Thu Feb 18 19:09:25 2010  
Subject: RE: Abstract preview - CUS results of SUPPORT NEURO secondary

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Sent: Thursday, February 18, 2010 4:03 PM  
To: Rosemary Higgins  
Cc: hcheng@rti.org; adas@rti.org; Dorothy Bulas; Slovis, Thomas; Neil Finer  
Subject: Abstract preview - CUS results of SUPPORT NEURO secondary

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Susan

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Susan R. Hintz, M.D., M.S. Epi  
Associate Professor of Pediatrics  
Division of Neonatal and Developmental Medicine  
Stanford University School of Medicine  
750 Welch Road, Suite 315  
Palo Alto, CA 94304  
ph: 650-723-5711  
fax: 650-725-8351



**From:** Susan Hintz  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** Re: Fw: Abstract preview - CUS results of SUPPORT NEURO secondary  
**Date:** Thursday, February 18, 2010 8:33:44 PM

---

That would be great. I am reading tomorrow 6-9 AM with Pacific time with Pat (as usual for Wed, Thurs, Frid), then have a few scattered appointments.

Thanks

S

>I am open all day tomorrow except 3-4 ET - do you want me to offer a  
>quick call in line to discuss with Tom and Dorothy??

>

>----- Original Message -----

>From: Slovis, Thomas <tslovis@med.wayne.edu>

>To: Susan Hintz <srhintz@stanford.edu>; Higgins, Rosemary (NIH/NICHD) [E]

>Cc: hcheng@rti.org <hcheng@rti.org>; adas@rti.org <adas@rti.org>;

>Dorothy Bulas <dbulas@cnmc.org>; Neil Finer <nfiner@ucsd.edu>

>Sent: Thu Feb 18 19:09:25 2010

>Subject: RE: Abstract preview - CUS results of SUPPORT NEURO secondary

>

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>consistent. The difference in CPAP and surfactant also appears

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>some important things that the neonatologists are deriving from the

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>From: Susan Hintz [srhintz@stanford.edu]

>Sent: Thursday, February 18, 2010 4:03 PM

>To: Rosemary Higgins

>Cc: hcheng@rti.org; adas@rti.org; Dorothy Bulas; Slovis, Thomas; Neil Finer

>Subject: Abstract preview - CUS results of SUPPORT NEURO secondary

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>well -

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>Susan

>

>--

>Susan R. Hintz, M.D., M.S. Epi  
>Associate Professor of Pediatrics  
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>750 Welch Road, Suite 315  
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>ph: 650-723-5711  
>fax: 650-725-8351

**From:** Susan Hintz  
**To:** Slovis, Thomas  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]; Dorothy Bulas; Neil Finer; adas@rti.org; hcheng@rti.org  
**Subject:** RE: Abstract preview - CUS results of SUPPORT NEURO secondary  
**Date:** Thursday, February 18, 2010 8:02:25 PM

---

Hi Tom

Yes, on many CUS outcomes you and Dorothy were quite stellar. We have done the formal kappa analysis for many CUS outcomes. Of note (and importance), the kappa for the composite late CUS outcome of interest (P-cyst, cPVL, mod-severe ventriculomegaly or shunt) was 0.88.

Thanks, and I am very sure you understand everything perfectly. You are a honorary neonatologist and so is Dorothy. I think the take home message is the low overall rate of severe adverse findings for the unique extremely preterm cohort, and more information that I couldn't squeeze in about progression of findings from early to late CUS>

Susan

>Hi, I see some good news in that Dorothy and I were quite  
>consistent. The difference in CPAP and surfactant also appears  
>real if the sample size was big enough. After all have replied,  
>perhaps Susan can talk to Dorothy and as I am sure we are missing  
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>Sent: Thursday, February 18, 2010 4:03 PM  
>To: Rosemary Higgins  
>Cc: hcheng@rti.org; adas@rti.org; Dorothy Bulas; Slovis, Thomas; Neil Finer  
>Subject: Abstract preview - CUS results of SUPPORT NEURO secondary  
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>Thank you all for you hard work on this - and continued hard work.  
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>Susan  
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>Susan R. Hintz, M.D., M.S. Epi  
>Associate Professor of Pediatrics  
>Division of Neonatal and Developmental Medicine  
>Stanford University School of Medicine  
>750 Welch Road, Suite 315  
>Palo Alto, CA 94304  
>ph: 650-723-5711  
>fax: 650-725-8351

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "wcarlo@peds.uab.edu"  
**Subject:** Re: New England Journal of Medicine 09-11781.R1  
**Date:** Thursday, February 18, 2010 7:57:57 PM

---

Excellent- also, once you have done that, we can send back to the subcommittee (if you approve).

Thanks for all the hard work!!!!

Rose

----- Original Message -----

**From:** Wally Carlo, M.D. <WCarlo@peds.uab.edu>  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Thu Feb 18 19:56:25 2010  
**Subject:** RE: New England Journal of Medicine 09-11781.R1

I am right now reviewing each change or comment. Everything is so minor!!! If I have any questions for you, I will email you. If you find a change you do not want me to accept, let me know.

I will send you a draft in the morning as I am not a good typist and need Marsha's help.

Wally Carlo, M.D.  
Edwin M. Dixon Professor of Pediatrics  
University of Alabama at Birmingham  
Director, Division of Neonatology  
Director, Newborn Nurseries  
619 South 20th Street  
525 New Hillman Building  
Birmingham, AL 35233-7335  
Phone: 205 934 4680  
FAX: 205 934 3100  
Cell: 205 266 (b)

-----Original Message-----

**From:** Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]  
**Sent:** Thursday, February 18, 2010 6:53 PM  
**To:** Wally Carlo, M.D.  
**Subject:** Re: New England Journal of Medicine 09-11781.R1

Awesome!!!!

----- Original Message -----

**From:** Wally Carlo, M.D. <WCarlo@peds.uab.edu>  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Thu Feb 18 19:15:10 2010  
**Subject:** RE: New England Journal of Medicine 09-11781.R1

Rose.

They did. I am so happy. There does not seem to be any problem.

Wally

Sent from my Windows Mobile phone

-----Original Message-----

From: Higgins, Rosemary (NIH/NICHD) [E] <higginsr@mail.nih.gov>  
Sent: Thursday, February 18, 2010 5:48 PM  
To: 'wcarlo@peds.uab.edu' <wcarlo@peds.uab.edu>  
Subject: Re: New England Journal of Medicine 09-11781.R1

Wally

I am not at a computer and can't see the comments - did they accept the response about the (b) (4)

----- Original Message -----

From: Wally Carlo, M.D. <WCarlo@peds.uab.edu>  
To: Higgins, Rosemary (NIH/NICHD) [E]  
Cc: nfiner@ucsd.edu <nfiner@ucsd.edu>; das@rti.org <das@rti.org>; Gantz, Marie <mgantz@rti.org>; wrich@ucsd.edu <wrich@ucsd.edu>  
Sent: Thu Feb 18 18:21:35 2010  
Subject: FW: New England Journal of Medicine 09-11781.R1

Hi Everyone:

Great news!!! Sorry for the delay. I have been in the NICU.

They are doing this fast!! They want them published soon, I think. I will work on this tonight.

Wally

Wally Carlo, M.D.  
Edwin M. Dixon Professor of Pediatrics  
University of Alabama at Birmingham  
Director, Division of Neonatology  
Director, Newborn Nurseries  
619 South 20th Street  
525 New Hillman Building  
Birmingham, AL 35233-7335  
Phone: 205 934 4680  
FAX: 205 934 3100  
Cell: 205 266 (b)

-----Original Message-----

From: onbehalfof+editorial+nejm.org@manuscriptcentral.com  
[mailto:onbehalfof+editorial+nejm.org@manuscriptcentral.com] On Behalf  
Of editorial@nejm.org  
Sent: Thursday, February 18, 2010 2:52 PM  
To: Wally Carlo, M.D.  
Subject: New England Journal of Medicine 09-11781.R1

Dear Wally:

I am writing again about your manuscript, "Oxygen Saturation Targets in Extremely Preterm Infants: The SUPPORT Trial." Your revision has been evaluated by the editors and addresses the key concerns raised previously. However, we do need to ask for some additional changes before it is accepted for publication.

At this point I am attaching a partially edited version of your manuscript in which I have inserted editorial comments and queries. (These comments are most easily viewed in Word by viewing in "reading layout" or "print layout.") In general, the changes I have suggested should be incorporated, unless there are places where I have inadvertently changed your meaning.

When you send in your revised manuscript, it is not necessary to provide a letter with responses to the inserted editorial comments, but please note anywhere that you did not make suggested changes (and why); it is fine to insert any responses in the associated comment box. Please return two copies of the revision: one in which the changes you have made are highlighted, and the other a clean copy.

Please include a word count for the text. As you know, the word count for text should not exceed 2700 words, and there should be no more than 5 tables or figures in the print version of the manuscript, though it is fine to include additional "web only" appendix tables.

Any changes in authorship must be made in writing, signed by all authors.

To revise your manuscript, log into <http://mc.manuscriptcentral.com/nejm> and enter For Authors, where you will find a button to "Submit a Revision."

Journal policy dictates that we must have on file a signed Copyright Transfer Agreement from each author before a manuscript can be accepted. If not already done, please ask all authors to sign and fax back the enclosed form as soon as possible to (781) 207-6529. This will eliminate unnecessary delays in the event that your manuscript is accepted.

The Universal Disclosure form is also attached. Each author must complete it. After you have filled in the appropriate information in the spaces provided, you may either e-mail your completed form to Brendan Abel at [babel@nejm.org](mailto:babel@nejm.org) or upload it to your Author Dashboard of ScholarOne Manuscripts. It is essential that you return the forms as soon as possible, because we cannot process your manuscript without them.

Please recall that the Journal requires that neither an article under consideration nor any part of its essential substance, tables, or figures has been or will be published or submitted elsewhere before appearing in the Journal.

We look forward to receiving your revised manuscript and will plan a prompt evaluation when it arrives. Please do not hesitate to contact me if you have questions.

Thank you again for your work.

Sincerely,

Caren Solomon

Caren G. Solomon, MD  
Deputy Editor

New England Journal of Medicine  
10 Shattuck Street  
Boston, MA 02115  
(617) 734-9800  
Fax: (617) 739-9864  
<http://www.nejm.org>



**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "srhintz@stanford.edu"  
**Subject:** Fw: Abstract preview - CUS results of SUPPORT NEURO secondary  
**Date:** Thursday, February 18, 2010 7:55:31 PM

---

I am open all day tomorrow except 3-4 ET - do you want me to offer a quick call in line to discuss with Tom and Dorothy??

----- Original Message -----

**From:** Slovis, Thomas <tslovis@med.wayne.edu>  
**To:** Susan Hintz <srhintz@stanford.edu>; Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** hcheng@rti.org <hcheng@rti.org>; adas@rti.org <adas@rti.org>; Dorothy Bulas <dbulas@cnmc.org>; Neil Finer <nfiner@ucsd.edu>  
**Sent:** Thu Feb 18 19:09:25 2010  
**Subject:** RE: Abstract preview - CUS results of SUPPORT NEURO secondary

Hi, I see some good news in that Dorothy and I were quite consistent. The difference in CPAP and surfactant also appears real if the sample size was big enough. After all have replied, perhaps Susan can talk to Dorothy and as I am sure we are missing some important things that the neonatologists are deriving from the study. Good work.  
Tom

---

**From:** Susan Hintz [srhintz@stanford.edu]  
**Sent:** Thursday, February 18, 2010 4:03 PM  
**To:** Rosemary Higgins  
**Cc:** hcheng@rti.org; adas@rti.org; Dorothy Bulas; Slovis, Thomas; Neil Finer  
**Subject:** Abstract preview - CUS results of SUPPORT NEURO secondary

Hello all,

Attached is a draft of the Late Breaker abstract for the SUPPORT Neuroimaging and Outcomes secondary (now dubbed the "NEURO" cohort).

Obviously these are very selected results due to space constraints.  
As it stands we are at 98.5%.

Please let me know your comments, edits, etc. Also, please pay particular attention to the paragraph I have highlighted in red - it is a required explanation for why this analysis did not meet the original abstract deadline. Comments and edits there are welcome as well -

Thank you all for your hard work on this - and continued hard work.

Susan

--

Susan R. Hintz, M.D., M.S. Epi  
Associate Professor of Pediatrics  
Division of Neonatal and Developmental Medicine  
Stanford University School of Medicine  
750 Welch Road, Suite 315  
Palo Alto, CA 94304  
ph: 650-723-5711  
fax: 650-725-8351

**From:** Susan Hintz  
**To:** [Finer, Neil](#)  
**Cc:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [hcheng@rti.org](mailto:hcheng@rti.org); [Dorothy Bulas](#); [Tom Slovis](#); [adas@rti.org](mailto:adas@rti.org)  
**Subject:** RE: Abstract preview - CUS results of SUPPORT NEURO secondary  
**Date:** Thursday, February 18, 2010 7:19:05 PM  
**Attachments:** [SHintz\\_05febRequest\\_16feb.xls](#)  
[Table1a\\_1b\\_16feb1.doc](#)

---

Hi Neil

Thanks for your input and for your support.

While it is true that the overall study did not find this, it is also true that the only difference we found between randomized groups was in LATE CUS findings, which the main trial did not look for specifically.

As for the lower % with ADVERSE early CUS outcomes in this group compared with the main trial - I think we all expected that because of course this subcohort represents a group that MADE it to at least around 34 weeks, so we would expect that some of the patients reported with Grade 3 or 4 in the main trial would have died before getting into this group.

We tried to emphasize more the *overall* findings of this cohort, and put those overall CUS outcomes (and progression from early to late CUS) on the front line.

As for looking at the 2 strata - as you know we adjusted for EGA strata in the regression analysis. But, I had also asked Helen Cheng to look JUST at the group with the adverse Late CUS findings, and parse those patients out by EGA strata. I am attaching that output (SHintz\_05febRequest\_16feb.xls). As you can see, the numbers are very small once you start slicing and dicing. But bottom line, she did look at randomized group by EGA strata (by Fisher's Exact because the numbers were so small) and did not find anything significant. You may look at it and say there seems to be a "trend", but again the numbers are very very small once the slicing and dicing begins.

The pre-randomization data tables for this subcohort show the groups to be well matched (see attached Table 1a). Formal comparisons were run on a number of these to make sure they really were similar. Also of note, the neonatal morbidities/interventions table (Table 1b) show - not surprisingly - findings that are consistent with the main trial (i.e., postnatal steroids in CPAP vs. surf, Severe ROP as defined by SUPPORT in High vs. Low)

We tried to be very clear - both in emphasizing that this is a *subcohort* and in our statements in the conclusions - that these findings may not represent the entire cohort. I hope you think that was emphasized enough in the abstract. Please let me know if you have ideas to re-word.

Thanks again

Susan

Hi Susan

Very nice and provocative

We obviously did not find this in the overall study. We will need to discuss the implications because of the selection bias and other issues

We did find more Gr 3-4 IVH in the CPAP infants but this was not significant -

CPAP 14.3% (92/642)

Surf 11.5% (72/628)

1.26 (0.94, 1.68)

0.12

Susan have you looked at the 2 strata?

Neil

-----Original Message-----

From: Susan Hintz [mailto:srhintz@stanford.edu]

Sent: Thursday, February 18, 2010 1:04 PM

To: Rosemary Higgins

Cc: hcheng@rti.org; adas@rti.org; Dorothy Bulas; Tom Slovis; Finer, Neil

Subject: Abstract preview - CUS results of SUPPORT NEURO secondary

Hello all,

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Susan

--

Susan R. Hintz, M.D., M.S. Epi

Associate Professor of Pediatrics

Division of Neonatal and Developmental Medicine Stanford University School of  
Medicine 750 Welch Road, Suite 315 Palo Alto, CA 94304

ph: 650-723-5711

fax: 650-725-8351

Only includes ppts who have one of following per table 3: CPVL/Pore cyst/mod-sev vent/shunt  
n/N (%)

	Reader 1			Reader 2		
	EGA			EGA		
	24/25 weeks	26/27 weeks	Fisher's p-val	24/25 weeks	26/27 weeks	Fisher's p-val
<b>Vent Strategy</b>						
CPAP	11/26 (42%)	15/26 (58%)	0.2619	12/27 (44%)	15/27 (56%)	0.1596
Surfactant	2/11 (18%)	9/11 (82%)		2/11 (18%)	9/11 (82%)	
<b>Oxygenation</b>						
High	6/19 (32%)	13/19 (68%)	0.7374	6/18 (33%)	12/18 (67%)	0.7449
Low	7/18 (39%)	11/18 (61%)		8/20 (40%)	12/20 (60%)	

Output file = Table3Misc\_16FEB10.xls

**Table 1a: Demographic and perinatal clinical characteristics of CUS cohort by ventilation and oxygenation randomized groups.**

	VENTILATION STRATEGY		OXYGENATION STRATEGY	
	CPAP	Surfactant	High sat	Low sat
N	282/572 (49%)	290/572 (51%)	302/572 (53%)	270/572 (47%)
BW (grams) (mean (SD))	851 (186)	845 (193)	838 (194)	859 (185)
EGA (weeks) (mean (SD))	25.9 (1.03)	25.8 (1.02)	25.9 (1.03)	25.8 (1.01)
% 24 -25 weeks	107/282 (38%)	113/290 (39%)	120/302 (40%)	100/270 (37%)
Multiple gestation	64/282 (23%)	70/290 (24%)	73/302 (24%)	61/270 (23%)
Race				
Non-hispanic Black	86/282 (30%)	88/289 (30%)	77/301 (26%)	97/270 (36%)
Non-hispanic White	122/282 (43%)	122/289 (42%)	136/301 (45%)	108/270 (40%)
Hispanic	63/282 (22%)	65/289 (22%)	73/301 (24%)	55/270 (20%)
Other	11/282 (4%)	14/289 (5%)	15/301 (5%)	10/270 (4%)
Male	149/282 (53%)	170/290 (59%)	174/302 (58%)	145/270 (54%)
Any antenatal steroids	273/282 (97%)	273/290 (94%)	286/302 (95%)	260/270 (96%)
Maternal hypertension	68/282 (24%)	76/290 (26%)	75/302 (25%)	69/270 (26%)
ROM >18 hours	107/282 (38%)	95/290 (33%)	110/302 (36%)	92/270 (34%)
Cesarean section	187/282 (66%)	205/290 (71%)	207/302 (69%)	185/270 (69%)
Apgar <3 at 5 minutes	8/282 (3%)	9/290 (3%)	11/302 (4%)	6/270 (2%)
Epinephrine or chest compressions in DR	15/282 (5%)	19/290 (7%)	19/302 (6%)	15/270 (6%)

**Table 1b: In hospital morbidities and characteristics of CUS cohort by ventilation and oxygenation randomized groups**

	VENTILATION STRATEGY		OXYGENATION STRATEGY	
	CPAP	Surfactant	High sat	Low sat
N	282/572 (49%)	290/572 (51%)	302/572 (53%)	270/572 (47%)
On ANY ventilator at any time	234/280 (84%)	289/289 (100%)	279/301 (93%)	244/268 (91%)
On high-frequency ventilation at any time	93/282 (33%)	115/290 (40%)	120/302 (40%)	88/270 (33%)
Surfactant treatment	195/282 (69%)	285/290 (98%)	257/302 (85%)	223/270 (83%)
PDA diagnosed	139/282 (49%)	150/290 (52%)	158/302 (52%)	131/270 (49%)
Surgery for PDA	36/282 (13%)	34/290 (12%)	35/302 (12%)	35/270 (13%)
Sepsis - Early	9/282 (3%)	10/290 (3%)	11/302 (4%)	8/270 (3%)
Sepsis - Late	89/282 (32%)	102/290 (35%)	107/302 (35%)	84/270 (31%)
NEC (definite) diagnosed	27/282 (10%)	18/290 (6%)	23/302 (8%)	22/270 (8%)
Surgery for NEC (lap OR drain)	11/282 (4%)	8/290 (3%)	11/302 (4%)	8/270 (3%)
ROP stage 3 or greater with plus	20/281 (7%)	21/285 (7%)	33/298 (11%)	8/268 (3%)
<b>Severe ROP as defined by SUPPORT (Marie G)</b>	<b>32/262 (12%)</b>	<b>36/265 (14%)</b>	<b>49/276 (18%)</b>	<b>19/251 (8%)</b>
Surgery for PDA or NEC or ROP	55/282 (20%)	60/290 (21%)	67/302 (22%)	48/270 (18%)
Postnatal steroids	20/282 (7%)	34/290 (12%)	29/302 (10%)	25/270 (9%)
<b>BPD (physiologic) (Marie G)</b>	<b>105/282 (37%)</b>	<b>112/290 (39%)</b>	<b>122/302 (40%)</b>	<b>95/270 (35%)</b>

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "nfiner@ucsd.edu"; "srhintz@stanford.edu"  
**Cc:** "hcheng@rti.org"; "adas@rti.org"; "dbulas@cnmc.org"; "tslovis@med.wayne.edu"  
**Subject:** Re: Abstract preview - CUS results of SUPPORT NEURO secondary  
**Date:** Thursday, February 18, 2010 5:42:32 PM

---

Have not looked at the strata

---

**From:** Finer, Neil <nfiner@ucsd.edu>  
**To:** Susan Hintz <srhintz@stanford.edu>; Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** hcheng@rti.org <hcheng@rti.org>; adas@rti.org <adas@rti.org>; Dorothy Bulas <dbulas@cnmc.org>; Tom Slovis <tslovis@med.wayne.edu>  
**Sent:** Thu Feb 18 17:30:38 2010  
**Subject:** RE: Abstract preview - CUS results of SUPPORT NEURO secondary

Hi Susan

Very nice and provocative

We obviously did not find this in the overall study. We will need to discuss the implications because of the selection bias and other issues

We did find more Gr 3-4 IVH in the CPAP infants but this was not significant -

CPAP 14.3% (92/642)	Surf 11.5% (72/628)	1.26 (0.94, 1.68)	0.12
---------------------	---------------------	-------------------	------

Susan have you looked at the 2 strata?

Neil

-----Original Message-----

**From:** Susan Hintz [mailto:srhintz@stanford.edu]  
**Sent:** Thursday, February 18, 2010 1:04 PM  
**To:** Rosemary Higgins  
**Cc:** hcheng@rti.org; adas@rti.org; Dorothy Bulas; Tom Slovis; Finer, Neil  
**Subject:** Abstract preview - CUS results of SUPPORT NEURO secondary

Hello all,

Attached is a draft of the Late Breaker abstract for the SUPPORT Neuroimaging and Outcomes secondary (now dubbed the "NEURO" cohort).

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Thank you all for your hard work on this - and continued hard work.

Susan

--

Susan R. Hintz, M.D., M.S. Epi  
Associate Professor of Pediatrics



**Division of Neonatal and Developmental Medicine Stanford University School of  
Medicine 750 Welch Road, Suite 315 Palo Alto, CA 94304  
ph: 650-723-5711  
fax: 650-725-8351**

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Susan Hintz"  
**Subject:** RE: Abstract preview - CUS results of SUPPORT NEURO secondary  
**Date:** Thursday, February 18, 2010 4:51:00 PM

---

Abhik is in India til March 6 - Dennis Wallace can look at it. I will forward you what I sent Seetha (I had to copy and paste)

Rose

-----Original Message-----

From: Susan Hintz [mailto:srhintz@stanford.edu]  
Sent: Thursday, February 18, 2010 4:50 PM  
To: Higgins, Rosemary (NIH/NICHD) [E]  
Subject: Re: Abstract preview - CUS results of SUPPORT NEURO secondary

Yes, I think it is fine to send it through for clearance - as long as you are OK with this version. Thanks. This is the first Neil has seen of this, but I suspect he won't have many or any edits.

Do you know if Abhik is back or if he is checking email? I would like his input - I did not put kappas on this version (space) but I could try if he thinks it is important.

No, I did not receive another version of abstract/table from Seetha.

Thanks.

S

Sent from my iPhone

On Feb 18, 2010, at 1:41 PM, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> wrote:

> Can I send this one through clearance and to the subcommittee?

>

> Also, did Seetha send you another version of her abstract with the table?

>

> -----Original Message-----

> From: Susan Hintz [mailto:srhintz@stanford.edu]  
> Sent: Thursday, February 18, 2010 4:04 PM  
> To: Higgins, Rosemary (NIH/NICHD) [E]  
> Cc: hcheng@rti.org; adas@rti.org; Dorothy Bulas; Tom Slovis; Neil  
> Finer  
> Subject: Abstract preview - CUS results of SUPPORT NEURO secondary

>

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- > particular attention to the paragraph I have highlighted in red - it
- > is a required explanation for why this analysis did not meet the
- > original abstract deadline. Comments and edits there are welcome as
- > well -
- >
- > Thank you all for your hard work on this - and continued hard work.
- >
- > Susan
- >
- > --
- > Susan R. Hintz, M.D., M.S. Epi
- > Associate Professor of Pediatrics
- > Division of Neonatal and Developmental Medicine
- > Stanford University School of Medicine
- > 750 Welch Road, Suite 315
- > Palo Alto, CA 94304
- > ph: 650-723-5711
- > fax: 650-725-8351

**From:** [Susan Hintz](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Cc:** [hcheng@rti.org](#); [adas@rti.org](#); [Dorothy Bulas](#); [Tom Slovis](#); [Neil Finer](#)  
**Subject:** Abstract preview - CUS results of SUPPORT NEURO secondary  
**Date:** Thursday, February 18, 2010 4:04:10 PM  
**Attachments:** [AbstractDraft\\_Feb18.docx](#)

---

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Susan

--

Susan R. Hintz, M.D., M.S. Epi  
Associate Professor of Pediatrics  
Division of Neonatal and Developmental Medicine  
Stanford University School of Medicine  
750 Welch Road, Suite 315  
Palo Alto, CA 94304  
ph: 650-723-5711  
fax: 650-725-8351

## 2010 PAS Annual Meeting

### Reason why the December deadline could not be met:

This work represents the cranial US results of the Neuroimaging and Neurodevelopmental Outcomes (NEURO) secondary to the Surfactant Positive Airway Pressure and Oximetry Trial (SUPPORT). This secondary involved central reading of more than 1100 cranial US by two masked neuroradiologists after trial enrollment was complete. Central reading and data analysis were therefore not completed until after the November abstract deadline.

### Title: Early and Late Cranial Ultrasound (CUS) findings in the SUPPORT Neuroimaging and Neurodevelopmental Outcomes (NEURO) cohort

S R Hintz, MD, MS Epi<sup>1</sup>, D Bulas, MD<sup>2</sup>, T L Slovis, MD<sup>3</sup>, H Cheng, MS<sup>4</sup>, N Finer, MD<sup>5</sup>, A Das, PhD<sup>4</sup>, R D Higgins, MD<sup>6</sup> and the SUPPORT Subcommittee and NICHD Neonatal Research Network (NRN). <sup>1</sup>Stanford University; <sup>2</sup>Children's National Medical Center; <sup>3</sup>Children's Hospital of Michigan; <sup>4</sup>RTI International; <sup>5</sup>UC San Diego and <sup>6</sup>NIH.

**Background:** The NICHD NRN SUPPORT study was a randomized, multicenter 2x2 trial of ventilation (CPAP vs. surfactant) and oxygenation (high vs. low) in 24-27+6/7 week EGA infants. It is not known whether these differing strategies are associated with early or later brain injury.

**Objective:** In a secondary to SUPPORT, to determine early (4-14 days) and late (34-42 weeks PMA) CUS findings, and compare early and late CUS outcomes between SUPPORT ventilation and oxygenation randomized groups.

**Design/Methods:** The NEURO study was a prospective secondary study of early and late CUS in a subcohort of infants enrolled in SUPPORT. Brain MRI was also obtained within 5 days of late CUS; future analyses will compare CUS and MRI to predict outcome at 18-22 months and school age. All CUS were read by 2 central readers. Rates of major early and late CUS findings were determined for the NEURO cohort overall, and compared between SUPPORT randomized groups. Hierarchical logistic regression determined independent risk of randomized intervention for adverse CUS outcomes, controlling for EGA strata and NRN center as a random effect.

**Results:** 572 infants had complete early and late CUS. Baseline characteristics were similar between randomized groups. Selected major CUS outcomes are shown in Table 1.

Early and Late CUS outcomes in the NEURO cohort

	Reader 1	Reader 2
<b>EARLY CUS</b>		
Normal	72%	72%
Any hemorrhage	19.6%	20.8%
Grade 3 or 4	6.8%	4.2%
<b>LATE CUS</b>		
Mod-severe ventriculomegaly	4.4%	4.2%
Cystic PVL, porencephalic cyst (P-cyst), mod-severe ventriculomegaly or shunt	6.5%	6.6%

Of those with normal early CUS, 81% remained normal on late CUS; ~25% of those with Grade 3/4 on early CUS had P-cyst on late CUS. There were no differences between high and low oxygenation groups on any major early or late CUS finding. However, the composite late CUS finding of cPVL, P-cyst, mod-severe vent, or shunt was more likely in CPAP vs. surfactant (Reader 1: 9% vs. 4%, OR 2.5 (95%CI 1.2-5.2), p=0.014; Reader 2: 10% vs. 4%, OR 2.6 (95%CI 1.2-5.3), p=0.012).

**Conclusions:** Rates of adverse early or late CUS findings were low overall, but a major adverse late CUS finding was more likely for CPAP vs. surfactant. Findings from this subcohort may not apply to the entire trial cohort, and will be further informed by brain MRI and follow-up.

**From:** Abel, Brendan  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: New England Journal of Medicine 09-11783.R1  
**Date:** Thursday, February 18, 2010 9:35:31 AM

---

Hi Rose,

Thanks so much. That will do it!

Brendan

-----Original Message-----

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Wednesday, February 17, 2010 1:45 PM  
**To:** Abel, Brendan; (b) (6)  
**Subject:** RE: New England Journal of Medicine 09-11783.R1

Brendan

Here are my forms with the corrections and also the copyright forms for the two manuscripts.

Let me know if you need anything else.

Thanks  
Rose

-----Original Message-----

**From:** onbehalfof+babel+nejm.org@manuscriptcentral.com  
[mailto:onbehalfof+babel+nejm.org@manuscriptcentral.com] On Behalf Of babel@nejm.org  
**Sent:** Wednesday, February 17, 2010 12:42 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; (b) (6)  
**Subject:** New England Journal of Medicine 09-11783.R1

Re: 09-11783.R1 - Early CPAP versus Surfactant in Extremely Preterm Infants: The SUPPORT Trial

Dear Dr. Higgins:

Thank you for submitting your ICMJE disclosure forms for both manuscripts 09-11783 and 09-11781. There are just a few changes that need to be made for the form to be fully completed.

Please choose in Sec. 2 whether or not you received travel support for the submitted works.

Please choose in Sec. 2 whether or not your institution received payment for writing or reviewing the submitted work.

Please clarify the name of entity and clarify (b) (6)

That should do it. Please make these changes to each of the disclosure forms and email them back to me.

Thanks very much.

Sincerely,

Brendan Abel  
Editorial Assistant  
New England Journal of Medicine

(617) 487-6584

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**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Newman, Jamie"  
**Subject:** FW: Inter-rater reliability and SUPPORT FUP  
**Date:** Wednesday, February 17, 2010 4:28:00 PM

---

Can you keep her on the FU PI list?

Thanks

Rose

---

**From:** Vaucher, Yvonne [mailto:yvaucher@ucsd.edu]  
**Sent:** Wednesday, February 17, 2010 4:25 PM  
**To:** Betty\_Vohr@brown.edu; Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** Inter-rater reliability and SUPPORT FUP

Dear Betty and Rose,

Please send me the inter-rater reliability table discussed in the last FUP PI conference call on Monday. I think we will do better this year as we now all understand how the video review will be used for this purpose. We should focus on achieving optimal reliability for those variables which are both ascertainable in the video and are most important in reporting neurodevelopmental outcome. There are some we will never be able to agree upon based on viewing the videos alone without having additional information.

The last FUP data book that we have access to on line through the NETWORK website is 2006. Are later ones available? If so, could you please forward the link?

Since I am part of the SUPPORT Trial follow-Up, it would be very helpful to participate regularly in monthly Follow-UP PI conference calls and in the SUPPORT Subcommittee even though we are not regular Network members. However, SUPPORT and related issues are regularly discussed in the conference calls and UCSD continues to participate in the major Network FUP meetings so it is important to remain in the "loop" as much as possible.

Is the 2010 Fall FUP meeting scheduled yet? If so, what are the dates?

Thanks,

Yvonne

Yvonne E. Vaucher, M.D., M.P.H.  
Attending Neonatologist  
Director, Infant Special Care Follow-Up Program  
Division of Neonatal/Perinatal Medicine  
Professor of Pediatrics  
UCSD School of Medicine

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FAX: 619-543-3812

**From:** [Juliann DiFiore](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Cc:** [Michele Walsh](#); [Richard Martin](#); [Julie Di Fiore](#)  
**Subject:** SUPPORT Intermittent Hypoxia  
**Date:** Wednesday, February 17, 2010 2:01:48 PM  
**Attachments:** [SUPPORT Intermittent Hypoxia.doc](#)

---

Dear Rose,

It was a pleasure meeting you at Hot Topics where we discussed the possibility of quantifying the desaturation events in the SUPPORT trial cohort. Attached is a copy of our secondary study proposal entitled *Intermittent Hypoxia in Preterm Infants enrolled in the SUPPORT trial* for your and the Neonatal Network Committee's review. Please let me know if you require any additional information.

Regards,

Julie

--

Juliann Di Fiore  
Research Engineer  
Rainbow Babies & Children's Hospital  
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Cleveland, OH 44106  
(216) 844-1478

## Intermittent Hypoxia in Preterm Infants enrolled in the SUPPORT trial

### Secondary Study

Juliann Di Fiore, BSEE, Ryan Foglyano, BSBE, Richard Martin, MD,

Chris Wilson PhD, Michele Walsh, MD

[Case Western Reserve University School of Medicine, Cleveland, OH]

#### Abstract

Episodes of oxygen saturation are almost universal in very low birthweight infants. Neither their incidence, nor potential adverse effects on later neurodevelopmental outcome are known. The NICHD Neonatal Research Network, of which we are a participant, has completed a multicenter trial in which preterm infants of 24-28 weeks gestation were randomized to high versus low levels of baseline oxygen saturation. We have previously received approval from the NICHD Neonatal Research Network to perform a secondary study on a subcohort of the SUPPORT trial infants, entitled *INCIDENCE AND CONSEQUENCES OF EPISODIC DESATURATION IN PRETERM INFANTS ENROLLED IN THE NICHD NEONATAL NETWORK OXYGEN SATURATION [SUPPORT] STUDY*, to 1) characterize and compare the incidence and magnitude of episodic desaturation episodes in infants randomized to high versus low baseline oxygen saturation targets in the SUPPORT Trial 2) correlate the incidence and magnitude of such desaturation episodes over the first month of life with neurodevelopmental outcome at 18-22 months and 3) correlate the incidence of early intermittent hypoxia with a history of sleep disordered breathing (SDB) at 18-22 months.

Field Code Changed

To accurately detect the incidence of desaturation episodes, our current secondary study only includes infants from the San Diego and Cleveland sites where pulse oximetry data were acquired at high resolution (2 sec averaging time and 2 second sample). In contrast, the SUPPORT trial oximetry data at all other sites have been acquired at low resolution (16 second averaging time and 10 second sample rate). With the SUPPORT trial findings of increased mortality in the low baseline saturation group, there is interest in expanding the secondary study database to include a second cohort of infants with low resolution data as well. This may be problematic as the prolonged averaging times will smooth the SaO<sub>2</sub> waveform and may decrease the accuracy of detection of desaturation events. The low sample rate of 10 sec may further exacerbate this problem.

#### A. Specific Aim:

The aim of this study is to expand our current database of infants with high resolution pulse oximetry data to include the remaining low resolution pulse oximetry data SUPPORT infants. Using these two separate infant cohorts we aim to:

1. Assess the effect of data resolution (2/2sec, averaging time/sample rate versus 16/10sec, averaging time/sample rate) on the incidence, duration and magnitude of desaturation events between low and high baseline SaO<sub>2</sub> infant groups.
2. Assess the relationship between the incidence of desaturation events and the development of Retinopathy of Prematurity (ROP).
3. Analyze the correlation between the incidence of desaturation events and neurodevelopmental outcome.
4. Analyze the correlation between the incidence of desaturation events and mortality.

**B. Hypothesis:**

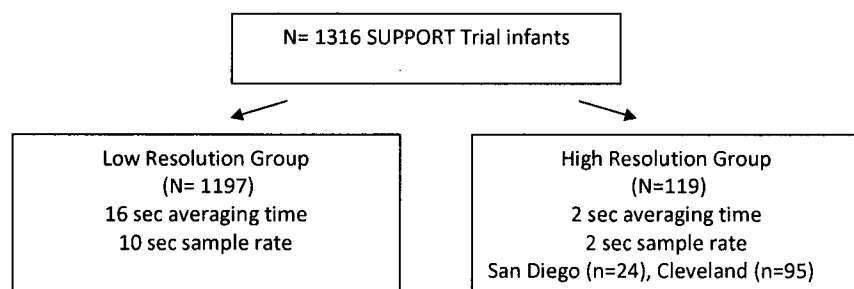
We hypothesize that:

1. Infants with low resolution oximetry data will have fewer desaturation events and of smaller magnitude than infants with high resolution data.
2. Infants with severe ROP requiring laser therapy will have a higher incidence of desaturation events.
3. A higher incidence of episodic desaturation in neonates is associated with greater neurodevelopmental handicap at 18-22 months.
4. A higher incidence of desaturation events is associated with an increase in infant mortality.

**C. Rationale:**

The SUPPORT Trial randomized infants to two ranges of SpO<sub>2</sub> in order to test the hypothesis that use of a lower SpO<sub>2</sub> range will result in an increase in survival of preterm infants without the occurrence of threshold retinopathy of prematurity [ROP] and/or the need for surgical intervention. However, the potential risk of a lower baseline SpO<sub>2</sub> range in increasing the incidence of episodic desaturation is unknown. In addition, prior studies in animal models have suggested that the neural effects of intermittent or episodic hypoxia may differ greatly than those of sustained hypoxia. Our previously approved secondary study represented a unique opportunity to acquire data to characterize the risk factors and consequences of episodic desaturation. Although we currently have 119 Infants in the high resolution cohort there are an additional 1316 infants enrolled in the SUPPORT trial in whom we may be able to extract additional desaturation data with low resolution. Although differences in monitor settings does not allow for combining the two infant cohorts, the larger sample size in the low resolution infant group may enable us to detect more subtle

associations between desaturation events and baseline saturation, ROP, mortality and detriments in neurodevelopmental outcome.



The low resolution group has a much larger sample size which increases the chances of finding a relationship between intermittent hypoxia and both morbidity and mortality. However, the low resolution of saturation data may limit the ability to accurately detect desaturation events in this cohort. Previous data (Ahmed) have suggested that application of a 16 sec averaging time window may result in an underestimation of short events (<30sec) and events of greater severity (<70%) and an overestimation of events of long duration (>300sec) when compared to application of a 2 sec averaging time window. If comparisons between low and high resolution groups reveal statistically significant differences in event detection parameters, interpretation of associations of desaturation events with baseline SaO<sub>2</sub> and morbidity may be limited to the infants in whom data were acquired with high resolution group (n=119). Due to the low incidence of infant mortality in the high resolution cohort we may not have the ability to assess the association between desaturation events and infant mortality.

If event parameters do not differ between low and high resolution groups the increased sample size of 1316 in the low resolution group may increase the ability to detect an association between these events and baseline SaO<sub>2</sub>, mortality, and neurodevelopmental outcome. Lastly, even if desaturation event detection is significantly compromised in the low resolution group, the low resolution may still be adequate to detect differences between the incidence of intermittent hypoxia and mortality/morbidity in this large infant cohort.

#### D. Methodologies:

##### Aim 1: Effect of data acquisition resolution and baseline SpO<sub>2</sub>

We request to be unblinded to the infant cohorts and have access to the saturation data corrected for the SUPPORT trial SpO<sub>2</sub> baseline randomization. None of the personnel involved in the saturation data analysis participate in developmental followup of the enrolled cohort and

thus cannot influence the outcome evaluations at CWRU, and thus are not a threat to the integrity of the main trial neurodevelopmental evaluations. To prevent inadvertent disclosure, all data files will be sequestered in the office of Ms. Juliann Di Fiore and will not be accessible to other members of the CWRU team. Further, data files will remain identified only by study number and not by the infant's name.

We will use currently developed software to document the occurrence, duration and magnitude of desaturation events  $\leq 80\%$  in the low resolution group. To comply with Nyquist sampling theorem limitations (2 x sample rate) and to distinguish intermittent hypoxia from prolonged changes in baseline SpO<sub>2</sub>, only events  $\geq 20$ sec and  $\leq 3$  min will be included in the analysis. Data will be analyzed for the first 8 weeks of life or shorter time periods for infants who completed the SUPPORT trial before 8 weeks post natal age. All desaturation events will be included regardless of the need for supplemental oxygen or ventilator support.

We will compare the occurrence, duration and magnitude of desaturation events for

1. Acquisition Resolution
  - a. High (2 sec average, 2 second sample rate) versus low (16 sec average and 10 sec sample rate) resolution in the low baseline SpO<sub>2</sub> infant groups
  - b. High versus low resolution in the high baseline SpO<sub>2</sub> infant groups
2. Baseline SpO<sub>2</sub>
  - a. Low versus High baseline SpO<sub>2</sub> in the low resolution group
  - b. Low versus High baseline SpO<sub>2</sub> in the high resolution group (previous secondary study)

#### Aim 2: Retinopathy of Prematurity

We will compare the incidence of desaturation events detected in Aim 1 between infants with and without severe retinopathy of prematurity (ROP). To minimize disparities in diagnosis of less severe forms of ROP, infants will be classified as 1) those requiring laser treatment for ROP or 2) those with either no ROP or ROP not severe enough to require laser therapy. The definitions used and reported in the SUPPORT main trial will be utilized for classifications of eye outcomes.

#### Aim 3: Neurodevelopmental Outcome

To analyze the correlation between the incidence of desaturation events and neurodevelopmental outcome we will include parameters acquired through the SUPPORT trial protocol including:

neurodevelopmental impairment at 18-22 months based on Bayley III using the accepted NRN definition

Death by discharge status  
BPD @36wks  
IVH  
PVL  
Cerebral palsy @ 18-22 months

#### Aim 4: Mortality

We will analyze the correlation between the incidence of desaturation events and mortality with and without the inclusion of baseline saturation randomization as a covariate.

#### Statistical Analyses

Statistical analyses will include a linear mixed model for repeated measures analysis to assess the time course of desaturation events for all infants and to identify the association between the number of events and ROP requiring laser treatment adjusting for baseline SpO<sub>2</sub> randomization group, gestational age, race, gender, and multiple births. Based on previous work [Di Fiore] the square root of the number of desaturation events will be used to better meet normality assumptions of the mixed model. A linear regression model will be used to assess the univariate relationship between continuous variables such as the number of desaturation events and mental and motor scores at 18-22 months. To compare the number of desaturation events between the low and high baseline SpO<sub>2</sub> groups, and mortality, we will use a two way ANOVA with repeated measures.

#### E. Discussion of Anticipated Results

We anticipate that a lower number of desaturation events will be detected in the low versus high resolution group. Previous work has suggested that the 16 second average time used in the SUPPORT trial may result in an underestimation of events <30 seconds and events of greater severity (<70%) and an overestimation of events of long duration (>300sec)[Ahmed]. This study will focus on desaturation events of ≤80% for ≥20 sec and ≤3min in duration. Thus, we do anticipate a significant difference between low and high resolutions due to events of greater severity or of long duration as proposed by Ahmed et al. However, the prolonged average time in the low resolution group may inhibit our ability to detect desaturation events between 20 and 30seconds in duration. We may have a further compromise in event detection due to the low sample rate of 10 seconds versus 2 seconds in the low and high resolution infant groups, respectively. Although a higher incidence of desaturation events has been shown to be associated with severe ROP [Di Fiore], it is currently unknown whether the characteristics of the desaturation event, in terms of duration and severity, are additional risk factors. Therefore, if short desaturation events are not as detrimental to the development of ROP, even with a compromise in detection of all desaturation events in the low resolution group we may still be able to detect differences in the number of events in the low and high baseline SpO<sub>2</sub> groups and in infants with and without severe ROP.

We speculate that if a higher incidence or desaturation events is found in the low baseline SpO<sub>2</sub> group, this will be associated with both infant mortality and lower neurodevelopmental outcome scores at 18-22 months of age.

If there is no difference in event detection in the high versus low resolution group, and no difference in the number of desaturation events between the low and high baseline SpO<sub>2</sub> infant groups we will conclude that keeping the infants in the low saturation target range does not put them at risk for episodic desaturation. If a difference in event detection is found between low and high resolution groups our conclusions between the low and high baseline saturation ranges will be limited by the ability to compare severe events and events of shorter duration.

#### F. Budget

##### Equipment:

We have previously acquired and analyzed desaturation data in 79 preterm infants with high resolution over a time period of comparable duration as the infants enrolled in the SUPPORT trial [Di Fiore]. Based on these infants, we estimate that the raw and processed data files for the 1316 SUPPORT trial infants will take approximately 400 gigabytes of storage space. For data safety/quality assurance concerns, we would like to purchase a password protected server dedicated to storage of this dataset. We estimate that the server with RAID 0 mirroring of the data will cost approximately \$1000. Only investigators working on this project will have access to the server. Additionally, we will maintain a backup of our datasets. Currently, a 1000 gigabyte hard drive costs \$200 through local computer stores. The server will be equipped with a writable DVD drive to maintain additional backups as needed. We currently use automated software to perform data backups once per week. Both the backup hard drive and DVDs will be stored in a locked cabinet in the locked office of Juliann Di Fiore and only she will have access to these backup devices. These files will be de-identified for patient confidentiality.

##### Salary Support and Project Duration:

Under Dr. Chris Wilson as PI, Juliann Di Fiore and Ryan Foglyano will currently be receiving grant funding to develop software to automate additional analyses of saturation data on the infants enrolled in the currently approved secondary study, INCIDENCE AND CONSEQUENCES OF EPISODIC DESATURATION IN PRETERM INFANTS ENROLLED IN THE NICHD NEONATAL NETWORK OXYGEN SATURATION [SUPPORT] STUDY. This infant cohort includes SUPPORT infants enrolled at the Cleveland and San Diego sites with high resolution, and 79 additional preterm infants at the Cleveland site that were not enrolled in the SUPPORT trial. The purpose of this grant is to develop a suite of linear and non-linear analysis algorithms to quantify patterns of intermittent hypoxia (IH), and to evaluate the relationship between IH patterns and severe ROP requiring laser surgery. The initial phase of this grant will require development of automated software code to identify desaturation events from the infant data files. Once developed, we plan to use this software for analysis of the additional 1197 SUPPORT trial infants.



Based on previous data analysis of desaturation events in 79 preterm infants with high resolution analyzed over a time period of comparable duration as the infants enrolled in the SUPPORT trial, we are currently able to analyze 5-7 infants per day. We anticipate an increase in the number of infants analyzed per day with automation of the software. Based on our previous experience and additional time needed for summary data analysis, we anticipate 10 months of time will be needed to complete this protocol.

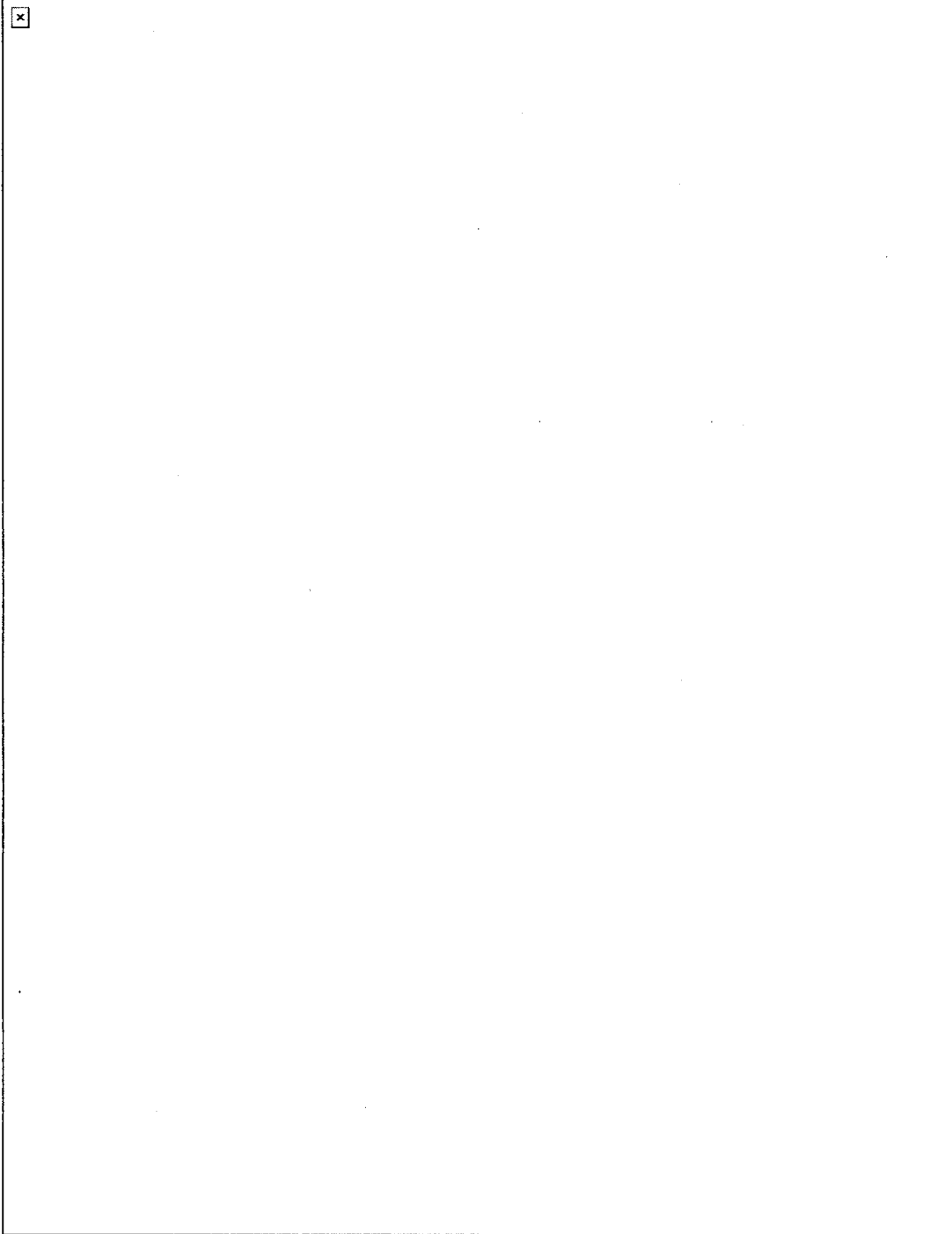
Salary support will include 50% for Juliann Di Fiore 33% for Ryan Foglyano and, as it is difficult to estimate, support for a biostatistician to be determined. (Table).

Travel:

We anticipate travel to RTI for statistical analysis (\$1500.00) and the steering committee meeting (\$1500.00) to present the results. (Table)

References:

1. Ahmed SJ, Rich W, Finer NN. The effect of averaging time on oximetry values in the premature infant. *Pediatrics* 2010:e115-e121.
2. Di Fiore JM, Bloom JN, Orge F, Schutt A, Schluchter M, Cheruvu VK, Walsh M, Finer N, Martin RJ. A higher incidence of intermittent hypoxemic episodes is associated with severe retinopathy of prematurity. *J of Peds* ( In press).



**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** FW: New England Journal of Medicine 09-11783.R1  
**Date:** Wednesday, February 17, 2010 1:45:00 PM  
**Attachments:** [copyright 83.pdf](#)  
[copyright -81.pdf](#)  
[Higgins-ICMJE-disclosure-83.pdf](#)  
[Higgins-ICMJE-disclosure-form-81.pdf](#)

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They have mine now.

Rose

-----Original Message-----

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Wednesday, February 17, 2010 1:45 PM  
**To:** 'babel@nejm.org'; (b) (6)  
**Subject:** RE: New England Journal of Medicine 09-11783.R1

Brendan

Here are my forms with the corrections and also the copyright forms for the two manuscripts.

Let me know if you need anything else.

Thanks  
Rose

-----Original Message-----

**From:** onbehalfof+babel+nejm.org@manuscriptcentral.com  
[mailto:onbehalfof+babel+nejm.org@manuscriptcentral.com] On Behalf Of babel@nejm.org  
**Sent:** Wednesday, February 17, 2010 12:42 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; (b) (6)  
**Subject:** New England Journal of Medicine 09-11783.R1

Re: 09-11783.R1 - Early CPAP versus Surfactant in Extremely Preterm Infants: The SUPPORT Trial

Dear Dr. Higgins:

Thank you for submitting your ICMJE disclosure forms for both manuscripts 09-11783 and 09-11781. There are just a few changes that need to be made for the form to be fully completed.

Please choose in Sec. 2 whether or not you received travel support for the submitted works.

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Please clarify the name of entity and clarify the nature of the "other" payments in Sec. 2.

That should do it. Please make these changes to each of the disclosure forms and email them back to me.

Thanks very much.

Sincerely,

Brendan Abel  
Editorial Assistant

New England Journal of Medicine  
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Contribution Number: 09-11783

Short Title or description of Contribution: Early CPAS vs Surfactant in Extremely Preterm Infants: SUPPORT Trial

Corresponding Author: Neil Finer

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Contribution Number: 09-11781

Short Title or description of Contribution: Oxygen Saturation Targets: SUPPORT Trial

Corresponding Author: Waldemar Carlo

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# ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

## ICMJE Uniform Disclosure Form for Potential Conflicts of Interest

### Section 1. Identifying Information.

Given Name:  
(or first)

Rosemary

Surname:  
(or last)

Higgins

Effective Date:

17-February-2010

Format example: 07-August-2008

Are you the corresponding author?  Yes  No

Corresponding author's name:

Neil Finer

Manuscript Title:

Early CPAP versus Surfactant in Extremely Preterm Infants: The SUPPORT Trial

Manuscript Identifying Number (if you know it):

09-11783

### Section 2. Information about the support of the work under consideration for publication.

Did you or your institution at any time receive payment or support in kind for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc...)?

No

Yes, specify nature of compensation

If you have more than one relationship, click "Add +" to add a row. Click "Del x" to delete an extra row.

Type	Money Paid to You*		Money to Your Institution		Name of Entity	Comments**	
	No	Yes	No	Yes			
Grant	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>			Del x
							Add +
Consulting fee or honorarium	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>			Del x
							Add +
Support for travel to meetings for the study or otherwise	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>			Del x
							Add +
Fees for participation in review activities such as data monitoring boards, statistical analysis, end point committees, and the like	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	As part of employment at NICHD		Del x
							Add +
Payment for writing or reviewing the manuscript	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	As part of employment at NICHD		Del x



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							Add +
Support in kind such as writing, provision of medicines or equipment, or administrative support	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	As part of employment support at NICHD		Del X
							Add +
Other	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>			Del X
							Add +

\*\*Use this section to provide any needed explanation

### Section 3. Information about relevant financial relationships outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with any entities that have an interest related to the submitted work. Use one line for each entity; add as many lines as you need. Use the comments column to indicate any additional information that you think a reader or editor would want to know about the compensation. Report relationships that were present during the 36 months prior to submission. In addition please disclose relationships that fall outside the 36-month window that readers may want to know about and could reasonably criticize you for not disclosing (for example, long-term financial relationships that are now ended).

If you have more than one relationship, click "Add +" to add a row. Click "Del X" to delete an extra row.

Type of Relationship (in alphabetical order)	No	Money Paid to You	Money to Your Institution	Entity	Comments	
Board membership	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del X
						Add +
Consultancy	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del X
						Add +
Employment	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	NICHD	Employee and Program Scientist	Del X
						Add +
Expert testimony	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del X
						Add +
Gifts	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del X
						Add +



# ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

## ICMJE Uniform Disclosure Form for Potential Conflicts of Interest

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Grants/grants pending	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del X
						Add +
Honoraria	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del X
						Add +
Payment for manuscript preparation	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del X
						Add +
Patents (planned, pending or issued)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del X
						Add +
Royalties	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del X
						Add +
Payment for development of educational presentations including service on speakers' bureaus	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del X
						Add +
Stock/stock options	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del X
						Add +
Travel/accommodations expenses covered or reimbursed	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del X
						Add +
Other (err on the side of full disclosure)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del X
						Add +

### Section 4. Information about financial relationships involving your spouse or partner or your children (under 18 years of age).

Do your children or your spouse or partner have financial relationships with entities that have an interest in the content of the submitted work?

- No other relationships/conditions/circumstances that present potential conflict of interest
- Yes, the following relationships/conditions/circumstances are present (explain below):



# ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

## ICMJE Uniform Disclosure Form for Potential Conflicts of Interest

### Section 5. Information about relevant nonfinancial associations.

Do you have any relevant nonfinancial associations or interests (personal, professional, political, institutional, religious, or other) that a reasonable reader would want to know about in relation to the submitted work?

- No relevant nonfinancial relationships/conditions/circumstances to report.
- Yes, the following relevant nonfinancial relationships/conditions/circumstances are present (explain below):

At the time of manuscript acceptance, journals will ask authors to confirm and, if necessary, update their disclosure statements. On occasion, journals may ask authors to disclose further information about reported relationships.

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# ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

## ICMJE Uniform Disclosure Form for Potential Conflicts of Interest

### INSTRUCTIONS:

The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. The form has five parts.

#### 1. Identifying information.

Each author should submit a separate form. Provide complete information and double-check the manuscript number. If you are NOT the corresponding author please insert his or her name.

#### 2. The work under consideration for publication.

Please provide information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The idea is to provide for the reader information about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. If you check the "No" box it means that you did the work without receiving any financial support from any third party -- that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds to pay you. If you or your institution did receive funds from a third party to support the work, check "Yes" along with the appropriate boxes to indicate the type of support and whether you or your institution received it.

#### 3. Relevant financial activities outside the submitted work.

Please report all sources of revenue relevant to the submitted work that accrued either directly to you or were paid to your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. If there is any question, it is usually better to disclose a relationship than not to do so. Please note that your interactions with the work's sponsor outside the submitted work should be listed here. For each category list each entity on a separate line. Use as many lines as necessary to provide complete information. In addition, please disclose relationships that fall outside the 36-month window that readers may want to know about and could reasonably criticize you for not disclosing (for example, long-term financial relationships that are now ended).

The goal of this section is to provide information for our reviewers and readers about your interactions with entities in the biomedical arena that could be perceived to influence, or that give the appearance of potentially influencing, what you wrote in the submitted work. You should disclose interactions with ANY entity that could be considered broadly relevant to the work. For example, if your article is about testing an epidermal growth factor receptor (EGFR) antagonist in lung cancer, you should report all associations with entities pursuing diagnostic or therapeutic strategies in cancer in general, not just in the area of EGFR or lung cancer. For grants you have received for work outside the submitted work, you should disclose support ONLY from entities that could be perceived to benefit financially from the published work, such as drug companies, or foundations supported by entities that could be perceived to have a financial stake in the outcome. Public funding sources, such as the NIH or the MRC, need not be disclosed. For example, if the NIH sponsored a piece of work you have been involved in but drugs were provided by a pharmaceutical company, you need only list the pharmaceutical company.

#### 4. Financial relationships involving your spouse or partner or your children (under 18 years of age).

If monies from the types of relationships listed in Section 3 were paid to your spouse or partner or dependent children, please list the type of activity and source of the money.

#### 5. Nonfinancial associations.

Please report any personal, professional, political, institutional, religious, or other associations that a reasonable reader would want to know about in relation to the submitted work.



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## ICMJE Uniform Disclosure Form for Potential Conflicts of Interest

### Section 1. Identifying Information.

Given Name:  Surname:  Effective Date:

Format example: 07-August-2008

Are you the corresponding author?  Yes  No

Corresponding author's name:

Manuscript Title:

Manuscript Identifying Number (if you know it):

### Section 2. Information about the support of the work under consideration for publication.

Did you or your institution at any time receive payment or support in kind for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc...)?

- No
- Yes, specify nature of compensation

If you have more than one relationship, click "Add +" to add a row. Click "Del x" to delete an extra row.

Type	Money Paid to You*		Money to Your Institution		Name of Entity	Comments**	
	No	Yes	No	Yes			
Grant	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>			Del x
							Add +
Consulting fee or honorarium	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>			Del x
							Add +
Support for travel to meetings for the study or otherwise	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>			Del x
							Add +
Fees for participation in review activities such as data monitoring boards, statistical analysis, end point committees, and the like	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	As part of employment at NICHD		Del x
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Support in kind such as writing, provision of medicines or equipment, or administrative support	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	As part of employment support at NICHD		Del X
Other	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>			Del X

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Employment	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	NICHD	Employee and Program Scientist	Del X
Expert testimony	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del X
Gifts	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del X



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						Add +
Honoraria	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del X
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Payment for manuscript preparation	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del X
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Patents (planned, pending or issued)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del X
						Add +
Royalties	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del X
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						Add +
Stock/stock options	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del X
						Add +
Travel/accommodations expenses covered or reimbursed	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del X
						Add +
Other (err on the side of full disclosure)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del X
						Add +

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- Yes, the following relevant nonfinancial relationships/conditions/circumstances are present (explain below):

At the time of manuscript acceptance, journals will ask authors to confirm and, if necessary, update their disclosure statements. On occasion, journals may ask authors to disclose further information about reported relationships.

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**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Walsh, Michele"  
**Subject:** RE: Breathing Outcomes - prelim data request  
**Date:** Wednesday, February 17, 2010 1:40:00 PM

---

Here is the timeline on Tim Steven's proposal

Concept 1/8/09  
Protocol submission 10/23/09  
Protocol review 11/16/09  
Revisions requested.

Originally, when Anna Maria's study came in, this was lined up, but you are correct, it has been slow to come into protocol review. If she wants to submit independent of Tim's, she can.

I also left a voicemail message.

Rose

---

**From:** Walsh, Michele [mailto:Michele.Walsh@UHhospitals.org]  
**Sent:** Wednesday, February 17, 2010 1:31 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Breathing Outcomes - prelim data request

Well I am confused bc we presented to SUPPORT subcommittee, Had their support as a secondary- but were told it was tied to Tim's.

Michele Walsh  
beeper (b) (6)  
Ph 216 844 3759

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Wednesday, February 17, 2010 1:25 PM  
**To:** Walsh, Michele  
**Subject:** RE: Breathing Outcomes - prelim data request

Do you want her to do a concept at the next meeting or perhaps on an SC call??

---

**From:** Walsh, Michele [mailto:Michele.Walsh@UHhospitals.org]  
**Sent:** Wednesday, February 17, 2010 1:23 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Breathing Outcomes - prelim data request

We had been told that it was a secondary  
But given the slow pace of Tim's it seems somewhat  
Unfair for it to be hostage.

Michele Walsh  
beeper (b) (6)  
Ph 216 844 3759

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Wednesday, February 17, 2010 10:31 AM  
**To:** Walsh, Michele  
**Subject:** RE: Breathing Outcomes - prelim data request

Not exactly sure – If she wants to follow all children in breathing outcomes for sleep disordered breathing, I guess it is a secondary study to this, unless she takes the lead and Tim's would be a secondary study

Rose

---

**From:** Walsh, Michele [mailto:Michele.Walsh@UHhospitals.org]  
**Sent:** Tuesday, February 16, 2010 5:04 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Breathing Outcomes - prelim data request

How does AM Hibbs proposal fit with this?  
Is it separate or integrated?

Michele Walsh  
beeper (b) (6)  
Ph 216 844 3759

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Tuesday, February 16, 2010 4:44 PM  
**To:** Finer, Neil; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Matthew Bizarro; Michelle Walsh; Mickey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOLDBERG; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; 'Zaterka-Baxter, Kristin'; Newman, Jamie  
**Subject:** Breathing Outcomes - prelim data request

Hi,  
Tim Stevens is preparing a revision to his school age breathing outcomes study protocol and would like the following information from the school age SUPPORT trial for the 6 and 12 month visits.

Pease let me know by February 23 if the data can be given at this time. Some of the infants have not yet completed the 12 month assessment.

Thanks  
Rose

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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:** Walsh, Michele  
**To:** Poindexter, Brenda B; Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; Luc.Brion@UTSouthwestern.edu; rohls@unm.edu; aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; ambal@uab.edu; Bradley.yoder@hsc.utah.edu; cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; Kristi Watterberg; kurt.schibler@cchmc.org; Matthew Bizzarro; Michelle Walsh; Mickey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOLdberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Newman, Jamie  
**Subject:** RE: Breathing Outcomes - prelim data request  
**Date:** Wednesday, February 17, 2010 1:25:03 PM

---

I agree: no unblended analysis.

Michele Walsh  
beeper (b) (6)  
Ph 216 844 3759

---

**From:** Poindexter, Brenda B [mailto:bpoindex@iupui.edu]  
**Sent:** Wednesday, February 17, 2010 10:11 AM  
**To:** 'Wally Carlo, M.D.'; Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; Luc.Brion@UTSouthwestern.edu; rohls@unm.edu; aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; ambal@uab.edu; Bradley.yoder@hsc.utah.edu; cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; Kristi Watterberg; kurt.schibler@cchmc.org; Matthew Bizzarro; Michelle Walsh; Mickey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOLdberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Newman, Jamie  
**Subject:** RE: Breathing Outcomes - prelim data request

I agree with Wally – if he needs data analyzed by treatment group (which it sounds like he would) then I think the answer should be no until all data collection is complete.

Brenda

---

**From:** Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]  
**Sent:** Wednesday, February 17, 2010 10:06 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; Luc.Brion@UTSouthwestern.edu; rohls@unm.edu; aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; ambal@uab.edu; Bradley.yoder@hsc.utah.edu; Poindexter, Brenda B; cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; Kristi Watterberg; kurt.schibler@cchmc.org; Matthew Bizzarro; Michelle Walsh; Mickey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOLdberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Newman, Jamie  
**Subject:** RE: Breathing Outcomes - prelim data request

I would think that some unmasked data evaluation not analyzed by treatment group may be ok. Any analysis by treatment group should wait until the data collection are completed.

Wally

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Wed 2/17/2010 9:02 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; 'Finer, Neil'; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; 'Abhik Das'; alaptook@WIHRI.org; Ambal (ambal@uab.edu);

Brad Yoder (Bradley.yoder@hsc.utah.edu); 'Brenda Poindexter'; Wally Carlo, M.D.; cotte010@mc.duke.edu; 'Dennis Wallace'; 'Ed Bell'; 'Ed Donovan'; 'Ehrenkranz Richard (E-mail)'; Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; 'Kristi Watterberg'; Kurt Schibler [kurt.schibler@cchmc.org]; 'Matthew Bizzarro'; 'Michelle Walsh'; 'MIckey Caplan'; 'Oh William (E-mail)'; 'Pablo Sanchez'; 'Poole Kenneth (E-mail)'; 'Roger Faix'; 'Ronald GOLdberg'; 'Seetha Shankaran'; 'Stevenson David (E-mail)'; 'Stoll Barbara (E-mail)'; 'Tyson Jon (E-mail)'; VanMeurs, Krisa  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; 'Zaterka-Baxter, Kristin'; 'Newman, Jamie'  
**Subject:** RE: Breathing Outcomes - prelim data request

Tim had sent the following as a basis for his request:

**One of the criticisms of the School Age Breathing Outcomes Proposal is the lack of preliminary data from Breathing Outcomes that supports longer term follow up. To address this concern Richard and I thought it would be helpful to have preliminary analyses of a few questions from Breathing Outcomes.**

The concept was approved by the steering committee and the protocol has been reviewed by protocol review subcommittee with a request for revisions. The data requested is to provide support for longer term FU (at school age). I hope this clarifies the subject.

Thanks  
Rose

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Tuesday, February 16, 2010 4:44 PM  
**To:** Finer, Neil; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Matthew Bizzarro; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOLdberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; 'Zaterka-Baxter, Kristin'; Newman, Jamie  
**Subject:** Breathing Outcomes - prelim data request

Hi,  
Tim Stevens is preparing a revision to his school age breathing outcomes study protocol and would like the following information from the school age SUPPORT trial for the 6 and 12 month visits.

Pease let me know by February 23 if the data can be given at this time. Some of the infants have not yet completed the 12 month assessment.

Thanks  
Rose

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**From:** Kurt Schibler  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** Re: Breathing Outcomes - prelim data request  
**Date:** Wednesday, February 17, 2010 12:51:48 PM

---

Hi Rose,  
I think it is premature to give out this information.  
ion. I vote no.  
Thanks,  
Kurt

>>> "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> 2/16/2010 4:43 PM >>>

Hi,  
Tim Stevens is preparing a revision to his school age breathing outcomes study protocol and would like the following information from the school age SUPPORT trial for the 6 and 12 month visits.

Please let me know by February 23 if the data can be given at this time. Some of the infants have not yet completed the 12 month assessment.

Thanks  
Rose



**From:** [onbehalfof+babel+nejm.org@manuscriptcentral.com](mailto:onbehalfof+babel+nejm.org@manuscriptcentral.com) on behalf of [babel@nejm.org](mailto:babel@nejm.org)  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; (b) (6)  
**Subject:** New England Journal of Medicine 09-11783.R1  
**Date:** Wednesday, February 17, 2010 12:41:56 PM  
**Attachments:** [Higgins-ICMJE-disclosure-form-81.pdf](#)  
[Higgins-ICMJE-disclosure-83.pdf](#)

---

Re: 09-11783.R1 - Early CPAP versus Surfactant in Extremely Preterm Infants: The SUPPORT Trial

Dear Dr. Higgins:

Thank you for submitting your ICMJE disclosure forms for both manuscripts 09-11783 and 09-11781. There are just a few changes that need to be made for the form to be fully completed.

Please choose in Sec. 2 whether or not you received travel support for the submitted works.

Please choose in Sec. 2 whether or not your institution received payment for writing or reviewing the submitted work.

Please clarify the name of entity and clarify the nature of the "other" payments in Sec. 2.

That should do it. Please make these changes to each of the disclosure forms and email them back to me.

Thanks very much.

Sincerely,

Brendan Abel  
Editorial Assistant  
New England Journal of Medicine  
(617) 487-6584



# ICMJE

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## INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

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Each author should submit a separate form. Provide complete information and double-check the manuscript number. If you are NOT the corresponding author please insert his or her name.

#### **2. The work under consideration for publication.**

Please provide information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The idea is to provide for the reader information about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. If you check the "No" box it means that you did the work without receiving any financial support from any third party -- that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds to pay you. If you or your institution did receive funds from a third party to support the work, check "Yes" along with the appropriate boxes to indicate the type of support and whether you or your institution received it.

#### **3. Relevant financial activities outside the submitted work.**

Please report all sources of revenue relevant to the submitted work that accrued either directly to you or were paid to your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. If there is any question, it is usually better to disclose a relationship than not to do so. Please note that your interactions with the work's sponsor outside the submitted work should be listed here. For each category list each entity on a separate line. Use as many lines as necessary to provide complete information. In addition, please disclose relationships that fall outside the 36-month window that readers may want to know about and could reasonably criticize you for not disclosing (for example, long-term financial relationships that are now ended).

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#### **4. Financial relationships involving your spouse or partner or your children (under 18 years of age).**

If monies from the types of relationships listed in Section 3 were paid to your spouse or partner or dependent children, please list the type of activity and source of the money.

#### **5. Nonfinancial associations.**

Please report any personal, professional, political, institutional, religious, or other associations that a reasonable reader would want to know about in relation to the submitted work.



# ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

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### Section 1. Identifying Information.

Given Name:  Surname:  Effective Date:   
 (or first) (or last) Format example: 07-August-2008

Are you the corresponding author?  Yes  No

Corresponding author's name:

Manuscript Title:

Manuscript Identifying Number (if you know it):

### Section 2. Information about the support of the work under consideration for publication.

Did you or your institution at any time receive payment or support in kind for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc...)?

- No  
 Yes, specify nature of compensation

If you have more than one relationship, click "Add +" to add a row. Click "Del x" to delete an extra row.

Type	Money Paid to You*		Money to Your Institution		Name of Entity	Comments**	
	No	Yes	No	Yes			
Grant	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>			Del x
Consulting fee or honorarium	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>			Del x
Support for travel to meetings for the study or otherwise	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>			Del x
Fees for participation in review activities such as data monitoring boards, statistical analysis, end point committees, and the like	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	As part of employment at NICHD		Del x
Payment for writing or reviewing the manuscript	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	As part of employment at NICHD		Del x



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Type	Money Paid to You*		Money to Your Institution		Name of Entity	Comments**	
Support in kind such as writing, provision of medicines or equipment, or administrative support	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	As part of employment support at NICHD		Del X
Other	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>			Del X
							Add +

\*\*Use this section to provide any needed explanation

### Section 3. Information about relevant financial relationships outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with any entities that have an interest related to the submitted work. Use one line for each entity; add as many lines as you need. Use the comments column to indicate any additional information that you think a reader or editor would want to know about the compensation. Report relationships that were present during the 36 months prior to submission. In addition please disclose relationships that fall outside the 36-month window that readers may want to know about and could reasonably criticize you for not disclosing (for example, long-term financial relationships that are now ended).

If you have more than one relationship, click "Add +" to add a row. Click "Del x" to delete an extra row.

Type of Relationship (in alphabetical order)	No	Money Paid to You	Money to Your Institution	Entity	Comments	
Board membership	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del X
Consultancy	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del X
Employment	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	NICHD	Employee and Program Scientist	Del X
Expert testimony	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del X
Gifts	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del X
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Grants/grants pending	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
Honoraria	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
Payment for manuscript preparation	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
Patents (planned, pending or issued)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
Royalties	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
Payment for development of educational presentations including service on speakers' bureaus	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
Stock/stock options	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
Travel/accommodations expenses covered or reimbursed	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
Other (err on the side of full disclosure)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		

### Section 4. Information about financial relationships involving your spouse or partner or your children (under 18 years of age).

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Do you have any relevant nonfinancial associations or interests (personal, professional, political, institutional, religious, or other) that a reasonable reader would want to know about in relation to the submitted work?

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### Section 1. Identifying Information.

Given Name:  
(or first)

Rosemary

Surname:  
(or last)

Higgins

Effective Date:

17-February-2010

Format example: 07-August-2008

Are you the corresponding author?  Yes  No

Corresponding author's name:

Neil Finer

Manuscript Title:

Early CPAP versus Surfactant in Extremely Preterm Infants: The SUPPORT Trial

Manuscript Identifying Number (if you know it):

09-11783

### Section 2. Information about the support of the work under consideration for publication.

Did you or your institution at any time receive payment or support in kind for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc...)?

No

Yes, specify nature of compensation

If you have more than one relationship, click "Add +" to add a row. Click "Del x" to delete an extra row.

Type	Money Paid to You*		Money to Your Institution		Name of Entity	Comments**	
	No	Yes	No	Yes			
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Consulting fee or honorarium	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>			Del x
Support for travel to meetings for the study or otherwise	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>			Del x
Fees for participation in review activities such as data monitoring boards, statistical analysis, end point committees, and the like	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	As part of employment at NICHD		Del x
Payment for writing or reviewing the manuscript	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	As part of employment at NICHD		Del x





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Expert testimony	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del X
Gifts	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			Del X
						Add +



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Patents (planned, pending or issued)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
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Travel/accommodations expenses covered or reimbursed	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
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**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** FW: Breathing Outcomes - prelim data request  
**Date:** Wednesday, February 17, 2010 12:35:00 PM

---

**From:** Bell, Edward [mailto:edward-bell@uiowa.edu]  
**Sent:** Wednesday, February 17, 2010 10:26 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Breathing Outcomes - prelim data request

If it's to go outside the Network, Wally has a point - the premature unblinding of outcome data may be inappropriate. So probably no, but I'll follow the unfolding discussion.

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Wednesday, February 17, 2010 9:20 AM  
**To:** Bell, Edward  
**Subject:** RE: Breathing Outcomes - prelim data request

This is for the protocol revision and possible application for funds from another institute

---

**From:** Bell, Edward [mailto:edward-bell@uiowa.edu]  
**Sent:** Wednesday, February 17, 2010 10:05 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Breathing Outcomes - prelim data request

If I understand correctly, that the request is just for internal Network use of the data, Iowa votes YES.

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Wednesday, February 17, 2010 9:02 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; 'Finer, Neil'; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; 'Abhik Das'; alaptook@WIHL.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); 'Brenda Poindexter'; 'Carlo Waldemar (E-mail)'; cotte010@mc.duke.edu; 'Dennis Wallace'; Bell, Edward; 'Ed Donovan'; 'Ehrenkranz Richard (E-mail)'; Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; 'Kristi Watterberg'; Kurt Schibler [kurt.schibler@cchmc.org]; 'Matthew Bizzarro'; 'Michelle Walsh'; 'Mickey Caplan'; 'Oh William (E-mail)'; 'Pablo Sanchez'; 'Poole Kenneth (E-mail)'; 'Roger Faix'; 'Ronald Goldberg'; 'Seetha Shankaran'; 'Stevenson David (E-mail)'; 'Stoll Barbara (E-mail)'; 'Tyson Jon (E-mail)'; VanMeurs, Krisa  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; 'Zaterka-Baxter, Kristin'; 'Newman, Jamie'  
**Subject:** RE: Breathing Outcomes - prelim data request

Tim had sent the following as a basis for his request:

**One of the criticisms of the School Age Breathing Outcomes Proposal is the lack of preliminary data from Breathing Outcomes that supports longer term follow up. To address this concern Richard and I thought it would be helpful to have preliminary analyses of a few questions from**

## **Breathing Outcomes.**

The concept was approved by the steering committee and the protocol has been reviewed by protocol review subcommittee with a request for revisions. The data requested is to provide support for longer term FU (at school age).

I hope this clarifies the subject.

Thanks

Rose

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]

**Sent:** Tuesday, February 16, 2010 4:44 PM

**To:** Finer, Neil; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Matthew Bizzarro; Michelle Walsh; Mickey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald Goldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa

**Cc:** Archer, Stephanie (NIH/NICHD) [E]; 'Zaterka-Baxter, Kristin'; Newman, Jamie

**Subject:** Breathing Outcomes - prelim data request

Hi,

Tim Stevens is preparing a revision to his school age breathing outcomes study protocol and would like the following information from the school age SUPPORT trial for the 6 and 12 month visits.

Pease let me know by February 23 if the data can be given at this time. Some of the infants have not yet completed the 12 month assessment.

Thanks

Rose

**From:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](mailto:Higgins.Rosemary@NIH.NICHD)  
**To:** [Archer, Stephanie \(NIH/NICHD\) \[E\]](mailto:Archer.Stephanie@NIH.NICHD)  
**Subject:** FW: Breathing Outcomes - prelim data request  
**Date:** Wednesday, February 17, 2010 12:20:00 PM

---

**From:** Laptook, Abbot [<mailto:ALaptook@WIHRI.org>]  
**Sent:** Wednesday, February 17, 2010 12:16 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** FW: Breathing Outcomes - prelim data request

I would agree with Wally. AL

---

**From:** Poindexter, Brenda B [<mailto:bpoindex@iupui.edu>]  
**Sent:** Wednesday, February 17, 2010 10:11 AM  
**To:** 'Wally Carlo, M.D.'; Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; Luc.Brion@UTSouthwestern.edu; rohls@unm.edu; aaf2@po.cwru.edu; Abhik Das; Laptook, Abbot; ambal@uab.edu; Bradley.yoder@hsc.utah.edu; cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; Kristi Watterberg; kurt.schibler@cchmc.org; Matthew Bizzarro; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOLdberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Newman, Jamie  
**Subject:** RE: Breathing Outcomes - prelim data request

I agree with Wally – if he needs data analyzed by treatment group (which it sounds like he would) then I think the answer should be no until all data collection is complete.

Brenda

---

**From:** Wally Carlo, M.D. [<mailto:WCarlo@peds.uab.edu>]  
**Sent:** Wednesday, February 17, 2010 10:06 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; Luc.Brion@UTSouthwestern.edu; rohls@unm.edu; aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; ambal@uab.edu; Bradley.yoder@hsc.utah.edu; Poindexter, Brenda B; cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); ifrantz@tuftsmedicalcenter.org; Kennedy, Kathleen A; Kristi Watterberg; kurt.schibler@cchmc.org; Matthew Bizzarro; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOLdberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin; Newman, Jamie  
**Subject:** RE: Breathing Outcomes - prelim data request

I would think that some unmasked data evaluation not analyzed by treatment group may be ok. Any analysis by treatment group should wait until the data collection are completed.

Wally

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [<mailto:higginsr@mail.nih.gov>]  
**Sent:** Wed 2/17/2010 9:02 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; 'Finer, Neil'; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; 'Abhik Das'; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); 'Brenda Poindexter'; Wally Carlo, M.D.;

cotte010@mc.duke.edu; 'Dennis Wallace'; 'Ed Bell'; 'Ed Donovan'; 'Ehrenkranz Richard (E-mail)'; Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; 'Kristi Watterberg'; Kurt Schibler [kurt.schibler@cchmc.org]; 'Matthew Bizarro'; 'Michelle Walsh'; 'Mickey Caplan'; 'Oh William (E-mail)'; 'Pablo Sanchez'; 'Poole Kenneth (E-mail)'; 'Roger Faix'; 'Ronald Goldberg'; 'Seetha Shankaran'; 'Stevenson David (E-mail)'; 'Stoll Barbara (E-mail)'; 'Tyson Jon (E-mail)'; VanMeurs, Krisa  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; 'Zaterka-Baxter, Kristin'; 'Newman, Jamie'  
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Tim had sent the following as a basis for his request:

**One of the criticisms of the School Age Breathing Outcomes Proposal is the lack of preliminary data from Breathing Outcomes that supports longer term follow up. To address this concern Richard and I thought it would be helpful to have preliminary analyses of a few questions from Breathing Outcomes.**

The concept was approved by the steering committee and the protocol has been reviewed by protocol review subcommittee with a request for revisions. The data requested is to provide support for longer term FU (at school age). I hope this clarifies the subject.

Thanks  
Rose

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Tuesday, February 16, 2010 4:44 PM  
**To:** Finer, Neil; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Matthew Bizarro; Michelle Walsh; Mickey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald Goldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; 'Zaterka-Baxter, Kristin'; Newman, Jamie  
**Subject:** Breathing Outcomes - prelim data request

Hi,  
Tim Stevens is preparing a revision to his school age breathing outcomes study protocol and would like the following information from the school age SUPPORT trial for the 6 and 12 month visits.

Pease let me know by February 23 if the data can be given at this time. Some of the infants have not yet completed the 12 month assessment.

Thanks  
Rose

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**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** FW: Breathing Outcomes - prelim data request  
**Date:** Wednesday, February 17, 2010 11:32:00 AM

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**From:** Shankaran, Seetha [mailto:sshankar@med.wayne.edu]  
**Sent:** Wednesday, February 17, 2010 11:18 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Bara, Rebecca; Pappas, Athina  
**Subject:** RE: Breathing Outcomes - prelim data request

Rose

So, I don't have a problem with the request---this is an internal look into data for development of concept already approved,

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:** Wednesday, February 17, 2010 11:11 AM  
**To:** Shankaran, Seetha  
**Subject:** RE: Breathing Outcomes - prelim data request

It is from breathing outcomes to develop the school age follow up

Thanks  
Rose

---

**From:** Shankaran, Seetha [mailto:sshankar@med.wayne.edu]  
**Sent:** Wednesday, February 17, 2010 11:06 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** FW: Breathing Outcomes - prelim data request

Rose

Maybe I misread and responded this morning---please can you see Becky's response below  
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:** Bara, Rebecca  
**Sent:** Tuesday, February 16, 2010 5:20 PM  
**To:** Shankaran, Seetha; Pappas, Athina  
**Subject:** RE: Breathing Outcomes - prelim data request

Hi Seetha,

The attachment is highlighting some of the questions asked on both the 6mo and 12mo Breathing Outcomes Interview data collection forms. Am confused about Rose's email reference to "the following information from the school age SUPPORT trial".

At our center the great majority of our kids have had the 6mo and 12mo interviews completed and keyed, and also with a majority having completed all the interviews (baseline, 6mo, 12mo, and 18mo).

Becky

---

**From:** Shankaran, Seetha  
**Sent:** Tuesday, February 16, 2010 5:03 PM  
**To:** Pappas, Athina; Bara, Rebecca  
**Subject:** FW: Breathing Outcomes - prelim data request

Athina, Becky  
Let me know  
Thanks  
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:** Tuesday, February 16, 2010 4:44 PM  
**To:** Finer, Neil; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptok@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Matthew Bizzarro; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOLdberg; Shankaran, Seetha; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; 'Zaterka-Baxter, Kristin'; Newman, Jamie  
**Subject:** Breathing Outcomes - prelim data request

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Thanks  
Rose

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** FW: Breathing Outcomes - prelim data request  
**Date:** Wednesday, February 17, 2010 11:04:00 AM

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---

**From:** Shankaran, Seetha [mailto:sshankar@med.wayne.edu]  
**Sent:** Wednesday, February 17, 2010 10:56 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Breathing Outcomes - prelim data request

Rose  
I am OK with this  
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

---

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**Sent:** Wednesday, February 17, 2010 10:02 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; 'Finer, Neil'; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; 'Abhik Das'; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); 'Brenda Poindexter'; 'Carlo Waldemar (E-mail)'; cotte010@mc.duke.edu; 'Dennis Wallace'; 'Ed Bell'; 'Ed Donovan'; 'Ehrenkranz Richard (E-mail)'; Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; 'Kristi Watterberg'; Kurt Schibler [kurt.schibler@ccchmc.org]; 'Matthew Bizzarro'; 'Michelle Walsh'; 'Mickey Caplan'; 'Oh William (E-mail)'; 'Pablo Sanchez'; 'Poole Kenneth (E-mail)'; 'Roger Faix'; 'Ronald GOLdberg'; Shankaran, Seetha; 'Stevenson David (E-mail)'; 'Stoll Barbara (E-mail)'; 'Tyson Jon (E-mail)'; VanMeurs, Krisa  
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I hope this clarifies the subject.

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Rose

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Tuesday, February 16, 2010 4:44 PM  
**To:** Finer, Neil; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Matthew Bizzarro; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOLDBERG; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa  
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Thanks  
Rose

## Higgins, Rosemary (NIH/NICHD) [E]

---

**From:** Finer, Neil <nfiner@ucsd.edu>  
**Sent:** Tuesday, February 16, 2010 6:13 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Matthew Bizzarro; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOLDBERG; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; 'Zaterka-Baxter, Kristin'; Newman, Jamie  
**Subject:** RE: Breathing Outcomes - prelim data request

Hi Rose

I would not give the data to Tim as his outcomes are all at 18-22 months. There would be no rational in seeing these as we are still collecting the data. I could not see any outcomes that were before this window. Does he want blinded data?? Perhaps I have missed the point of his question.

Can you further clarify what he wants to do with the data??

Thanks

Neil

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Tuesday, February 16, 2010 1:44 PM  
**To:** Finer, Neil; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Matthew Bizzarro; Michelle Walsh; MIckey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOLDBERG; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa  
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Thanks

Rose

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** Fw: Breathing Outcomes - prelim data request  
**Date:** Tuesday, February 16, 2010 6:00:57 PM

---

**From:** Kennedy, Kathleen A <Kathleen.A.Kennedy@uth.tmc.edu>  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Tue Feb 16 17:33:26 2010  
**Subject:** RE: Breathing Outcomes - prelim data request

Yes.

Kathleen A. Kennedy, MD, MPH  
Richard W. Mithoff Professor of Pediatrics  
Director, Division of Neonatal-Perinatal Medicine  
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, February 16, 2010 3:44 PM  
**To:** Finer, Neil; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Carlo Waldemar (E-mail); cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Matthew Bizzarro; Michelle Walsh; Mickey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald Goldberg; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson, Jon E; VanMeurs, Krisa  
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Rose

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**To:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** Fw: Breathing Outcomes - prelim data request  
**Date:** Tuesday, February 16, 2010 6:00:33 PM

---

**From:** Wally Carlo, M.D. <WCarlo@peds.uab.edu>  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Tue Feb 16 17:45:51 2010  
**Subject:** RE: Breathing Outcomes - prelim data request

OK

Wally Carlo, M.D.  
Edwin M. Dixon Professor of Pediatrics  
University of Alabama at Birmingham  
Director, Division of Neonatology  
Director, Newborn Nurseries  
619 South 20th Street  
525 New Hillman Building  
Birmingham, AL 35233-7335  
Phone: 205 934 4680  
FAX: 205 934 3100  
Cell: 205 266 (b)

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Tuesday, February 16, 2010 3:44 PM  
**To:** Finer, Neil; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; Abhik Das; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); Brenda Poindexter; Wally Carlo, M.D.; cotte010@mc.duke.edu; Dennis Wallace; Ed Bell; Ed Donovan; Ehrenkranz Richard (E-mail); Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; Kristi Watterberg; Kurt Schibler [kurt.schibler@cchmc.org]; Matthew Bizzarro; Michelle Walsh; Mickey Caplan; Oh William (E-mail); Pablo Sanchez; Poole Kenneth (E-mail); Roger Faix; Ronald GOLDBERG; Seetha Shankaran; Stevenson David (E-mail); Stoll Barbara (E-mail); Tyson Jon (E-mail); VanMeurs, Krisa  
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**Subject:** Breathing Outcomes - prelim data request

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Rose



**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** Fw: Breathing Outcomes - prelim data request  
**Date:** Tuesday, February 16, 2010 6:00:19 PM

---

**From:** Kristi Watterberg <KWatterberg@salud.unm.edu>  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Tue Feb 16 17:46:27 2010  
**Subject:** Re: Breathing Outcomes - prelim data request

to be used for study design? then yes - Kristi

>>> "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> 2/16/2010 2:43 PM >>>

Hi,

Tim Stevens is preparing a revision to his school age breathing outcomes study protocol and would like the following information from the school age SUPPORT trial for the 6 and 12 month visits.

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Thanks  
Rose

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "dale\_phelps@umc.rochester.edu"; "Finer, Neil"; "O'Shea, Michael"; "Duara, Shahnaz"; "wrich@ucsd.edu"; "nxs5@cwru.edu"; "anthony\_piazza@oz.ned.emory.edu"; "Brenda Morris"; "nirupama\_laroja@umc.rochester.edu"; "vivek.narendran@cchmc.org"; "bsood@med.wayne.edu"; (Luc.Brion@UTSouthwestern.edu); (rohls@unm.edu); aaf2@po.cwru.edu; "Abhik Das"; alaptook@WIHRI.org; Ambal (ambal@uab.edu); Brad Yoder (Bradley.yoder@hsc.utah.edu); "Brenda Poindexter"; "Carlo Waldemar (E-mail)"; cotte010@mc.duke.edu; "Dennis Wallace"; "Ed Bell"; "Ed Donovan"; "Ehrenkranz Richard (E-mail)"; Ivan Frantz (ifrantz@tuftsmedicalcenter.org); Kennedy, Kathleen A; "Kristi Watterberg"; Kurt Schibler (kurt.schibler@cchmc.org); "Matthew Bizzarro"; "Michelle Walsh"; "Mickey Caplan"; "Oh William (E-mail)"; "Pablo Sanchez"; "Poole Kenneth (E-mail)"; "Roger Faix"; "Ronald Goldberg"; "Seetha Shankaran"; "Stevenson David (E-mail)"; "Stoll Barbara (E-mail)"; "Tyson Jon (E-mail)"; VanMeurs, Krisa  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; "Cunningham, Meg"; "Zaterka-Baxter, Kristin"  
**Subject:** CONFIDENTIAL: SUPPORT OXIMETRY PAPER  
**Date:** Friday, February 12, 2010 5:08:00 PM  
**Attachments:** SUPPORT O2 11 10 TRACKED FINAL NEJM MASTER!!!.doc  
O2 Sats NEJM Response 2 10 10.doc  
**Importance:** High

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Hello,  
Attached is the resubmission of the CPAP Oximetry paper.

We have allocated time on the upcoming Steering Committee PI call on 2/23 at 3 PM for discussion.

Thanks to everyone for all their effort!!!

The CPAP paper was sent in a separate email.

Rose

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network



February 12, 2010

Caren G. Solomon, M.D.  
Michael F. Greene, M.D.  
New England Journal of Medicine  
10 Shattuck Street  
Boston, MA 02115

RE: 09-11781 - The SUPPORT Trial: Randomized Trial of Oxygen Saturation Targets in Extremely Premature Infants

Dear Drs. Solomon and Greene:

Enclosed is a revised version of the manuscript that addresses the editors' and reviewers' comments. A point-by-point response is provided below.

We have addressed the concerns raised by the statistical reviewer regarding (b) (4)

(b) (4)

. Due to word limitations for the Journal, we prefer not to include the list in the Methods as all pre-specified outcomes are listed in the tables independent of the statistical analysis (as we are near the word limit, unless additional space can be granted).

The Copyright Transfer Agreement and Universal Disclosure forms are being completed by each author.

I have prepared the "Disclosure" following your instructions and samples of recent *New England Journal of Medicine* publications as follows:

The SUPPORT Trial: Randomized Trial of Oxygen Saturation Targets in Extremely Premature Infants is a product of The SUPPORT Trial and was funded thru NIH grant numbers listed in the acknowledgements section. The concepts and goals of The SUPPORT Trial were established by the SUPPORT Trial Subcommittee of the NICHD Neonatal Research Network who designed the trial. Data for the trial were gathered from multiple centers by research staff listed in the

1

acknowledgements. The data were compiled and analyzed by RTI, the data coordinating center for the NICHD Neonatal Research Network (NRN). The Principal Investigators for The SUPPORT Trial are Neil Finer and me. Drs. Marie Gantz and Ahbik Das performed the analysis of the data gathered at the 20 participating sites for the trial and vouch for its veracity and accuracy. I wrote the first draft of this paper and received comments and suggestions from the SUPPORT Subcommittee members of the NICHD NRN. Writing assistance was not provided. The manuscript was approved by the Neonatal Research Network Steering Committee members who collectively decided to publish the paper. We did not have industry sponsors. There are agreements in place concerning confidentiality of the data. Neither I nor any of the authors have anything relevant to disclose, and I have indicated this in the acknowledgement section.

The Massimo Company provided the altered pulse oximeters at the usual oximeter cost, but did not sponsor the trial or have any other role in it.

The manuscript includes a full, accurate, and up-to-date report of adverse events.

The article nor any part has been published or will be submitted elsewhere before appearing in the *New England Journal of Medicine*.

We have a related manuscript on the antenatal consent process that is accepted with revisions in *Pediatrics*. This manuscript does not contain results of the trial. We do not have other manuscripts by me or the co-authors addressing similar or related research questions in preparation or under consideration at other journals. Secondary studies on growth, neuro-imaging, and neurodevelopmental follow up at 18-22 months corrected age are underway.

Sincerely,

Wally Carlo, M.D.  
Edwin M. Dixon Professor of Pediatrics  
University of Alabama at Birmingham  
PI for the Oxygen Saturation Trial of the SUPPORT Trial

Enclosure: American Academy of Pediatrics Policy Statement. Age terminology during the perinatal period. *Pediatrics* 2004; 114:1362-1364.

<b>Division of Neonatology</b>	The University of
525 New Hillman Building	Alabama at Birmingham
620 South 20 <sup>th</sup> Street	Mailing Address:
205.934.4680	525 NHB
Fax 205.934.3100	619 South 19 <sup>th</sup> Street
www.chsys.org • www.peds.uab.edu	Birmingham, AL 35249-7335



(b) (4)

This is now clarified in the Methods section.

(b) (4)

were submitted originally and appear at the website.

(b) (4)

(b) (4)

as per the American Academy of Pediatrics Policy Statement enclosed (b) (4).

(b) (4)

The sentence has been rewritten.

(b) (4)

(b) (4)

Reviewer: 2

**Comments for the Author**

**1. General Comments:**

(b) (4)

Thanks

(b) (4)

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**2. Specific Comments:**

**Abstract:** (b) (4)

Thanks

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Thanks. (b) (4)

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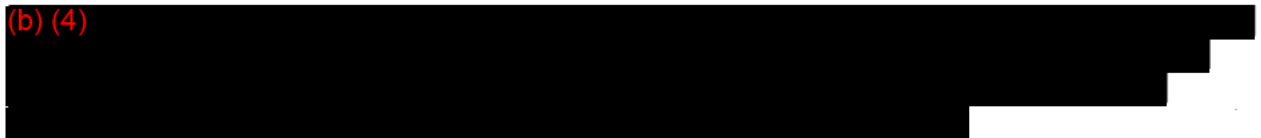


**Discussion:**

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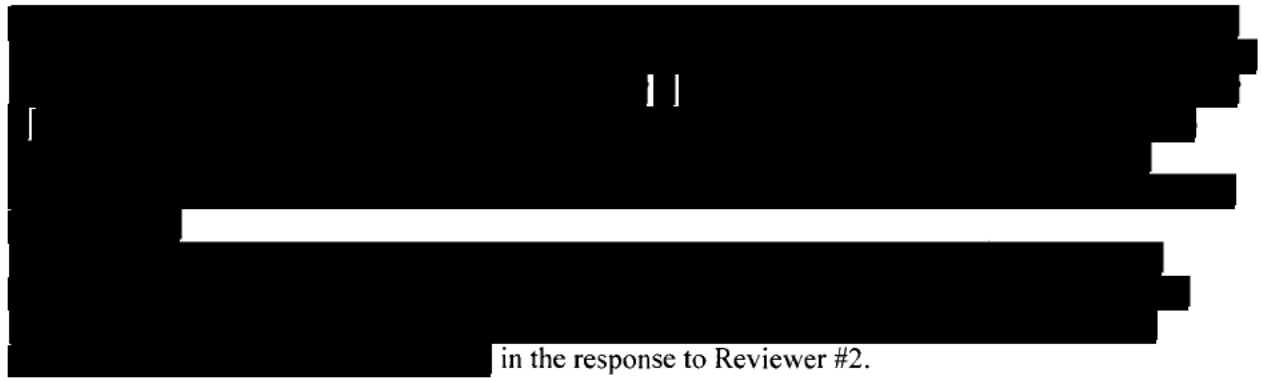
Statistical Reviewer: 1

**Comments for the Author:**

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in the response to Reviewer #2.

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ADDITIONAL COMMENTS OF THE EDITORS

**Title should be shortened to no more than 75 characters.**

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[Redacted]

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "nxs5@cwru.edu"  
**Subject:** FW: CONFIDENTIAL:CPAP SUPPORT PAPER RESUBMISSION  
**Date:** Friday, February 12, 2010 5:07:00 PM  
**Attachments:** [NEJM Letter to EditorRevision Feb 11 2010.pdf](#)  
[NEJM Tables and Figure Feb 9Final.pdf](#)  
[SUPPORT NEJM Revision Final Feb 12.pdf](#)  
**Importance:** High

---

Not sure I got you on the first email

Rose

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Friday, February 12, 2010 4:49 PM  
**To:** 'dale\_phelps@urmc.rochester.edu'; 'Finer, Neil'; 'Duara, Shahnaz'; 'O'Shea, Michael'; 'wrich@ucsd.edu'; 'Gantz, Marie'; 'vivek.narendran@cchmc.org'; 'Brenda Morris'; 'susie.buchter@oz.ped.emory.edu'; 'nirupama.laroya@urmc.rochester.edu'; 'bsood@med.wayne.edu'; 'vineet.bhandari@yale.edu'; ' (Luc.Brion@UTSouthwestern.edu)'; ' (rohls@unm.edu)'; 'aaf2@po.cwru.edu'; 'Abhik Das'; 'alaptook@WIHRI.org'; 'Ambal (ambal@uab.edu)'; 'Brad Yoder (Bradley.yoder@hsc.utah.edu)'; 'Brenda Poindexter'; 'Carlo Waldemar (E-mail)'; 'cotte010@mc.duke.edu'; 'Dennis Wallace'; 'Ed Bell'; 'Ed Donovan'; 'Ehrenkranz Richard (E-mail)'; 'Ivan Frantz (ifrantz@tuftsmedicalcenter.org)'; 'Kennedy, Kathleen A'; 'Kristi Watterberg'; 'Kurt Schibler [kurt.schibler@cchmc.org]'; 'Matthew Bizzarro'; 'Michelle Walsh'; 'MIckey Caplan'; 'Oh William (E-mail)'; 'Pablo Sanchez'; 'Poole Kenneth (E-mail)'; 'Roger Faix'; 'Ronald GOLDBERG'; 'Seetha Shankaran'; 'Stevenson David (E-mail)'; 'Stoll Barbara (E-mail)'; 'Tyson Jon (E-mail)'; 'VanMeurs, Krisa'  
**Cc:** 'Cunningham, Meg'; Archer, Stephanie (NIH/NICHD) [E]; 'Zaterka-Baxter, Kristin'  
**Subject:** CONFIDENTIAL:CPAP SUPPORT PAPER RESUBMISSION  
**Importance:** High

Hello to all

Attached is the resubmission of the CPAP SUPPORT paper.

We have allocated time on the upcoming Steering Committee PI call on 2/23 at 3 PM for discussion.

Thanks to everyone for all their effort!!!

The Oximetry paper will be sent in a separate email.

Rose  
Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network



Division of Neonatology  
Department of Pediatrics

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San Diego, CA 92103-8774  
(619) 543-3759

Date: 11 Feb, 2010

Caren G. Solomon, MD Deputy Editor  
Michael F. Greene, MD Associate Editor  
New England Journal of Medicine  
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Boston, MA 02115  
(617) 734-9800  
Fax: (617) 739-9864  
<http://www.nejm.org>

Dear Drs Solomon and Green

Thank you for your response to our submission "Early CPAP versus Surfactant in Very Preterm Infants: The SUPPORT Trial". We have examined all the critiques by reviewers and the editors and below we have outlined our response to each query and the changes made to the manuscript as a result of each.

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Neither I nor any of the authors have anything relevant to disclose, and I have indicated this above the Acknowledgement Section.

We have a related manuscript entitled Rich W, Auten K, Gantz M, Hale E, Hensman A, Newman N, Finer N. Antenatal consent in a trial of immediate neonatal management: Challenges, costs and representative enrollment. This paper has been accepted with revisions in Pediatrics.

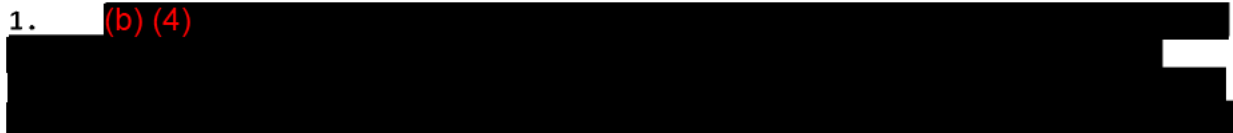
Response to reviewers and Editors: **Our responses in bold.**

Reviewer # 1

**We thank this reviewer for the detailed and helpful comments.**

Introduction:

1. (b) (4)



(b) (4)

2. There is a typographical error at the top of page 11.  
Corrected spelling.

(b) (4)

4. (b) (4)

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Original Manuscript)

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Results:



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14. (b) (4) [Redacted]

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**We thank this reviewer for the detailed and helpful comments.**

**<b>Comments for the Author</b>**

**(b) (4)** [Redacted]

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2. **(b) (4)** [Redacted]

We agree and have **(b) (4)** [Redacted].

3. **(b) (4)** [Redacted]

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Introduction  
Comments

1. **(b) (4)** [Redacted]

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2. **(b) (4)** [Redacted]

We totally agree with this comment and **(b) (4)** [Redacted]

3. **(b) (4)** [Redacted]

Thank you – We have corrected this

4. (b) (4) [Redacted]

The reviewer is correct and we (b) (4) [Redacted]

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We agree – (b) (4) [Redacted]

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We have changed this to read as follows:

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Please see response (b) (4)

(b) (4)

We have corrected this


Statistical Reviewer: 1  
Comments for the Author:

(b) (4)

(b) (4)



(b) (4)

A large rectangular area of the document is completely redacted with black ink, covering approximately the top third of the page.A rectangular area of the document is completely redacted with black ink, covering approximately the middle section of the page.A very large rectangular area of the document is completely redacted with black ink, covering the majority of the lower half of the page.

Editorial Comments:

(b) (4)

A rectangular area of the document is completely redacted with black ink, covering a portion of the editorial comments section.

We have (b) (4) believe that we have addressed these issues.

The current Title is 76 characters including spaces.

Abstract:

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*We have so clarified.* (b) (4)  
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*We hope that revised manuscript and Tables are now acceptable for publication in the NEJM. We thank you and your reviewers for their constructive comments and suggestions.*

*Yours Truly*

*Neil Finer MD – Principal Investigator – SUPPORT Study*

**From:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**To:** ["nirupama\\_laroia@urmc.rochester.edu"](#); ["dale\\_phelps@urmc.rochester.edu"](#); ["dale\\_phelps@urmc.rochester.edu"](#); ["Finer, Neil"](#); ["Duara, Shahnaz"](#); ["O'Shea, Michael"](#); ["wrich@ucsd.edu"](#); ["Gantz, Marie"](#); ["vivek.narendran@cchmc.org"](#); ["Brenda Morris"](#); ["susie.buchter@oz.ped.emory.edu"](#); ["nirupama.laroia@urmc.rochester.edu"](#); ["bsood@med.wayne.edu"](#); ["vineet.bhandari@yale.edu"](#); ["\(Luc.Brion@UTSouthwestern.edu\)"](#); ["rohls@unm.edu"](#); ["aaf2@po.cwru.edu"](#); ["Abhik Das"](#); ["alaptook@WIHRI.org"](#); ["Ambal \(ambal@uab.edu\)"](#); ["Brad Yoder \(Bradley.yoder@hsc.utah.edu\)"](#); ["Brenda Poindexter"](#); ["Carlo Waldemar \(E-mail\)"](#); ["cotte010@mc.duke.edu"](#); ["Dennis Wallace"](#); ["Ed Bell"](#); ["Ed Donovan"](#); ["Ehrenkranz Richard \(E-mail\)"](#); ["Ivan Frantz \(ifrantz@tuftsmedicalcenter.org\)"](#); ["Kennedy, Kathleen A"](#); ["Kristi Watterberg"](#); ["Kurt Schibler \[kurt.schibler@cchmc.org\]"](#); ["Matthew Bizzarro"](#); ["Michelle Walsh"](#); ["Mickey Caplan"](#); ["Oh William \(E-mail\)"](#); ["Pablo Sanchez"](#); ["Poole Kenneth \(E-mail\)"](#); ["Roger Faix"](#); ["Ronald Goldberg"](#); ["Seetha Shankaran"](#); ["Stevenson David \(E-mail\)"](#); ["Stoll Barbara \(E-mail\)"](#); ["Tyson Jon \(E-mail\)"](#); ["VanMeurs, Krisa"](#)  
**Cc:** ["Cunningham, Meg"](#); ["Archer, Stephanie \(NIH/NICHD\) \[E\]"](#); ["Zaterka-Baxter, Kristin"](#)  
**Subject:** CONFIDENTIAL:CPAP SUPPORT PAPER RESUBMISSION  
**Date:** Friday, February 12, 2010 4:48:00 PM  
**Attachments:** [NEJM Letter to EditorRevision Feb 11 2010.pdf](#)  
[NEJM Tables and Figure Feb 9Final.pdf](#)  
[SUPPORT NEJM Revision Final Feb 12.pdf](#)  
**Importance:** High

---

Hello to all

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Thanks to everyone for all their effort!!!

The Oximetry paper will be sent in a separate email.

Rose

Rosemary D. Higgins, MD

Program Scientist for the Neonatal Research Network



Division of Neonatology  
Department of Pediatrics

Medical Center – Hillcrest  
200 West Arbor Drive  
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Date: 11 Feb, 2010

Caren G. Solomon, MD Deputy Editor  
Michael F. Greene, MD Associate Editor  
New England Journal of Medicine  
10 Shattuck Street  
Boston, MA 02115  
(617) 734-9800  
Fax: (617) 739-9864  
<http://www.nejm.org>

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Response to reviewers and Editors: **Our responses in bold.**

Reviewer # 1

**We thank this reviewer for the detailed and helpful comments.**

Introduction:

1. (b) (4)

[REDACTED]

(b) (4) [Redacted]

2. There is a typographical error at the top of page 11.  
Corrected spelling.

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Results:

9. When infants in the "CPAP" arm of the study were intubated in the delivery room (b) (4)

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**We thank this reviewer for the detailed and helpful comments.**

**<b>Comments for the Author</b>**

**(b) (4)** [Redacted]

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2. **(b) (4)** [Redacted]

We agree and have **(b) (4)** [Redacted]

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Introduction  
Comments

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We totally agree with this comment and **(b) (4)** [Redacted]

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Thank you – We have corrected this



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We have changed this to read as follows:

(b) (4)

2. (b) (4)

Please see response (b) (4)

References

1. Reference 12 is titled Neonatal Resuscitation Textbook.

We have corrected this

Statistical Reviewer: 1

Comments for the Author:

(b) (4)

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Editorial Comments:

(b) (4)

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*Neil Finer MD – Principal Investigator – SUPPORT Study*

**From:** [onbehalfof+editorial+nejm.org@manuscriptcentral.com](mailto:onbehalfof+editorial+nejm.org@manuscriptcentral.com) on behalf of [editorial@nejm.org](mailto:editorial@nejm.org)  
**To:** [wcarlo@peds.uab.edu](mailto:wcarlo@peds.uab.edu); [nfner@ucsd.edu](mailto:nfner@ucsd.edu); [michele.walsh@cwru.edu](mailto:michele.walsh@cwru.edu); [wrich@ucsd.edu](mailto:wrich@ucsd.edu); [mgantz@rti.org](mailto:mgantz@rti.org); [alaptok@wihri.org](mailto:alaptok@wihri.org); [Bradley.yoder@hsc.utah.edu](mailto:Bradley.yoder@hsc.utah.edu); [roger.faix@hsc.utah.edu](mailto:roger.faix@hsc.utah.edu); [adas@rti.org](mailto:adas@rti.org); [poo@rti.org](mailto:poo@rti.org); [kurt.schibler@cchmc.org](mailto:kurt.schibler@cchmc.org); [Nancy.Newman@UHhospitals.org](mailto:Nancy.Newman@UHhospitals.org); [nambalavanan@peds.uab.edu](mailto:nambalavanan@peds.uab.edu); [\(b\) \(6\) \[REDACTED\]@tufts-nemc.org"> \(b\) \(6\) \[REDACTED\]@tufts-nemc.org](mailto); [Pablo.Sanchez@UTSouthwestern.edu](mailto:Pablo.Sanchez@UTSouthwestern.edu); [anthony\\_piazza@oz.ped.emory.edu](mailto:anthony_piazza@oz.ped.emory.edu); [\(b\) \(6\) \[REDACTED\]@urmc.rochester.edu"> \(b\) \(6\) \[REDACTED\]@urmc.rochester.edu](mailto); [nirupama\\_laroja@urmc.rochester.edu](mailto:nirupama_laroja@urmc.rochester.edu); [dale\\_phelps@urmc.rochester.edu](mailto:dale_phelps@urmc.rochester.edu); [bpoindex@iupui.edu](mailto:bpoindex@iupui.edu); [cotte010@mc.duke.edu](mailto:cotte010@mc.duke.edu); [vanmeurs@stanford.edu](mailto:vanmeurs@stanford.edu); [sduara@med.miami.edu](mailto:sduara@med.miami.edu); [vivek.narendran@cchmc.org](mailto:vivek.narendran@cchmc.org); [bsood@med.wayne.edu](mailto:bsood@med.wayne.edu); [moshea@wfubmc.edu](mailto:moshea@wfubmc.edu); [edward-bell@uiowa.edu](mailto:edward-bell@uiowa.edu); [richard.ehrenkranz@yale.edu](mailto:richard.ehrenkranz@yale.edu); [kwatterberg@salud.unm.edu](mailto:kwatterberg@salud.unm.edu); [Higgins, Rosemary \(NIH/NICHD\)](mailto:Higgins.Rosemary@NIH/NICHD) [E]; [\(b\) \(6\) \[REDACTED\]@urmc.rochester.edu"> \(b\) \(6\) \[REDACTED\]@urmc.rochester.edu](mailto)  
**Subject:** New England Journal of Medicine - 09-11781.R1  
**Date:** Friday, February 12, 2010 4:08:02 PM

---

Dear Dr. Carlo and co-authors,

Thank you for submitting your revision, of "Oxygen Saturation Targets in Extremely Preterm Infants: The SUPPORT Trial" to the New England Journal of Medicine.

Your submission will be forwarded to the editor, and may be sent out for review as necessary.

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

New England Journal of Medicine  
10 Shattuck Street  
Boston, MA 02115  
(617) 734-9800  
Fax: (617) 739-9864  
<http://www.nejm.org>

## **Higgins, Rosemary (NIH/NICHD) [E]**

---

**From:** Finer, Neil <nfiner@ucsd.edu>  
**Sent:** Friday, February 12, 2010 4:05 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; 'Wally Carlo, M.D.'  
**Subject:** RE: SUPPORT trial manuscripts

Great Rose

Kathleen did raise the question of having the papers circulated – I thought she had been prompted  
Neil

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Friday, February 12, 2010 12:55 PM  
**To:** 'Wally Carlo, M.D.'; Finer, Neil  
**Subject:** RE: SUPPORT trial manuscripts

I called him (I usually like to address issues and concerns straight on) –Jon thought there should be more time for steering committee discussion, but realizes that this was not feasible. I did tell him that for the past main trials, the study subcommittee does the lion's share of the work. I did offer to have the SUPPORT trial as an agenda item for the 2/23 3 PM standing monthly SC call and Jon seemed ok with that. I will send the submitted papers to folks over the weekend. I will also speak to Mickey about this in advance of the 2/23 call discussion.

Also, after Richard Ehrenkranz made the statement that the steering committee should endorse what the subcommittee had done and get the papers in, did Kathleen raise any comments? I can't recall. Jon apparently had to leave for part of the discussion and I can't remember specific objections being made.

We can have a discussion on 2/23 – I doubt that we will have heard back from NEJM and the papers will be grammatically different.

More to follow

Rose  
Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network

---

**From:** Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]  
**Sent:** Friday, February 12, 2010 3:36 PM  
**To:** Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: SUPPORT trial manuscripts

Rose:

I agree. He is stubborn on this issue and it is best if we calm him down. He will not give in. I have talked at length to him about this. He knows we never intended 0.02 for analysis as we have never done it. We did not do it for the SAVE trial that was also factorial. Indeed, we always agreed these papers were going to be analyzed separately and each at the 0.05 level.

Wally

Wally Carlo, M.D.  
Edwin M. Dixon Professor of Pediatrics  
University of Alabama at Birmingham  
Director, Division of Neonatology  
Director, Newborn Nurseries  
619 South 20th Street  
525 New Hillman Building  
Birmingham, AL 35233-7335  
Phone: 205 934 4680

FAX: 205 934 3100  
Cell: 205 266 (b)

---

**From:** Finer, Neil [mailto:nfiner@ucsd.edu]  
**Sent:** Friday, February 12, 2010 2:36 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Wally Carlo, M.D.  
**Subject:** FW: SUPPORT trial manuscripts

Rose

If you want to take Jon on, I will be available - My advice— don't do it  
You will just be aggravated.

Neil

---

**From:** Tyson, Jon E [mailto:Jon.E.Tyson@uth.tmc.edu]  
**Sent:** Friday, February 12, 2010 11:50 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Wally Carlo, M.D.; Wally Carlo, M.D.; Finer, Neil  
**Subject:** RE: SUPPORT trial manuscripts

Rose, are you free to discuss by phone.

Jon E. Tyson, MD, MPH  
Center for Clinical Research & Evidence-Based Medicine  
UT Medical School at Houston  
6431 Fannin St., MSB 2.106  
Houston, TX 77030  
voice 713-500-5651  
fax 713-500-0519

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Friday, February 12, 2010 10:30 AM  
**To:** Tyson, Jon E; 'nfiner@ucsd.edu'; 'wcarlo@peds.uab.edu'  
**Subject:** Re: SUPPORT trial manuscripts

Jon

I will get the papers to the co-authors.

We will report CI's at the 95th percent CI's. They are in the paper (we are not reporting 98th for secondary outcomes).

In going through the author lists, Brenda is the designated author on both papers from UT houston- let us know asap if this is NOT correct. kathleen had told us this.

Thanks  
Rose

---

**From:** Tyson, Jon E <Jon.E.Tyson@uth.tmc.edu>  
**To:** Neil N Finer <nfiner@ucsd.edu>; Wally Carlo, M.D. <WCarlo@peds.uab.edu>  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Fri Feb 12 11:21:06 2010  
**Subject:** SUPPORT trial manuscripts

If you will send me the manuscripts, I will provide prompt comments. I really do not want to offend you but given the concerns that I raised previously, I am not comfortable submitting with my name on this without having an opportunity to seeing the manuscript and have a chance to have input.

Did I understand Neil to say that confidence intervals would not be included? That doesn't seem to be something that the Network should do without discussion of the Steering Committee.

Jon E. Tyson, MD, MPH  
Center for Clinical Research & Evidence-Based Medicine  
UT Medical School at Houston  
6431 Fannin St., MSB 2.106  
Houston, TX 77030  
voice 713-500-5651  
fax 713-500-0519

## **Higgins, Rosemary (NIH/NICHD) [E]**

---

**From:** Finer, Neil <nfiner@ucsd.edu>  
**Sent:** Friday, February 12, 2010 3:34 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Wally Carlo, M.D.; Das, Abhik  
**Subject:** FW: SUPPORT trial manuscripts

Rose

We decided not to report the 98% CI at all in either paper – as doing so gives credence to the  $p=0.02$  issue and we have agreed that the protocol always specified that the primary would be tested at the 0.05 level.

Neil

---

**From:** Tyson, Jon E [mailto:Jon.E.Tyson@uth.tmc.edu]  
**Sent:** Friday, February 12, 2010 11:50 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Wally Carlo, M.D.; Wally Carlo, M.D.; Finer, Neil  
**Subject:** RE: SUPPORT trial manuscripts

Rose, are you free to discuss by phone.

Jon E. Tyson, MD, MPH  
Center for Clinical Research & Evidence-Based Medicine  
UT Medical School at Houston  
6431 Fannin St., MSB 2.106  
Houston, TX 77030  
voice 713-500-5651  
fax 713-500-0519

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Friday, February 12, 2010 10:30 AM  
**To:** Tyson, Jon E; 'nfiner@ucsd.edu'; 'wcarlo@peds.uab.edu'  
**Subject:** Re: SUPPORT trial manuscripts

Jon

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In going through the author lists, Brenda is the designated author on both papers from UT houston- let us know asap if this is NOT correct. kathleen had told us this.

Thanks  
Rose

---

**From:** Tyson, Jon E <Jon.E.Tyson@uth.tmc.edu>  
**To:** Neil N Finer <nfiner@ucsd.edu>; Wally Carlo, M.D. <WCarlo@peds.uab.edu>  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Fri Feb 12 11:21:06 2010  
**Subject:** SUPPORT trial manuscripts

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Jon E. Tyson, MD, MPH  
Center for Clinical Research & Evidence-Based Medicine  
UT Medical School at Houston  
6431 Fannin St., MSB 2.106  
Houston, TX 77030  
voice 713-500-5651  
fax 713-500-0519

## **Higgins, Rosemary (NIH/NICHD) [E]**

---

**From:** Finer, Neil <nfiner@ucsd.edu>  
**Sent:** Friday, February 12, 2010 3:29 PM  
**To:** Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: SUPPORT trial manuscripts

Agreed!!!!  
Neil

---

**From:** Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]  
**Sent:** Friday, February 12, 2010 9:00 AM  
**To:** Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: SUPPORT trial manuscripts

I do not think we should back off on the issue of the 0.02. This was Jon's misunderstanding and he misguided the group.

Wally Carlo, M.D.  
Edwin M. Dixon Professor of Pediatrics  
University of Alabama at Birmingham  
Director, Division of Neonatology  
Director, Newborn Nurseries  
619 South 20th Street  
525 New Hillman Building  
Birmingham, AL 35233-7335  
Phone: 205 934 4680  
FAX: 205 934 3100  
Cell: 205 266 (b)

---

**From:** Tyson, Jon E [mailto:Jon.E.Tyson@uth.tmc.edu]  
**Sent:** Friday, February 12, 2010 10:21 AM  
**To:** Neil N Finer; Wally Carlo, M.D.  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** SUPPORT trial manuscripts

If you will send me the manuscripts, I will provide prompt comments. I really do not want to offend you but given the concerns that I raised previously, I am not comfortable submitting with my name on this without having an opportunity to seeing the manuscript and have a chance to have input.

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Jon E. Tyson, MD, MPH  
Center for Clinical Research & Evidence-Based Medicine  
UT Medical School at Houston  
6431 Fannin St., MSB 2.106  
Houston, TX 77030  
voice 713-500-5651  
fax 713-500-0519



**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Matt Laughon"  
**Cc:** "Danny Benjamin"  
**Subject:** RE: K99R00 question  
**Date:** Friday, February 12, 2010 2:35:00 PM

---

Perfect- do I call the number below

919-962 (b) (6)

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network

---

**From:** Matt Laughon [mailto:matt\_laughon@med.unc.edu]  
**Sent:** Friday, February 12, 2010 2:40 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** 'Danny Benjamin'  
**Subject:** RE: K99R00 question

Let's do 315. Is that ok Rose?

Matt

Matthew M. Laughon, MD, MPH  
Division of Neonatal-Perinatal Medicine  
Department of Pediatrics  
The University of North Carolina at Chapel Hill  
Chapel Hill, NC 27599-7596  
Phone: (919) 966-5063  
Facsimile: (919) 966-3034

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Friday, February 12, 2010 2:22 PM  
**To:** 'Matt Laughon'  
**Cc:** 'Danny Benjamin'  
**Subject:** RE: K99R00 question

I have a call that starts at 4 PM –will it take more than 15 minutes? Sorry – I should have told you

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network

---

**From:** Matt Laughon [mailto:matt\_laughon@med.unc.edu]  
**Sent:** Friday, February 12, 2010 2:29 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** 'Danny Benjamin'  
**Subject:** RE: K99R00 question

Hi Rose,

I will open up a conference call line at 3:45 PM: 919-962 (b) (6)

Thanks,  
Matt

Matthew M. Laughon, MD, MPH  
Division of Neonatal-Perinatal Medicine  
Department of Pediatrics  
The University of North Carolina at Chapel Hill  
Chapel Hill, NC 27599-7596  
Phone: (919) 966-5063  
Facsimile: (919) 966-3034

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Friday, February 12, 2010 1:30 PM  
**To:** 'matt\_laughon@med.unc.edu'  
**Cc:** Danny Benjamin  
**Subject:** RE: K99R00 question

Could we do it this afternoon?

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network

---

**From:** matt\_laughon@med.unc.edu [mailto:matt\_laughon@med.unc.edu]  
**Sent:** Friday, February 12, 2010 1:25 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Danny Benjamin  
**Subject:** Re: K99R00 question

Hi Rose,

Danny and I would like to discuss the K with you next week-what day/time works for you?

Matt  
Matthew M. Laughon, MD, MPH  
Division of Neonatal-Perinatal Medicine  
Department of Pediatrics  
101 Manning Drive  
CB# 7596, 4th Floor, UNC Hospitals  
Chapel Hill, NC 27599-7596  
Office: (919) 966-5063  
Fax: (919) 966-3034

---

**From:** "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>  
**Date:** Fri, 12 Feb 2010 10:10:06 -0500  
**To:** Matt\_Laughon@med.unc.edu<matt\_laughon@med.unc.edu>  
**Cc:** 'Danny Benjamin'<danny.benjamin@duke.edu>  
**Subject:** FW: K99R00 question

Matt\_  
Just so you have this – see below

Rose

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network

---

**From:** Taymans, Susan (NIH/NICHD) [E]  
**Sent:** Friday, February 12, 2010 10:07 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Hayunga, Eugene G. (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Raju, Tonse (NIH/NICHD) [E]; Twombly, Dennis (NIH/NICHD) [E]  
**Subject:** RE: K99R00 question

Hi Rose,

I've pasted some guidance below. Dennis Twombly is now the K99 guru for NICHD—I've copied him on this in case he has something to add.

From the K99 FAQs on eligibility (Emphasis added)  
[http://grants1.nih.gov/grants/new\\_investigators/OsandAs.htm#eindividual](http://grants1.nih.gov/grants/new_investigators/OsandAs.htm#eindividual)

#### **1. Who can apply to be supported as a principal investigator?**

Outstanding postdoctoral candidates who have terminal clinical or research doctorates (or equivalent doctoral degrees) and who have no more than 5 years of postdoctoral research training experience at the time of initial application receipt date, or subsequent resubmission(s) are eligible. Parental leave or other well justified leave from postdoctoral research training for pressing personal or family situations of generally less than 12 months duration is not included in the 5-year eligibility limit. ***In addition, clinical training time with no research involvement (e.g., residency training) is not counted against the 5 year limit (see also question 4 below).***

#### **4. Do postgraduate clinical training experiences count toward the 5-year research training eligibility limit?**

***No. Time spent conducting postgraduate clinical training that does not involve research is not considered as part of the 5-year research training eligibility limit.***

Only time dedicated to research activities would count toward the 5-year limit. Therefore, applicants with postgraduate clinical training experience remain eligible and are encouraged to apply for the Pathway to Independence award.

Your candidate should have eligibility left, equivalent to the time spent in residency. The candidate should document that in a cover letter and in the personal statement so everyone is clear about eligibility. Just in general though, we try to steer our MDs to K08s or K23s, because our PhDs only have the K99 option.

Susan

Susan Taymans, Ph.D.  
Program Director, Reproductive Genetics and Epigenetics, and Basic Ovarian Biology  
The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)  
Reproductive Sciences Branch

6100 Executive Blvd., Room 8B01  
Rockville, MD 20892-7510  
(fed ex or courier use: Rockville, MD 20852)  
301-496-6517  
TaymansS@mail.nih.gov

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]

**Sent:** Friday, February 12, 2010 9:51 AM  
**To:** Taymans, Susan (NIH/NICHD) [E]  
**Cc:** Hayunga, Eugene G. (NIH/NICHD) [E]; Spong, Catherine (NIH/NICHD) [E]; Raju, Tonse (NIH/NICHD) [E]  
**Subject:** K99R00 question

Hi,  
For a neonatologist interested in a K99R00, the rules state

- Eligible Principal Investigators include outstanding postdoctoral candidates who have terminal clinical or research doctorates (including Ph.D., M.D., D.O., D.C., N.D., D.D.S., D.V.M., Sc.D., D.N.S. or equivalent doctoral degrees) who have no more than 5 years of postdoctoral research training at the time of initial application or resubmission(s).

If the neonatologist has been out of training slightly more than 5 years (and has done approximately 18-24 months of clinical time), they haven't had the equivalent of 5 years of post-doctoral research training.

Therefore, the individual would be eligible, correct? I think I have previously asked this question.

Thanks for your help

Rose  
Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "nfiner@ucsd.edu"  
**Subject:** Re: SUPPORT trial manuscripts  
**Date:** Friday, February 12, 2010 11:46:03 AM

---

Thanks - I had sent it to him also

----- Original Message -----

From: Finer, Neil <nfiner@ucsd.edu>  
To: Tyson, Jon E <Jon.E.Tyson@uth.tmc.edu>  
Cc: Wally Carlo, M.D. <WCarlo@peds.uab.edu>; Higgins, Rosemary (NIH/NICHD) [E]; Abhik Das <adas@rti.org>; Rich, Wade <wrich@ucsd.edu>  
Sent: Fri Feb 12 11:44:42 2010  
Subject: Re: SUPPORT trial manuscripts

Jon

We argued that we should present the 95percent CI and not the 98 percent CI

They will have to decide

We are presenting the actual CI for both papers

Neil

Sent from my iPhone

On Feb 12, 2010, at 8:21 AM, "Tyson, Jon E" <Jon.E.Tyson@uth.tmc.edu<<mailto:Jon.E.Tyson@uth.tmc.edu>>> wrote:

If you will send me the manuscripts, I will provide prompt comments. I really do not want to offend you but given the concerns that I raised previously, I am not comfortable submitting with my name on this without having an opportunity to seeing the manuscript and have a chance to have input.

Did I understand Neil to say that confidence intervals would not be included? That doesn't seem to be something that the Network should do without discussion of the Steering Committee.

Jon E. Tyson, MD, MPH  
Center for Clinical Research & Evidence-Based Medicine  
UT Medical School at Houston  
6431 Fannin St., MSB 2.106  
Houston, TX 77030  
voice 713-500-5651  
fax 713-500-0519

**From:** onbehalfof+editorial+nejm.org@manuscriptcentral.com on behalf of editorial@nejm.org  
**To:** nfiner@ucsd.edu; wcarlo@peds.uab.edu; michele.walsh@cwru.edu; wrich@ucsd.edu; mgantz@rti.org; alaptook@wihri.org; Bradley.yoder@hsc.utah.edu; roger.faix@has.utah.edu; adas@rti.org; poo@rti.org; nambalayanan@peds.uab.edu; (b) (6); edward.donovan@cchmc.org; vivek.narendran@cchmc.org; nxs5@cwru.edu; ifrantz@tufts-nemc.org; Pablo.Sanchez@UTSouthwestern.edu; susie.buchter@oz.ped.emory.edu; (b) (6); nirupama\_laroia@umc.rochester.edu; bpindex@iupui.edu; cotte010@mc.duke.edu; vanmeurs@leland.stanford.edu; bsood@med.wayne.edu; sduara@med.miami.edu; moshea@wfubmc.edu; edward.bell@uiowa.edu; vineet.bhandari@yale.edu; kwatterberg@salud.unm.edu; Higgins, Rosemary (NIH/NICHD) [E]; (b) (6)  
**Subject:** New England Journal of Medicine - 09-11783.R1  
**Date:** Friday, February 12, 2010 11:20:13 AM

---

Dear Dr. Finer and co-authors,

Thank you for submitting your revision, of "Early CPAP versus Surfactant in Extremely Preterm Infants: The SUPPORT Trial" to the New England Journal of Medicine.

Your submission will be forwarded to the editor, and may be sent out for review as necessary.

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

New England Journal of Medicine  
10 Shattuck Street  
Boston, MA 02115  
(617) 734-9800  
Fax: (617) 739-9864  
<http://www.nejm.org>

## Higgins, Rosemary (NIH/NICHD) [E]

---

**From:** Finer, Neil <nfiner@ucsd.edu>  
**Sent:** Thursday, February 11, 2010 2:44 PM  
**To:** Walsh, Michele; Higgins, Rosemary (NIH/NICHD) [E]; wcarlo@peds.uab.edu; alaptook@WIHRI.org; adas@rti.org; kurt.schibler@cchmc.org; Bradley.yoder@hsc.utah.edu; Roger.Faix@hsc.utah.edu; mcw3@po.cwru.edu; nxs5@cwru.edu; Rich, Wade; mgantz@rti.org  
**Cc:** mcunningham@rti.org; kzaterka@rti.org; petrie@rti.org; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: SUPPORT paper

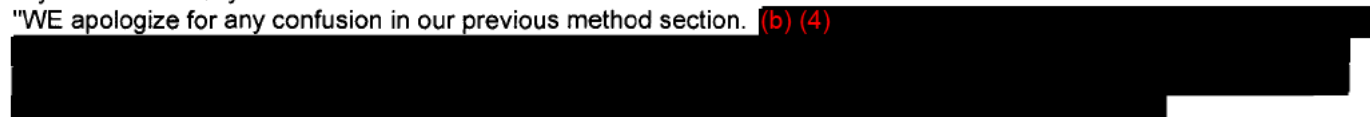
Michelle  
This is great  
Thanks  
Neil

---

**From:** Walsh, Michele [mailto:Michele.Walsh@UHhospitals.org]  
**Sent:** Thursday, February 11, 2010 10:47 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; wcarlo@peds.uab.edu; alaptook@WIHRI.org; adas@rti.org; kurt.schibler@cchmc.org; Bradley.yoder@hsc.utah.edu; Roger.Faix@hsc.utah.edu; mcw3@po.cwru.edu; nxs5@cwru.edu; Rich, Wade; mgantz@rti.org  
**Cc:** mcunningham@rti.org; kzaterka@rti.org; petrie@rti.org; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** RE: SUPPORT paper  
**Importance:** High

Try this- I would say:

"WE apologize for any confusion in our previous method section. (b) (4)



Michele

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Wed 2/10/2010 4:19 PM  
**To:** 'nfiner@ucsd.edu'; 'wcarlo@peds.uab.edu'; 'alaptook@WIHRI.org'; 'adas@rti.org'; 'kurt.schibler@cchmc.org'; 'Bradley.yoder@hsc.utah.edu'; 'Roger.Faix@hsc.utah.edu'; 'mcw3@po.cwru.edu'; 'nxs5@cwru.edu'; 'wrich@ucsd.edu'; 'mgantz@rti.org'  
**Cc:** 'mcunningham@rti.org'; 'kzaterka@rti.org'; 'petrie@rti.org'; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** Fw: SUPPORT paper

For discussion by the SUPPORT subcommittee at tomorrow's meeting

---

**From:** Wally Carlo, M.D. <WCarlo@peds.uab.edu>  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Wally Carlo, M.D. <WCarlo@peds.uab.edu>  
**Sent:** Wed Feb 10 15:58:58 2010  
**Subject:** SUPPORT paper

Dear Rose:

Enclosed are the revised O2 saturation manuscript with tracked changes and the letter to the editor; the legend, figures, and Appendix tables (3 attachments). Please distribute to all the authors or let me know if you want me to do it.

Thanks  
Wally

Wally Carlo, M.D.  
Edwin M. Dixon Professor of Pediatrics  
University of Alabama at Birmingham  
Director, Division of Neonatology  
Director, Newborn Nurseries  
Phone: 205 934 4680  
FAX: 205 934 3100  
Cell: 205 266 (b)

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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:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Wally Carlo, M.D."; "nfiner@ucsd.edu"  
**Subject:** RE: Disclosure draft for The SUPPORT Trial: Randomized Trial of Oxygen Saturation Targets in Extremely Premature Infants  
**Date:** Thursday, February 11, 2010 2:18:00 PM  
**Attachments:** [The SUPPORT Trial Disclosure draft.doc](#)

---

Try this

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network

-----Original Message-----

From: Wally Carlo, M.D. [<mailto:WCarlo@peds.uab.edu>]  
Sent: Thursday, February 11, 2010 2:05 PM  
To: Higgins, Rosemary (NIH/NICHD) [E]; [nfiner@ucsd.edu](mailto:nfiner@ucsd.edu)  
Subject: FW: Disclosure draft for The SUPPORT Trial: Randomized Trial of Oxygen Saturation Targets in Extremely Premature Infants

Here is the draft following their style and instructions, We do not have to do it exactly this way but here is a draft.

Wally Carlo, M.D.  
Edwin M. Dixon Professor of Pediatrics  
University of Alabama at Birmingham  
Director, Division of Neonatology  
Director, Newborn Nurseries  
619 South 20th Street  
525 New Hillman Building  
Birmingham, AL 35233-7335  
Phone: 205 934 4680  
FAX: 205 934 3100  
Cell: 205 266 (b) [REDACTED]

-----Original Message-----

From: Marcus Humphrey  
Sent: Wednesday, February 10, 2010 12:32 AM  
To: Wally Carlo, M.D.  
Subject: Disclosure draft for The SUPPORT Trial: Randomized Trial of Oxygen Saturation Targets in Extremely Premature Infants

Here is my first draft for the disclosure paragraph for The SUPPORT Trial: Randomized Trial of Oxygen Saturation Targets in Extremely Premature Infants, I have not received the disclosure forms from the other authors so there are a lot of blanks on this draft. The second section is just a template that has to be repeated for each author based off of their disclosure form. I have a list of authors but I don't know what they did for the paper if you can help filling in those blanks and who should I contact to get the other authors disclosure forms or do we need to contact each one individually?

The SUPPORT Trial: Randomized Trial of Oxygen Saturation Targets in Extremely Premature Infants is a product of The SUPPORT Trial and was funded thru NIH grant numbers listed in the acknowledgements section. The concepts and goals of The SUPPORT Trial were established by the SUPPORT Trial Subcommittee of the NICHD Neonatal Research Network. Data for the trial was gathered from multiple centers by research staff listed in the acknowledgements. The data was compiled and analyzed by RTI, the data coordinating center for the NICHD NRN. The Principal Investigators for The SUPPORT Trial are Neil Finer and Waldemar Carlo. Drs. Marie Gantz and Ahbik Das performed the analysis of the data gathered at the 20 participating sites for the trial. Dr. Waldemar Carlo wrote the first draft of this paper and received comments and suggestions from SUPPORT Subcommittee of the NICHD NRN. The Paper was submitted before the \_\_\_\_\_ subcommittee and collectively decided to publish the paper.

Dr. \_\_\_\_\_ has a relationship with \_\_\_\_\_ (company) as a \_\_\_\_\_. This company produced the following products \_\_\_\_\_. Dr. \_\_\_\_\_ provided \_\_\_\_\_ to The SUPPORT Trial or this paper.

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "nfiner@ucsd.edu"; "wcarlo@peds.uab.edu"; "alaptook@WIHRI.org"; "adas@rti.org"; "kurt.schibler@cchmc.org"; "Bradley.yoder@hsc.utah.edu"; "Roger.Faix@hsc.utah.edu"; "mcw3@po.cwru.edu"; "nxs5@cwru.edu"; "wrjch@ucsd.edu"; "mgantz@rti.org"  
**Cc:** "mcunningham@rti.org"; "kzaterka@rti.org"; "petrie@rti.org"; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** Fw: SUPPORT paper  
**Date:** Wednesday, February 10, 2010 4:19:22 PM  
**Attachments:** Legends.FINAL.NEJM.2.11.10.doc  
Figure 1,2,3.NEJM.2.11.10.doc  
Appendix Table 1, 2.FINAL.NEJM.2.11.10.doc  
SUPPORT O2.10.10.TRACKED.FINAL.NEJM.doc  
O2.Sats.NEJM.Response.2.10.10.doc

---

For discussion by the SUPPORT subcommittee at tomorrow's meeting

---

**From:** Wally Carlo, M.D. <WCarlo@peds.uab.edu>  
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**Cc:** Wally Carlo, M.D. <WCarlo@peds.uab.edu>  
**Sent:** Wed Feb 10 15:58:58 2010  
**Subject:** SUPPORT paper

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Wally

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Edwin M. Dixon Professor of Pediatrics  
University of Alabama at Birmingham  
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Phone: 205 934 4680  
FAX: 205 934 3100  
Cell: 205 266 (b)

Caren G. Solomon, MD Deputy Editor  
Michael F. Greene, MD Associate Editor  
New England Journal of Medicine  
10 Shattuck Street  
Boston, MA 02115  
(617) 734-9800  
Fax: (617) 739-9864  
<http://www.nejm.org>

Dear Drs Solomon and Green

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Response to reviewers and Editors:

Reviewer # 1

We thank this reviewer for the detailed and helpful comments.

Introduction:

1. (b) (4)



We agree that (b) (4) [redacted]

2. There is a typographical error at the top of page 11.  
Corrected spelling.

(b) (4) [redacted]

[redacted]

4. (b) (4) [redacted]

[redacted]

5. (b) (4) [redacted]

[redacted]

6. (b) (4) [redacted]

(b) (4) [redacted]  
Original Manuscript)

7. (b) (4) [redacted]

(b) (4)

8. (b) (4)

(b) (4)

10. (b) (4)

11. (b) (4)

12. (b) (4)

13. (b) (4)

[Redacted]

[Redacted]

14. (b) (4)

[Redacted]

(b) (4)

[Redacted]

Reviewer: 2

We thank this reviewer for the detailed and helpful comments.

<b>Comments for the Author</b>

(b) (4)

[Redacted]

[Redacted]

[Redacted]

(b) (4) [Redacted]

2. (b) (4) [Redacted]

We agree and (b) (4) [Redacted]

3. (b) (4) [Redacted]

[Redacted]

Introduction

Comments

1. The reference used in the first paragraph appears to be 12 but I think it should be 1, 2.

This is correct - (b) (4) [Redacted]

2. (b) (4) [Redacted]

[Redacted]

3. (b) (4) [Redacted]

Thank you - We have corrected this



4. (b) (4) [Redacted]

The reviewer is correct and we (b) (4) [Redacted]

5. (b) (4) [Redacted]

[Large redacted block]

(b) (4) [Redacted]

[Redacted]

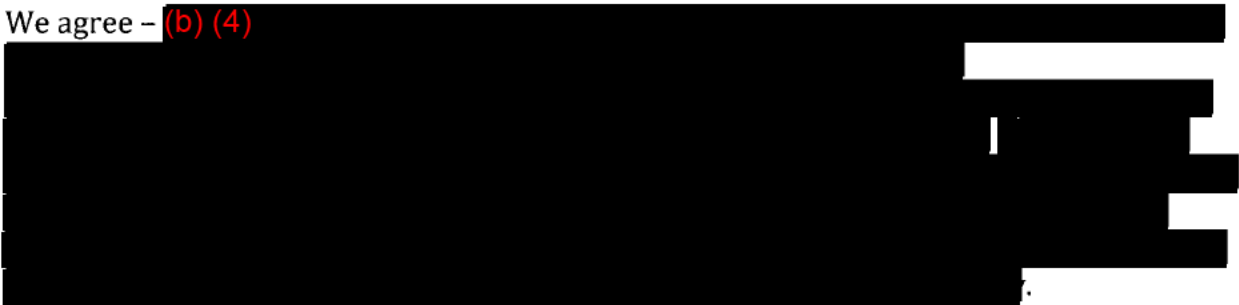
(b) (4)

A large rectangular area of the document is completely redacted with black ink. The text "(b) (4)" is written in red at the top left corner of this redacted area.

2. (b) (4)

A single line of text is redacted with black ink. The text "(b) (4)" is written in red at the beginning of the line.

We agree - (b) (4)

A paragraph of text is redacted with black ink. The text "(b) (4)" is written in red at the beginning of the paragraph.

3. (b) (4)

A single line of text is redacted with black ink. The text "(b) (4)" is written in red at the beginning of the line.

(b) (4)

A large rectangular area of the document is completely redacted with black ink. The text "(b) (4)" is written in red at the top left corner of this redacted area.

4. (b) (4)

[Redacted]

5. (b) (4)

[Redacted]

6. (b) (4)

(b) (4)

7. (b) (4)

We are happy to (b) (4)

8. (b) (4)

Either one

9. (b) (4)

We agree (b) (4)

10. (b) (4)

(b) (4)

11. (b) (4)

[Redacted]

12. (b) (4)

[Redacted]

13. (b) (4)

[Redacted]

14. Randomizing multiple births to the same arm of the trial poses

(b) (4)

[Redacted]

(b) (4) [Redacted]

15. (b) (4) [Redacted]

(b) (4) [Redacted]

(b) (4)  
(b) (4)  
1. (b) (4) [Redacted]

[Redacted]

2. (b) (4) [Redacted]

We agree. (b) (4) [Redacted]

3. (b) (4) [Redacted]

[Redacted]

4. (b) (4) [Redacted]

[Redacted]

5. (b) (4) [Redacted]

The reviewer is correct (b) (4) [Redacted]

(b) (4)

6. (b) (4)

(b) (4)

7. (b) (4)

We agree - (b) (4)

(b) (4)

We believe that (b) (4)

2. (b) (4)

(b) (4)

3. (b) (4)  
[Redacted]

[Redacted]

3. (b) (4)  
[Redacted]

We agree - (b) (4)  
[Redacted]

(b) (4)  
[Redacted]

We have changed this to read as follows:

(b) (4)  
[Redacted]

2. (b) (4)  
[Redacted]

Please see response (b) (4) [redacted]

(b) (4) [redacted]

We have corrected this

Statistical Reviewer: 1  
Comments for the Author:

(b) (4) [redacted]

[redacted]

[redacted]

(b) (4) [redacted]



(b) (4)




(b) (4)



(b) (4)



(b) (4)



Editorial Comments:

(b) (4)



We have revised (b) (4) and believe that we have addressed these issues.

ADDITIONAL COMMENTS OF THE EDITORS

Title: should be no more than 75 characters.

The current Title is 71 characters including spaces.

Abstract:

(b) (4)



Introduction:

(b) (4) [Redacted text block]

[Redacted text block]

[Redacted text block]

Methods:

(b) (4) [Redacted text block]

[Redacted text block]

Results:

(b) (4) [Redacted text block]

This has been done

(b) (4) [Redacted text block]

[Redacted text block]

[Redacted text block]

(b) (4) [Redacted text block]

(b) (4) [Redacted text block]

[Redacted text block]

[Redacted text block]

[Redacted text block]

[Redacted text block]

(b) (4) [Redacted text block]

[Redacted text block]

[Redacted text block]

*We have so clarified.* (b) (4) [Redacted text block]

(b) (4) [Redacted]

[Redacted]

[Redacted]

[Redacted]

*We hope that revised manuscript and Tables are now acceptable for publication in the NEJM. We thank you and your reviewers for their constructive comments and suggestions.*

*Yours Truly*

*Neil Finer MD - Principal Investigator - SUPPORT Study*

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "nfiner@ucsd.edu"; "wcarlo@peds.uab.edu"; "mcw3@po.cwru.edu"; "kurt.schibler@cchmc.org"; "alaptook@WIHRI.org"; "wrich@ucsd.edu"; "nxs5@cwru.edu"; "mgantz@rti.org"; "adas@rti.org"; "Bradley.yoder@hsc.utah.edu"; "Roger.Falx@hsc.utah.edu"  
**Cc:** "mcunningham@rti.org"; "kzaterka@rti.org"; Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** Fw: Remainder of CPAP reviewer Q&A  
**Date:** Tuesday, February 09, 2010 2:32:24 PM  
**Attachments:** [NEJM Letter to Editor Feb 8 2010.doc](#)  
[SUPPORT NEJM Revision1 all changes acc Feb8.doc](#)  
[NEJM Tables and Figure Feb 9Final.doc](#)

---

Here is the CPAP paper revisions and letter for thursday's subcommittee discussion  
The saturation paper will come in the next day or two

Thanks  
Rose  
Rose

---

**From:** Finer, Neil <nfiner@ucsd.edu>  
**To:** Gantz, Marie <mgantz@rti.org>; Wally Carlo, M.D. <WCarlo@peds.uab.edu>; Das, Abhik <adas@rti.org>; Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Rich, Wade <wrich@ucsd.edu>  
**Sent:** Tue Feb 09 13:02:05 2010  
**Subject:** RE: Remainder of CPAP reviewer Q&A

Hello Everyone

Here are the following – a revised manuscript, a letter to the editor which I think is complete and I hope is OK, and the final figures and Tables

Please review. If OK then do whatever is next regarding NRBN approval. When this is done I can upload. Wally and I should upload at similar times.

Il look forward to your responses.

Wally, I was in briefly to give my talk - Then I had to get back – Sorry I missed you

Neil

Caren G. Solomon, MD Deputy Editor  
Michael F. Greene, MD Associate Editor  
New England Journal of Medicine  
10 Shattuck Street  
Boston, MA 02115  
(617) 734-9800  
Fax: (617) 739-9864  
<http://www.nejm.org>

Dear Drs Solomon and Green

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Introduction:

1. (b) (4)



We agree that (b) (4) [redacted]

2. There is a typographical error at the top of page 11.  
Corrected spelling.

Methods:

3. (b) (4) [redacted]

(b) (4) [redacted]

4. (b) (4) [redacted]

[redacted]

5. (b) (4) [redacted]

(b) (4) [redacted]

6. (b) (4) [redacted]

[redacted]

Original Manuscript)

7. (b) (4) [redacted]

[redacted]



(b) (4)

8. (b) (4)

(b) (4)

Results:

9. (b) (4)

10. (b) (4)

11. (b) (4)

12. (b) (4)

13. (b) (4)

[Redacted]

[Redacted]

14. (b) (4)

[Redacted]

[Redacted]

Reviewer: 2

We thank this reviewer for the detailed and helpful comments.

<b>Comments for the Author</b>

(b) (4)

(b) (4)

Abstract

Comments

1. (b) (4)

[Redacted]

(b) (4)

2. (b) (4)

We agree and (b) (4)

3. (b) (4)

(b) (4)

Introduction  
Comments

1. (b) (4)

This is correct - (b) (4)

2. (b) (4)

(b) (4)

3. (b) (4)

Thank you - We have corrected this

4. (b) (4) [Redacted]

The reviewer is correct and (b) (4) [Redacted]

5. (b) (4) [Redacted]

[Large redacted block]

Methods  
Comments

1. (b) (4) [Redacted]

[Redacted]

(b) (4)

2. (b) (4)

We agree - (b) (4)

3. (b) (4)

4. (b) (4) [Redacted]

[Redacted]

5. (b) (4) [Redacted]

[Redacted]

6. (b) (4) [Redacted]

[Redacted]

7. (b) (4) [Redacted]

We are happy to (b) (4) [Redacted].

8. (b) (4) [Redacted]

Either one

9. (b) (4) [Redacted]

We agree and (b) (4) [Redacted]

10. (b) (4) [Redacted]

(b) (4) [Redacted]

11. (b) (4) [Redacted]

[Redacted]

12. (b) (4) [Redacted]

(b) (4) [Redacted]

[Redacted]

14. (b) (4) [Redacted]

[Redacted]

(b) (4) [Redacted]

15. (b) (4) [Redacted]

[Redacted]

Results

Comments

1. (b) (4) [Redacted]

[Redacted]

2. (b) (4) [Redacted]

We agree. (b) (4) [Redacted]

3. (b) (4) [Redacted]

[Redacted]

4. (b) (4) [Redacted]

[Redacted]

5. (b) (4) [Redacted]

[Redacted]



(b) (4)

6. (b) (4)

Please see (b) (4)

7. (b) (4)

We agree - (b) (4)

Discussion  
Comments

1. (b) (4)

We believe that (b) (4)

2. (b) (4)

(b) (4)

3. (b) (4) [Redacted]

[Redacted]

3. (b) (4) [Redacted]

We agree - (b) (4) [Redacted]

Conclusion  
Comments

1. (b) (4) [Redacted]

We have changed this to read as follows:

(b) (4) [Redacted]

2. (b) (4) [Redacted]

Please see response to previous comment and (b) (4)

References

1. (b) (4)

We have corrected this

Statistical Reviewer: 1  
Comments for the Author:


(b) (4)

(b) (4)


(b) (4)

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(b) (4)



(b) (4)



(b) (4)

[Redacted text block]

Editorial Comments:

(b) (4)

[Redacted text block]

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(b) (4)

[Redacted text block]

Introduction:

(b) (4) [Redacted text block]

[Redacted text block]

[Redacted text line]

(b) (4) [Redacted text block]

[Redacted text block]

[Redacted text block]

This has been done

(b) (4) [Redacted text line]

[Redacted text block]

[Redacted text line]

(b) (4)

(b) (4)

Discussion:

(b) (4)

(b) (4)

(b) (4)

[Redacted]

[Redacted]

[Redacted]

*We hope that revised manuscript and Tables are now acceptable for publication in the NEJM. We thank you and your reviewers for their constructive comments and suggestions.*

*Yours Truly*

*Neil Finer MD - Principal Investigator - SUPPORT Study*



**From:** Gantz, Marie  
**To:** Finer, Neil  
**Cc:** Wally Carlo, M.D.; Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]; Rich, Wade  
**Subject:** Remainder of CPAP reviewer Q&A  
**Date:** Monday, February 08, 2010 3:51:04 PM  
**Attachments:** Neil Letter to Editor - Revision1 28 10 adrev MG2.doc  
NEJM Tables and Figure Nov 30 Final Revised MG2.doc  
HFV in Surfactant group - 08FEB10.doc

---

Neil,

Attached are the remainder of my answers to the NEJM reviewers' questions. Please let me know if you need anything else.

Thanks,  
Marie

Marie Gantz, Ph.D.  
Research Statistician  
RTI International  
mgantz@rti.org  
828-254-6255

Caren G. Solomon, MD Deputy Editor  
Michael F. Greene, MD Associate Editor  
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1. (b) (4)  
[Redacted]

[Redacted]

2. (b) (4)  
I can't find this??

Methods:

3. (b) (4)

(b) (4)  
[Redacted]

4. (b) (4)  
[Redacted]

(b) (4)

5. (b) (4)

[Redacted]

6. (b) (4)

[Redacted]

Original Manuscript)

7. (b) (4)

[Redacted]

8. (b) (4)

(b) (4)

Results:

9. (b) (4) ?

(b) (4)

Comment [AD1]: Let's not say that we powered on another outcome; they may want us to adjust the Type I error further for that then!

Comment [AD2]: I agree that providing some data on this may be useful.

Formatted: Highlight

(b) (4)

10. (b) (4)

11. (b) (4)

( Marie can you provide??

Thanks] (b) (4)

[ !

12. (b) (4)

(b) (4)

Marie - do you have any information for (b) (4) ? If so can you let me see it.

Thanks See document (b) (4)

13. (b) (4)

(b) (4)

(b) (4)

14. (b) (4)

[Redacted]

Reviewer: 2  
We thank this reviewer for the detailed and helpful comments.

<b>Comments for the Author</b>  
(b) (4)

[Redacted]

Abstract  
Comments  
1. [Redacted]

[Redacted]

(b) (4)

2. (b) (4)

We agree and (b) (4)

3. (b) (4)

(b) (4)

Introduction  
Comments

1. (b) (4)

This is correct (b) (4)

2. (b) (4)

(b) (4)

3. (b) (4)

Thank you - We have corrected this

4. (b) (4)

The reviewer is correct and (b) (4) [redacted]

5. (b) (4) [redacted]

[redacted]

Methods

Comments

1. (b) (4) [redacted]

[redacted]

(b) (4)

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Comment [MG3]: Is there any need to comment on (b) (4)

2. (b) (4)

[Redacted text block]

We agree - (b) (4)

[Redacted text block]

3. (b) (4)

[Redacted text block]

[Redacted text block]

4. (b) (4)

[Redacted text block]



(b) (4)

5.

(b) (4)

6.

(b) (4)

7.

(b) (4)

We are happy to use (b) (4)

8.

(b) (4)

Either one

9.

(b) (4)

(b) (4)

- Marie do we know this??

(b) (4)

10. (b) (4)

11. (b) (4)

12. (b) (4)

(b) (4)

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13. (b) (4)

Please see the answer to (b) (4)

14. (b) (4)

(b) (4)

(b) (4)

(Abhik - feel free to weigh in here!!) (Ken may also wish to weigh in as

15. (b) (4)

Comment [MG4]: I believe this is what Abhik meant to say.

(Abhik - knock yourself out!!) (b) (4)

Results

Comments

1. (b) (4)

2. (b) (4)

We agree. (b) (4).

3. (b) (4)

(b) (4)

4. (b) (4)

(b) (4)

5. (b) (4)

(b) (4)

Comment [MG5]: Note that the (b) (4)

6. (b) (4)

(b) (4)

(b) (4)

7. (b) (4)

We agree - (b) (4)

Discussion  
Comments

1. (b) (4)

We believe that we (b) (4)

2. (b) (4)

(b) (4)

3. (b) (4)

(b) (4)

**Comment [AD6]:** I understand your point; but do you want to phrase the response more diplomatically?

Thanks (b) (4)

⌋ ⌋ !!

3. (b) (4)

We agree - (b) (4)

[Redacted]

Conclusion

Comments

1. (b) (4)

[Redacted]

We have changed this to read as follows :

(b) (4)

[Redacted]

2. (b) (4)

[Redacted]

Please see response to previous comment and our (b) (4)

References

**Comment [AD7]:** Do you want to start by first saying flat out that the primary outcome was not significantly different between the groups? This may appease them.

1. (b) (4) [Redacted]

We have corrected this

Statistical Reviewer: 1  
Comments for the Author:

(b) (4) [Redacted]

[Redacted]

[Redacted]

Abhik - Please write an appropriate reply - Good luck!!

(b) (4) [Redacted]

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(b) (4)

[REDACTED]

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[REDACTED]

[REDACTED]

(b) (4)

[REDACTED]



(b) (4)

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Editorial Comments:

(b) (4)

A single line of text in the editorial comments section is redacted with black ink.

We have revised (b) (4) and believe that we have addressed these issues.

ADDITIONAL COMMENTS OF THE EDITORS

Title: should be no more than 75 characters.

The current Title is 71 characters including spaces.

Abstract:

(b) (4)

The abstract section is completely redacted with black ink, covering approximately 10 lines of text.

(b) (4)

A single line of text at the bottom of the page is redacted with black ink.

Introduction:

(b) (4) [Redacted text]

[Redacted text]

[Redacted text]

Methods:

(b) (4) [Redacted text]

[Redacted text]

**Comment [MG8]:** Do we need to note in the paper that this interaction was tested and not found to be significant?

Results:

(b) (4) [Redacted text]

[Redacted text]

[Redacted text]

Marie - Please supply -- Thanks

(b) (4) [Redacted text]

(b) (4)

Marie – Please supply - Thanks

(b) (4)

(b) (4)

Discussion:

(b) (4)

*Abhik I will let you write this area – I note that the editor has indicated* (b) (4)

**Comment [MG9]:** Perhaps they are referring to the type of statement made by the statistical reviewer that the (b) (4)

**Comment [AD10]:** I am actually not sure what they want us to do here. Do they want us to reinstate something like the statements below that were in a previous draft? (b) (4)

*We have so clarified*

(b) (4)

*Marie - Please redo as requested. - Thanks*

(b) (4)

*We hope that revised manuscript and Tables are now acceptable for publication in the NEJM. We thank you and your reviewers for their constructive comments and suggestions.*

*Yours Truly*

*Neil Finer MD - Principal Investigator - SUPPORT Study*

**From:** Das, Abhik  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: SC Conferece Call Information  
**Date:** Monday, February 08, 2010 2:48:47 PM

---

I hadn't thought about this before; but having the SUPPORT call in the middle of all these other calls during the same day may mean that we have a bigger group on the phone than we may want at this stage! It is your call.

Thanks

Abhik

---

**From:** Cunningham, Meg  
**Sent:** Monday, February 08, 2010 2:44 PM  
**To:** 'Cbackstrom@salud.unm.edu'; 'mbball@leland.stanford.edu'; 'rbara@med.wayne.edu'; 'mcollins@peds.uab.edu'; 'scosby@peds.uab.edu'; 'sandra.grimes@duke.edu'; 'grisbyca@ucmail.uc.edu'; 'ellen\_hale@oz.ped.emory.edu'; 'ahensman@wihri.org'; 'karen-johnson@uiowa.edu'; 'monica.konstantino@yale.edu'; 'BMackinnon@tuftsmedicalcenter.org'; 'Georgia.E.McDavid@uth.tmc.edu'; 'Nancy.Miller@UTSouthwestern.edu'; 'nxs5@cwru.edu'; 'Karen.Osborne@hsc.utah.edu'; 'ldw@iupui.edu'; 'NAmbalavanan@peds.uab.edu'; 'dpcarit@emory.edu'; 'cotte010@mc.duke.edu'; 'WOH@Lifespan.org'; 'rohls@salud.unm.edu'; 'dstevenson@stanford.edu'; 'jon.e.tyson@uth.tmc.edu'; 'bsood@med.wayne.edu'; 'bradley.yoder@hsc.utah.edu'; 'zhangj@exchange.nih.gov'; 'archerst@mail.nih.gov'; 'edward-bell@uiowa.edu'; 'wcarlo@peds.uab.edu'; 'richard.ehrenkranz@yale.edu'; 'Roger.Faix@hsc.utah.edu'; 'ifrantz@tuftsmedicalcenter.org'; 'goldb008@mc.duke.edu'; 'higginsr@mail.nih.gov'; 'Kathleen.A.Kennedy@uth.tmc.edu'; 'alaptook@WIHRI.org'; 'bpindex@iupui.edu'; 'Pablo.Sanchez@UTSouthwestern.edu'; 'kurt.schibler@cchmc.org'; 'sshankar@med.wayne.edu'; [SCRN] Stoll, Barbara; 'vanmeurs@leland.stanford.edu'; 'mcw3@cwru.edu'; 'kwatterberg@salud.unm.edu'; 'mcaplan@northshore.org'; 'Luc.Brion@utsouthwestern.edu'; Cunningham, Meg; Zaterka-Baxter, Kristin; Das, Abhik; Pickett, James; Gantz, Marie; Auman, Jeanette O.; Poole, W. Kenneth; Huitema, Carolyn Petrie; Nolen, Tracy; Wallace, Dennis; 'bbatton@siumed.edu'; 'BENJA005@dcri.duke.edu'; 'alexis.davis@stanford.edu'; 'dale\_phelps@urmc.rochester.edu'; 'mblakely@utm.edu'; 'efernandez@salud.unm.edu'; 'srhintz@stanford.edu'; 'tarah-colaizy@uiowa.edu'; 'julie-lindower@uiowa.edu'; 'schelonk@ohsu.edu'; 'debra.camputar@yale.edu'; 'jwaidne@emory.edu'; 'gonza025@mc.duke.edu'; 'axt25@po.cwru.edu'; 'Karen.Kirby@UTSouthwestern.edu'; 'lmoore@med.wayne.edu'; 'Nancy.M.Smith@uth.tmc.edu'; 'msumner@peds.uab.edu'; 'bvecchio@careNE.org'; 'janiwall@iupui.edu'; 'twrencox@uthsc.edu'; 'jonathan-klein@uiowa.edu'; 'gsokol@iupui.edu'; 'kimberly.fisher@duke.edu'; 'stephanie.crosby@duke.edu'; Kendrick, Douglas E. (in StatEpi); 'dclark@med.unc.edu'; 'dhwilson@iupui.edu'; 'Matt\_Laughon@med.unc.edu'; 'bvohr@wihri.org'; Irene, Amanda; Cathy Grisby (cathy.grisby@uc.edu); 'Grisby, Cathy'; 'Hale, Ellen'; Auman, Jeanette O.; Leblond, David; Brinkley, Margo F.; 'Caplan, Michael'; 'jeff-murray@uiowa.edu'; nfiner@ucsd.edu; wrich@ucsd.edu; 'McConnell, Susie'; (pamela.neville@duke.edu); 'Blaisdell, Carol (NIH/NHLBI) [E]'; Bob Ward (Robert.Ward@hsc.utah.edu)  
**Subject:** SC Conferece Call Information  
**Importance:** High

Hello All,

Here is a revised agenda for the meeting, now that we are meeting via phone. The Hydrocortisone, NEST and Term Hypotension subcommittee meetings have be cancelled and Robin Webb will be sending out a message to get availability for conference call times to be held in the next few weeks. The coordinator's meeting has also been cancelled, and we will meet at our regular time next Thursday.

We will use the same conference call line that we usually do for this meeting:  
Dial 866-675-(b)

Passcode: (b) (6)

***Please send me any handouts and PowerPoint Presentation by the end of the day tomorrow. These will all be posted on the private gateway of the NRN website.***

We will also set up a web conference to stream the presentations – details to follow shortly.

**CONCEPT VOTING** – Lastly, following each concept, I ask that you email me your vote (mcunningham@rti.org), yes or no, and any comments you want included.

Let me know if you have any questions.

Thanks,  
Meg

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Das, Abhik; Susan Hintz  
**Subject:** RE: first attempt- SUPPORT Neuroimaging abstract  
**Date:** Monday, February 08, 2010 12:24:03 PM

---

Two suggestions to "temper" the abstract -  
Include the total number of infants enrolled in SUPPORT (1316).  
For the CPAP group - say the rate of adverse outcome is "slightly" increased. The numbers of infants in the study are low. There were also more deaths in the surf group so that should be incorporated.

Thanks

(How's Hank???)

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 20592

301-435-7909

301-496-5575

301-496-3790 (FAX)

[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

---

**From:** Das, Abhik [[adas@rti.org](mailto:adas@rti.org)]  
**Sent:** Monday, February 08, 2010 10:48 AM  
**To:** Susan Hintz  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: first attempt- SUPPORT Neuroimaging abstract

This is a tough one. It is indeed difficult to strike a balance between stressing the importance of the result and being careful about the limitations. On balance, I think you have done a good job of it. See attached for comments and some suggested changes. The one thing I wondered about (more for the presentation than the abstract) is our rationale for just adjusting for site and nothing else.

Thanks

Abhik

-----Original Message-----

**From:** Susan Hintz [<mailto:srhintz@stanford.edu>]  
**Sent:** Monday, February 08, 2010 12:36 AM  
**To:** Rosemary Higgins  
**Cc:** Das, Abhik  
**Subject:** first attempt- SUPPORT Neuroimaging abstract

Hi Rose and Abhik

Attached is my first go at the abstract for the CUS findings of the SUPPORT Neuroimaging cohort. I struggled a bit with this over the

weekend because I wanted to get the highlights in, make the importance of the cohort clear, but still be honest about what we know and do not know. A few things -

1) It is too long - I need to work on that

2) We never settled on a cohort name - NINDO is what I said originally, but I am very open to other suggestions and ideas. NINDO is really a placeholder until someone more clever than I can come up with something great.

3) The table shows findings for the secondary cohort overall - I think trying to break it down further by randomized group gets crazy. However, I could add kappa (95%CI) to the table in a final column.

4) Do you think the importance of the cohort and serial CUS findings are emphasized enough? I note on the call for late breakers (sent on 2/1) that they seem quite strict in what is considered "important" enough for a late breaker.

5) I have no idea how the politics works in terms of authorship for this - am I supposed to put everyone from the secondary subcommittee on as an author? Or is saying "for the SUPPORT Neuroimaging Subcommittee" good enough?

Input appreciated.

Thanks

Susan

--

Susan R. Hintz, M.D., M.S. Epi  
Associate Professor of Pediatrics  
Division of Neonatal and Developmental Medicine Stanford University  
School of Medicine 750 Welch Road, Suite 315 Palo Alto, CA 94304  
ph: 650-723-5711  
fax: 650-725-8351



**From:** Das, Abhik  
**To:** Susan Hintz  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: first attempt- SUPPORT Neuroimaging abstract  
**Date:** Monday, February 08, 2010 11:52:41 AM

---

That is fine with me. In the interest of time, Helen can just do that for the outcomes you talk about in the abstract and make sure nothing changes. We should likely also test for a GA by CPAP/surf interaction.

Thanks

Abhik

-----Original Message-----

**From:** Susan Hintz [mailto:srhintz@stanford.edu]  
**Sent:** Monday, February 08, 2010 11:50 AM  
**To:** Das, Abhik  
**Cc:** Rosemary Higgins  
**Subject:** Re: first attempt- SUPPORT Neuroimaging abstract

Yes, the adjusting for site only thing worries me too. Why not adjust for EGA strata as well? I know that the groups look balanced with respect to pre-randomization variables, but the main trial results were adjusted for EGA strata.

S

Sent from my iPhone

On Feb 8, 2010, at 7:48 AM, "Das, Abhik" <adas@rti.org> wrote:

> This is a tough one. It is indeed difficult to strike a balance  
> between  
> stressing the importance of the result and being careful about the  
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> attached for comments and some suggested changes. The one thing I  
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> rationale for just adjusting for site and nothing else.

>  
> Thanks

>  
> Abhik

>

>

> -----Original Message-----

> **From:** Susan Hintz [mailto:srhintz@stanford.edu]  
> **Sent:** Monday, February 08, 2010 12:36 AM  
> **To:** Rosemary Higgins  
> **Cc:** Das, Abhik  
> **Subject:** first attempt- SUPPORT Neuroimaging abstract

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>  
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> author? Or is saying "for the SUPPORT Neuroimaging Subcommittee" good  
> enough?  
>  
> Input appreciated.  
>  
> Thanks  
>  
> Susan  
>  
> --  
> Susan R. Hintz, M.D., M.S. Epi  
> Associate Professor of Pediatrics  
> Division of Neonatal and Developmental Medicine Stanford University  
> School of Medicine 750 Welch Road, Suite 315 Palo Alto, CA 94304  
> ph: 650-723-5711  
> fax: 650-725-8351  
> <DRAFTNeuro\_SUPPPORT\_CUS\_PASabstract\_Feb\_07\_10 adrev.doc>

**From:** Susan Hintz  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** adas@rti.org  
**Subject:** first attempt- SUPPORT Neuroimaging abstract  
**Date:** Monday, February 08, 2010 12:36:00 AM  
**Attachments:** DRAFTNeuro\_SUPPPORT\_CUS\_PASabstract\_Feb\_07\_10.doc

---

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Susan

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Stanford University School of Medicine  
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ph: 650-723-5711  
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**Title: Early and Late Cranial Ultrasound (CUS) findings in the SUPPORT Neuroimaging and Neurodevelopmental Outcomes (NINDO) cohort**

Susan R Hintz, MD, MS, Dorothy Bulas, MD Thomas Slovis, MD, Helen Cheng, PhD, Neil Finer, MD, Qing Yao, PhD, Abhik Das, PhD, Rosemary D. Higgins, MD, for the SUPPORT Neuroimaging and Neurodevelopmental Outcomes Subcommittee of the NICHD Neonatal Research Network

**Background:** The NICHD Neonatal Research Network (NRN) SUPPORT study was a randomized, multicenter 2x2 trial of ventilation (CPAP vs. surfactant) and oxygenation (high vs. low) strategies in 24-27+6/7 week EGA infants. It is not known whether these differing management approaches are associated with early or later brain injury. Furthermore, detailed data regarding serial CUS findings in recent extremely preterm cohorts are limited.

**Objective:** In a secondary study to SUPPORT, we sought to determine early CUS (4-14 days) and late CUS (35-42 weeks postmenstrual age (PMA)) findings, and to compare early and late CUS findings between SUPPORT ventilation and oxygenation randomized groups.

**Design/Methods:** The NINDO study was a prospective secondary study of early and late CUS among a subcohort of infants enrolled in SUPPORT; brain MRI was also obtained at the time of late CUS, and future analyses will compare CUS and brain MRI to predict neurodevelopmental outcome at 18-22 months and at school age. All CUS were read by 2 central readers. Rates of major early and late CUS outcomes were determined for the NINDO cohort overall, and compared between SUPPORT randomized groups. Logistic regression analyses determined independent risk of randomized intervention for adverse CUS outcomes, controlling for NRN center as a random effect.

**Results:** 572 patients were enrolled and had complete early and late CUS. Baseline characteristics were similar between CPAP vs. surfactant, and high and low oxygenation groups. Rates of selected major CUS findings are shown in Table 1.

Early and Late CUS findings in SUPPORT NINDO secondary cohort

	Central reader #1 (N=572)	Central reader #2 (N=572)
<b>EARLY CUS</b>		
Normal	72%	72%
Any hemorrhage	19.6%	20.8%
Grade 3 or 4	6.8%	9.6%
<b>LATE CUS</b>		
Moderate-severe ventriculomegaly	4.4%	4.2%
Cystic PVL, porencephalic cyst, mod-severe ventriculomegaly or shunt	6.5%	6.6%

The majority of those with normal early CUS remained normal on late CUS

(Reader 1: 81%; Reader 2: 82%). There were no differences between high and low oxygenation groups on any major early or late CUS finding. However, those randomized to CPAP were more likely to have cystic PVL, porencephalic cyst, mod-severe ventriculomegaly or shunt on late CUS compared with surfactant (Reader 1: 9% vs 4%, OR 2.5 (95%CI 1.21-5.20),  $p=0.014$ ; Reader 2: 10% vs. 4%, OR 2.55 (95%CI 1.23-5.29),  $p=0.012$ ).

**Conclusions:** Rates of adverse early or late CUS findings were low overall in this unique extremely preterm cohort. A major adverse late CUS finding was more likely for CPAP vs. surfactant, but this finding may not be representative of the trial cohort overall. Our findings will be further informed by brain MRI and neurodevelopmental follow-up.

**From:** Das, Abhik  
**To:** Susan Hintz  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: first attempt- SUPPORT Neuroimaging abstract  
**Date:** Monday, February 08, 2010 10:48:09 AM  
**Attachments:** DRAFTNeuro\_SUPPPORT\_CUS\_PASabstract\_Feb\_07\_10\_adrev.doc

---

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Thanks

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**Subject:** first attempt- SUPPORT Neuroimaging abstract

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**Objective:** In a secondary study to SUPPORT, we sought to determine early CUS (4-14 days) and late CUS (35-42 weeks postmenstrual age (PMA)) findings, and to compare early and late CUS findings between SUPPORT ventilation and oxygenation randomized groups.

**Design/Methods:** The NINDO study was a prospective secondary study of early and late CUS among a subcohort of infants enrolled in SUPPORT; brain MRI was also obtained at the time of late CUS, and future analyses will compare CUS and brain MRI to predict neurodevelopmental outcome at 18-22 months and at school age. All CUS were read by 2 central readers. Rates of major early and late CUS outcomes were determined for the NINDO cohort overall, and compared between SUPPORT randomized groups. Hierarchical Logistic regression analyses determined independent risk of randomized intervention for adverse CUS outcomes, controlling for NRN center as a random effect.

**Results:** 572 patients were enrolled and had complete early and late CUS. Baseline characteristics were similar between CPAP vs. surfactant, and high and low oxygenation groups. Rates of selected major CUS findings are shown in Table 1.

Comment [ADas1]: Agree that we should add kappa to this table.

Early and Late CUS findings in SUPPORT NINDO secondary cohort

	Central reader #1 (N=572)	Central reader #2 (N=572)
<b>EARLY CUS</b>		
Normal	72%	72%
Any hemorrhage	19.6%	20.8%
Grade 3 or 4	6.8%	9.6%
<b>LATE CUS</b>		
Moderate-severe ventriculomegaly	4.4%	4.2%
Cystic PVL, porencephalic cyst, mod-severe ventriculomegaly or shunt	6.5%	6.6%

The majority of those with normal early CUS remained normal on late CUS



(Reader 1: 81%; Reader 2: 82%). There were no differences between high and low oxygenation groups on any major early or late CUS finding. However, those randomized to CPAP were more likely to have cystic PVL, porencephalic cyst, mod-severe ventriculomegaly or shunt on late CUS compared with surfactant (Reader 1: 9% vs 4%, OR 2.5 (95%CI 1.21-5.20), p=0.014; Reader 2: 10% vs. 4%, OR 2.55 (95%CI 1.23-5.29), p=0.012).

**Comment [ADas2]:** This OR is for the composite of all the outcomes above?

**Conclusions:** Rates of adverse early or late CUS findings were low overall in this unique extremely preterm cohort, but a major adverse late CUS finding was more likely for CPAP vs. surfactant, but this finding may not be representative of the trial cohort overall. Our findings from this sub-cohort may not apply to the entire trial cohort, and will be further informed by brain MRI and neurodevelopmental follow-up.

**From:** Ed Bell  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** Re: CONFIDENTIAL:New England Journal of Medicine 09-11783 and 09-11781  
**Date:** Sunday, February 07, 2010 8:59:55 AM

---

Wow! Keep warm and safe.

Sent from my phone

---

**From:** "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>  
**Date:** Sun, 7 Feb 2010 08:55:21 -0500  
**To:** 'edward-bell@uiowa.edu' <edward-bell@uiowa.edu>; Archer, Stephanie (NIH/NICHD) [E] <archerst@mail.nih.gov>  
**Subject:** Re: CONFIDENTIAL:New England Journal of Medicine 09-11783 and 09-11781

81 is oximetry  
83 is cpap

The snow is of mammoth proportion - stephanie did not have power as of yesterday. The plows are trying to get the main roads and interstates clear - our street is not passable. We haven't seen a plow since early Friday evening.

We are doing fine, though!  
Take care  
Rose

---

**From:** Bell, Edward <edward-bell@uiowa.edu>  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Archer, Stephanie (NIH/NICHD) [E]  
**Sent:** Sun Feb 07 08:38:28 2010  
**Subject:** RE: CONFIDENTIAL:New England Journal of Medicine 09-11783 and 09-11781

Good morning, Rose and Stephanie. I hope you are enjoying the snow. Which manuscript number (09-11781, 09-1783) goes with which paper? We need the numbers for the copyright and conflict forms?  
Thanks,  
Ed

-----Original Message-----

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Tuesday, January 26, 2010 4:06 PM  
**To:** Wally Carlo, M.D.; 'Michele Walsh'; 'Finer, Neil'; 'Abbot Laptook'; Rich, Wade; Gantz, Marie; 'Roger Faix'; 'Bradley Yoder'; 'Das, Abhik'; Poole Kenneth (E-mail); 'Kurt Schibler'; 'Nancy Newman'; Ambal (ambal@uab.edu); 'Frantz, Ivan'; Pablo.Sanchez@UTSouthwestern.edu; Anthony Piazza (Anthony.Piazza@oz.ped.emory.edu); (b) (6); Laroia, Nirupama; 'Phelps, Dale'; bpoindex@iupui.edu; 'Michael Cotten'; 'Krisa Van Meurs'; 'Duara, Shahnaz'; Vivek Narendran; 'Sood, Beena'; 'Michael O'Shea'; Bell, Edward; 'Richard Ehrenkranz'; kwatterberg@salud.unm.edu; 'Ed Donovan'; (susie.buchter@oz.ped.emory.edu); 'vineet.bhandari@yale.edu'  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; Cunningham, Meg; Zaterka-Baxter, Kristin; Huitema, Carolyn Petrie  
**Subject:** CONFIDENTIAL:New England Journal of Medicine 09-11783 and 09-11781  
**Importance:** High

Hi,  
Both Wally and Neil got news today from the NEJM. Revisions are requested for both papers and the subcommittee will work on these. Please fill out the attached forms and return them to NICHD @ 301-496-3790 (FAX).

Also included in the reviews are the following statements:

Please note that we are also inviting a revised version of the companion manuscript. If/when both manuscripts are satisfactorily revised, we would anticipate publishing them back to back.

This is an important clinical trial. The study was well designed and was conducted at centers with excellent research credentials. The paper is clear and succinctly written.

The results demonstrating substantial reduction in severe ROP but increased in-hospital mortality in the lower saturation target group are noteworthy with the potential to change clinical practice. This is a timely topic that is the source of great clinical controversy and practice variation. Contemporary, well designed clinical investigations to enlighten the debate are long overdue.

This large RCT in such a difficult area is a fantastic achievement and you need to be congratulated.

We will need the attached forms once the papers are revised.

Please keep the information on review and status confidential. The New England journal has a strict embargo policy.

Thanks to everyone for all of the effort for this important study!!

Best regards  
Rose

**From:** [Kiley, James \(NIH/NHLBI\) \[E\]](#)  
**To:** [Blaisdell, Carol \(NIH/NHLBI\) \[E\]](#); [McDonough, Sally \(NIH/NHLBI\) \[E\]](#); [Gail, Dorothy \(NIH/NHLBI\) \[E\]](#)  
**Cc:** [Dambrauskas, Susan \(NIH/NIDCD\) \[E\]](#); [Striar, Diane \(NIH/NHLBI\) \[E\]](#); [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#); [Bock, Robert \(NIH/NICHD\) \[E\]](#)  
**Subject:** Re: Attachment: ATS 2009 Preview edition  
**Date:** Friday, February 05, 2010 3:53:24 PM

---

This looks good to me. Jim

---

**From:** Blaisdell, Carol (NIH/NHLBI) [E]  
**To:** McDonough, Sally (NIH/NHLBI) [E]; Kiley, James (NIH/NHLBI) [E]; Gail, Dorothy (NIH/NHLBI) [E]  
**Cc:** Dambrauskas, Susan (NIH/NHLBI) [E]; Striar, Diane (NIH/NHLBI) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]  
**Sent:** Fri Feb 05 15:22:37 2010  
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*Quote from Carol Blaisdell (NHLBI) and Rosemary Higgins (NICHD):*

(b) (5)



Carol J. Blaisdell, M.D.  
Medical Officer  
Lung Developmental Biology and  
Pediatric Pulmonary Diseases  
Division of Lung Diseases, NHLBI/NIH  
(301) 435-0222 phone

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**Cc:** Dambrauskas, Susan (NIH/NHLBI) [E]; Striar, Diane (NIH/NHLBI) [E]; McDonough, Sally (NIH/NHLBI) [E]  
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**From:** Rhiannon Ross [mailto:rross@ascendmedia.com]  
**Sent:** Wednesday, February 03, 2010 4:32 PM  
**To:** Blaisdell, Carol (NIH/NHLBI) [E]  
**Subject:** Attachment: ATS 2009 Preview edition

My apologies. I neglected to attach a copy of the 2009 Preview edition of the *ATS Daily Bulletin*.

----- Forwarded Message

**From:** Rhiannon Ross <rross@ascendmedia.com>  
**Date:** Wed, 03 Feb 2010 15:25:19 -0600  
**To:** <blaisdellcj@nhlbi.nih.gov>  
**Conversation:** ATS Preview Edition: Interview Request  
**Subject:** RE: ATS Preview Edition: Interview Request

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Thank you for your assistance,

Rhiannon Ross  
Medical Editor  
Ascend Media  
7015 College Blvd., Ste. 600  
Overland Park, KS 66210  
Office: 913-344-1478  
Fax: 913-469-1126  
Mobile: 913-596(b)

----- End of Forwarded Message

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Subject:** Fw: Attachment: ATS 2009 Preview edition  
**Date:** Friday, February 05, 2010 3:25:20 PM

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FYI

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**From:** Blaisdell, Carol (NIH/NHLBI) [E]  
**To:** McDonough, Sally (NIH/NHLBI) [E]; Kiley, James (NIH/NHLBI) [E]; Gail, Dorothy (NIH/NHLBI) [E]  
**Cc:** Dambraskas, Susan (NIH/NHLBI) [E]; Striar, Diane (NIH/NHLBI) [E]; Higgins, Rosemary (NIH/NICHD) [E]; Bock, Robert (NIH/NICHD) [E]  
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(b) (5)



Carol J. Blaisdell, M.D.  
Medical Officer  
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(301) 435-0222 phone

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**Sent:** Wednesday, February 03, 2010 4:32 PM  
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**Subject:** Attachment: ATS 2009 Preview edition

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Thank you for your assistance,

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Medical Editor  
Ascend Media  
7015 College Blvd., Ste. 600  
Overland Park, KS 66210  
Office: 913-344-1478  
Fax: 913-469-1126  
Mobile: 913-596-(b)

----- End of Forwarded Message

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Bock, Robert (NIH/NICHD) [E]; Blaisdell, Carol (NIH/NHLBI) [E]  
**Subject:** Fw: Attachment: ATS 2009 Preview edition  
**Date:** Friday, February 05, 2010 3:19:59 PM

---

Carol  
I am ok with this - please send to your media folks -  
Bob - are you ok with this??

Thanks  
Rose

---

**From:** Blaisdell, Carol (NIH/NHLBI) [E]  
**To:** Blaisdell, Carol (NIH/NHLBI) [E]; Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Fri Feb 05 15:16:03 2010  
**Subject:** RE: Attachment: ATS 2009 Preview edition

Rose, please confirm these edits are ok with you and then I will circulate to our media folks.  
May have not been clear when I sent this earlier today, as I left the names of the media folks on the beginning of the email I never sent them.

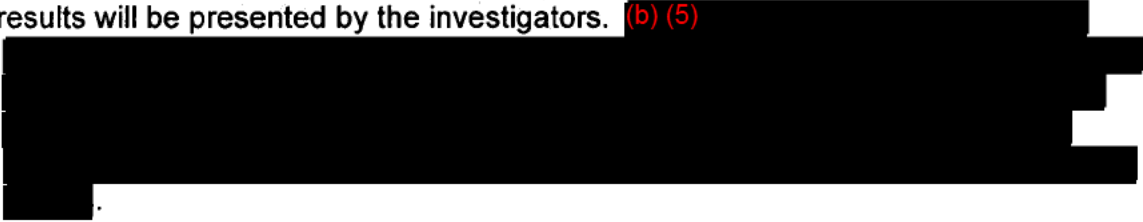
Carol

---

**From:** Blaisdell, Carol (NIH/NHLBI) [E]  
**Sent:** Friday, February 05, 2010 11:18 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Attachment: ATS 2009 Preview edition

Rose, made some edits---check if these are ok--cb

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TRIAL IN EXTREMELY LOW BIRTH WEIGHT (ELBW) INFANTS",  
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**From:** Kiley, James (NIH/NHLBI) [E]  
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**To:** Blaisdell, Carol (NIH/NHLBI) [E]; Gail, Dorothy (NIH/NHLBI) [E]  
**Cc:** Dambrauskas, Susan (NIH/NHLBI) [E]; Striar, Diane (NIH/NHLBI) [E]; McDonough, Sally (NIH/NHLBI) [E]  
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**Sent:** Wednesday, February 03, 2010 4:32 PM  
**To:** Blaisdell, Carol (NIH/NHLBI) [E]  
**Subject:** Attachment: ATS 2009 Preview edition

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**Subject:** RE: ATS Preview Edition: Interview Request

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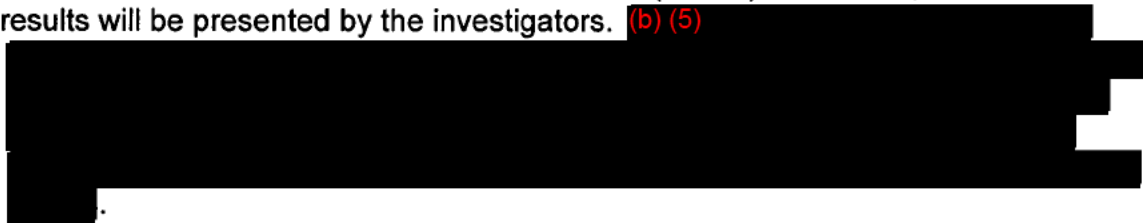
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**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Subject:** RE: Attachment: ATS 2009 Preview edition  
**Date:** Friday, February 05, 2010 11:17:56 AM

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Susan, Diane, and Sally

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Mobile: 913-596-(b)

----- End of Forwarded Message

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Blaisdell, Carol (NIH/NHLBI) [E]  
**Cc:** Bock, Robert (NIH/NICHD) [E]  
**Subject:** RE: Attachment: ATS 2009 Preview edition  
**Date:** Friday, February 05, 2010 9:52:00 AM  
**Attachments:** Paragraph for ATS 2010 meeting flyer.doc

---

Try this

Our press person, Bob Bock is fine with it--  
Let me know if you want to discuss --  
I will be in the office until about noon and then working from home

703-827-(b) (home)  
703-395-(b) (6) (cell)

I have calls from 11-12, 2-3, and 3-4.

Rose

---

**From:** Blaisdell, Carol (NIH/NHLBI) [E]  
**Sent:** Thursday, February 04, 2010 12:18 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** FW: Attachment: ATS 2009 Preview edition

Dear Rose,

The ATS is interested in a brief "quote" to use for the newsletter about SUPPORT.  
See attached for the way this newsletter highlights clinical studies presentations at ATS 2009.  
I would be happy to coordinate with you a quote, or if you prefer I can do it with our press office at NHLBI.

I am at review this AM, but around a bit this afternoon or tomorrow most of the day if you want to discuss.

Carol  
(301) 435-0222 phone

---

**From:** Rhiannon Ross [mailto:rross@ascendmedia.com]  
**Sent:** Wednesday, February 03, 2010 4:32 PM  
**To:** Blaisdell, Carol (NIH/NHLBI) [E]  
**Subject:** Attachment: ATS 2009 Preview edition

My apologies. I neglected to attach a copy of the 2009 Preview edition of the *ATS Daily Bulletin*.

----- Forwarded Message

**From:** Rhiannon Ross <rross@ascendmedia.com>  
**Date:** Wed, 03 Feb 2010 15:25:19 -0600  
**To:** <blaisdellcj@nhlbi.nih.gov>



**Conversation:** ATS Preview Edition: Interview Request

**Subject:** RE: ATS Preview Edition: Interview Request

Hello Dr. Blaisdell,

My company will once again produce the *ATS Daily Bulletin*, the newspaper that is distributed prior to and during the annual American Thoracic Society International Conference. Working with ATS communications staff Suzy Logan and Brian Kell, I am writing an overview about the 21 clinical trials/research initiatives that will be presented this year for the Preview edition of this publication. I am highlighting four of these sessions in the article and would like to include your session: **L4: "Outcomes from the NHLBI-NICHD Support Trial: The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Weight (ELBW) Infants."**

If you are agreeable, I would like to obtain a quote or two from you about this trial to include in the article. I am attaching a copy of the article on clinical trials/research initiatives that ran in last year's Preview edition to give you an idea of what I'm looking for in terms of a quote (See: "Conference Features Sessions on Research Efforts, Clinical Trials," bottom of page 1, continuing on page 9). I will structure the 2010 article on this 2009 article.

You may e-mail me your quote, or if you prefer, I can call you. I should only need about five or 10 minutes of your time. Just let me know what time and day work best for you. I am also available this weekend. (Note that I am in the Central Time Zone.) Once I have a draft, I will send it to you for your comments. Then the ATS communications staff will edit and I will send you a final version for approval. The Preview edition will be mailed to ATS members in March.

Thank you for your assistance,

Rhiannon Ross  
Medical Editor  
Ascend Media  
7015 College Blvd., Ste. 600  
Overland Park, KS 66210  
Office: 913-344-1478  
Fax: 913-469-1126  
Mobile: 913-596-(b)

----- End of Forwarded Message

During the OUTCOMES FROM THE NHLBI-NICHD SUPPORT TRIAL: THE (SURFACTANT POSITIVE AIRWAY PRESSURE AND PULSE OXIMETRY) TRIAL IN EXTREMELY LOW BIRTH WEIGHT (ELBW) INFANTS, results from the SUPPORT Trial will be presented by the investigators. (b) (5)

[REDACTED]

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Subject:** Paragraph for ATS 2010 meeting flyer  
**Date:** Friday, February 05, 2010 9:30:00 AM  
**Attachments:** Paragraph for ATS 2010 meeting flyer.doc  
**Importance:** High

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use this version - I put the session title into it

Rose

**During the OUTCOMES FROM THE NHLBI-NICHD SUPPORT TRIAL: THE SURFACTANT POSITIVE AIRWAY PRESSURE AND PULSE OXIMETRY TRIAL IN EXTREMELY LOW BIRTH WEIGHT (ELBW) INFANTS, results from the SUPPORT Trial will be presented by the investigators. (b) (5)**

[REDACTED]

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Bock, Robert (NIH/NICHD) [E]  
**Cc:** Spong, Catherine (NIH/NICHD) [E]  
**Subject:** FW: Attachment: ATS 2009 Preview edition  
**Date:** Friday, February 05, 2010 9:22:00 AM  
**Attachments:** [ATS Preview.pdf](#)  
[Paragraph for ATS 2010 meeting flyer.doc](#)  
**Importance:** High

---

Bob

The SUPPORT Trial will be presented at ATS on Sunday May 16. NHLBI is requesting a little "blurb" for the ATS meeting flyer – is what I have attached ok? I need to send this to NHLBI TODAY!!

Rose

---

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Mobile: 913-596-(b)

----- End of Forwarded Message



# ATS DAILY BULLETIN

We help the world breathe  
PULMONARY • CRITICAL CARE • SLEEP

P3 SLEEP, MV POSTGRAD COURSES

P5 2009 PAR SYMPOSIUM

P6 KEY ASSEMBLY ABSTRACTS

MEETING HIGHLIGHT

## ATS 2009 in San Diego Offers Best in Pulmonary, Critical Care, Sleep Science

The American Thoracic Society's 2009 International Conference is shaping up to be one of the most exciting conferences for the ATS, making attendance at this outstanding educational venue well-worth the effort of pulmonary, critical care and sleep scientists and clinicians. Because of the 5,395 abstracts received this year, conference planners anticipate great attendance for ATS 2009 in San Diego.

"Generally, West Coast conferences are well-attended. Attendees like San Diego, the nearby attractions are appealing, the weather is usually great and the convention center is nicely designed," said conference committee chair Monica Kraft, M.D. "The main draw, though, is the science and education we offer."

ATS President Jo Rae Wright, Ph.D., concurs. "The conference provides an outstanding blend of basic, clinical and translational science and up-to-date overviews of the state of the art in research and clinical care," Dr. Wright said. "There is a strong interdisciplinary approach in planning the conference to tackle the biggest problems facing patients, their families and the health of the public."

The ATS International Conference Committee always incorporates new elements to keep programming fresh. New this year, Dr. Kraft said, are late-breaking clinical trials; an increased focus on genetics and genomics; more attention to sleep medicine; discus-

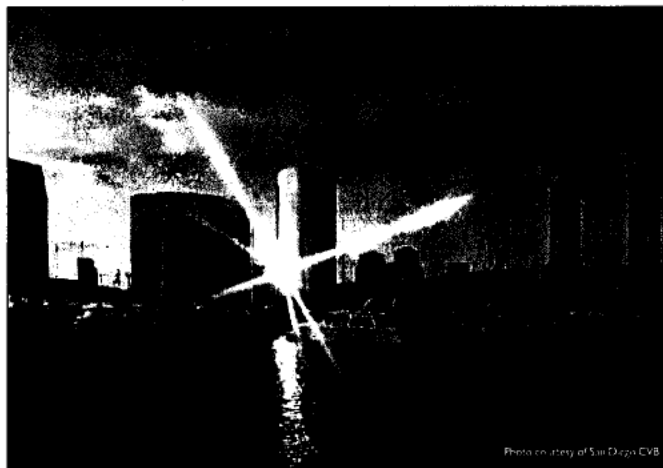


Photo courtesy of San Diego CVB

Make plans now to attend the 2009 ATS International Conference May 15-20 in San Diego.

sion of personalized medicine and what that means for patients; programming from the new ATS Assembly on Pulmonary Rehabilitation; and increased emphasis on serving the needs of pulmonary, critical care and sleep medicine trainees.

At the same time, blockbuster mainstays return to the program year after year. These include the ATS Awards Session from 4:30 to 6:30 p.m., on Sunday, May 17, where the

Amberson Lecture is presented; the ATS Public Advisory Roundtable symposium on pulmonary fibrosis from 1:30 to 4 p.m., also on Sunday; and the ATS Membership Meeting, which includes the President's Lecture, from 11:30 a.m. to 1 p.m., on Tuesday, May 19. The ever-popular Clinical Year in Review morning sessions are scheduled Sunday through Wednesday, May 20, while see ATS 2009, page 4

### Pre-register Today for ATS 2009 International Conference

Pre-register on or before April 20 to secure the discounted rate to attend the American Thoracic Society's 2009 International Conference in San Diego.

FROM APRIL 21 FORWARD, REGISTRANTS will pay the full conference fee, a full \$50 more than the fee up to April 20.

Conference attendees are strongly encouraged to pre-register by visiting the ATS Web site at [www.thoracic.org/go/international-conference](http://www.thoracic.org/go/international-conference). Attendees may also pre-register by phone at (866) 635-3582 or (508) 743-8518, by fax at (508) 759-4552 or by mail at International Conference San Diego 2009, c/o Convention Data Services, 107 Waterhouse Road, Bourne, MA 02532.

Pre-registration is open for ATS 2009 any time prior to the start of the conference on May 15 when the first post-graduate courses begin in San Diego. If you prefer, you can also register onsite at any time during the meeting at the registration counters outside of Hall D on the ground level of the San Diego Convention Center.

### Plenty of Fun in the Sun



Photo courtesy of San Diego CVB

Adjacent to the San Diego Convention Center, Seaport Village offers many shopping and dining choices and four miles of tree-lined paths.

### Conference Features Sessions on Research Efforts, Clinical Trials

Each year, researchers, scientists and clinicians gather at the American Thoracic Society's International Conference to hear about the latest findings of ongoing clinical trials and other research initiatives. ATS 2009 will feature 19 sessions sponsored by organizations like the National Heart, Lung, and Blood Institute (NHLBI), the National Aeronautics and Space Administration (NASA), the U.S. Food and Drug Administration (FDA) and the National Institute of Occupational Safety and Health. These sessions will address everything from the connection between urban environment and childhood asthma to the effect of moon dust on lungs.

At the Recruitment Pavilion in the 2800 row of the Exhibit Hall, attendees interested in breaking research will also have the opportunity to browse the organizations and institutions seeking to recruit



ATS 2009 presents the latest in ongoing clinical trials and research initiatives.

pulmonary, critical care or sleep medicine professionals for involvement in clinical trials or research studies. The Exhibit Hall will be open from May 17 to 19.

Among the 19 clinical trial sessions is

a key one that addresses "Urban Environment and Childhood Asthma (URECA): Insights to Early Markers of Immune Development and Asthma in the Inner City" which will take place from noon to 1 p.m. on Sunday, May 17. Sponsored by the National Institute of Allergy and Infectious Disease (NIAID) and the Inner City Asthma Consortium, the session will be chaired by Peter J. Gergen, M.D., M.P.H., medical officer of NIAID's Division of Allergy, Immunology and Transplantation.

In URECA, "investigators created a birth cohort, now several years in progress, where cytokines were measured in cord blood of infants who were then followed very closely for development of wheezing, allergic disease, food allergies and aeroallergens over the first years of life," Dr. Gergen said. "We want to present early birth cohort see RESEARCH, page 9



**We help the world breathe**  
FOR RESPIRATORY HEALTH CARE

2009 International Conference  
San Diego

**EVENING  
POSTGRADUATE SEMINAR**

SESSION 3

# COPD: A Systemic Disease?

Douglas Pavilion C/D, Manchester Grand Hyatt Hotel  
Sunday 17th May 2009 6:30pm - 9:00pm

## Agenda

- 6:30pm - 7:00pm: Introduction  
Tad Brown, Center for Autoimmune, Michigan, USA
- 7:00pm - 7:30pm: COPD  
Lutz Fabbri, MD  
University of Modena & Reggio Emilia, Italy
- 7:30pm - 8:00pm: COPD: A Systemic Disease?  
Stephen Seaward, MD  
University of Nebraska Medical Center, Omaha, Nebraska
- 8:00pm - 8:30pm: Systemic manifestations of COPD  
Barbara Grun, MD  
St. Elizabeth's Medical Center, Boston, Massachusetts
- 8:30pm - 9:00pm: Endothelial dysfunction, systemic inflammation and COPD  
Karin Rabe, MD  
Leiden University Medical Center, Leiden, The Netherlands
- 9:00pm - 9:30pm: COPD: A Systemic Disease? Systemic manifestations of disease  
Peter Hawcock, MD  
Oxley's Hospital, Ashford, Kent, United Kingdom
- 9:30pm - 9:00pm: Panel Discussion

For more information  
visit us online

**NICHD**



# SAN DIEGO FUN FACTS

Photos courtesy of San Diego CVB

## A Dozen Fun Facts Prove San Diego as Ideal Destination

The facts are incontrovertible. San Diego is a big draw for the convention, tourist, business, manufacturing and entertainment sectors. These 12 fun facts demonstrate why.



Balboa Park

**1** The sun shines 264 days of the year, and temperatures remain relatively constant year-round. Daytime temperatures range from 70 to 78 degrees in the summer and 63 to 67 degrees in the winter.

**2** San Diego is surrounded by 70 miles of beaches. Other major tourist destinations include Balboa Park, the San Diego Zoo, SeaWorld San Diego, nearby Wild Animal Park and Legoland.

**3** San Diego hosted two World's Fairs (1915 and 1935), the Panama-California Exposition in 1915 and the California Pacific International Exposition in 1935. Many of the Spanish/Baroque-style buildings in Balboa Park were built for these expositions.

**4** The San Diego Zoo is home to 4,000 animals of more than 800 species and is one of few zoos in the world to house pandas.

**5** The Hotel del Coronado on Coronado Island is the largest wooden structure in the United States. Presidents and celebrities have enjoyed lodging at this stately hotel, which is located on one of the best beaches in the U.S.

**6** Since 1898, more than 500 movies and television programs have been filmed in San Diego. The first 1898 Edison Company production featured a short street scene of downtown, complete with a double-decker trolley.

**7** With 2.8 million residents, San Diego is the nation's eighth largest city. Its leading industries are manufacturing, defense, tourism and agriculture. Telecommunications, software and biotech are among the fastest growing sectors.

**8** San Diego owes much of its economy to the Port of San Diego, which manages the maritime operations of San Diego harbor. The port houses the only major submarine and shipbuilding yards on the West Coast, the largest naval fleet in the world and the winter terminal for four major cruise ship lines.

**9** San Diego County produces more than 40 percent of California's avocado crop, which in turn produces 95 percent of the nation's avocados.



**10** According to U.S. Census Bureau education rankings, 40.4 percent of San Diego residents ages 25 and older have bachelor's degrees.

**11** Downtown San Diego has undergone extensive urban renewal since the early 1980s, beginning with the opening of the Horton Plaza shopping mall, the revival of the Gaslamp Quarter and the expansion of the San Diego Convention Center. The 16-block historic Gaslamp Quarter is famous for its turn-of-the-century Victorian architecture and is home to boutiques, art galleries and specialty shops.

**12** San Diego is home of the first European settlement on the West Coast. The first European to visit the region was Portuguese-born explorer Juan Rodriguez Cabrillo, who sailed under the Spanish flag.



Gaslamp Quarter

## Postgraduate Courses Present Latest in Sleep Medicine, Mechanical Ventilation

Four PG courses on Friday and Saturday, May 15 and 16, will provide attendees with the latest on sleep disorders and mechanical ventilation.

### Sleep Medicine

"The ATS considers sleep medicine one of its three pillars, and our aim is to provide postgraduate courses that reflect this prominence," said Mary J. Morrell, Ph.D., chair of the ATS Assembly on Sleep and Respiratory Neurobiology. "These day-long courses will provide attendees with a review of the latest advances in the field by international experts. The opportunity to interact with this faculty is an added value for attendees."

The sleep postgraduate courses are not normally linked, said course co-chair Ilene M. Rosen, M.D., program director of the Penn Sleep Fellowship at the Hospital of the University of Pennsylvania in Philadelphia. Dr. Rosen co-chairs the sleep postgraduate courses with Sushel P. Patil, M.D., Ph.D., an instructor in pulmonary and critical care medicine, and Brian McGinley, M.D., assistant professor in pediatric pulmonology, both of Johns Hopkins Medicine, in Baltimore.

"By attending both days, you will get a great overview of sleep medicine, which will include in-depth coverage of sleep biology and the non-pulmonary disorders, as well as pulmonary-related disorders, including pediatric ailments," Dr. Rosen said. "Pulmonary attendees had given us

feedback that they would like more in-depth coverage of the non-pulmonary sleep topics."

Both days will include a pre-test assessment with session review to identify areas of weakness that require further study, said Dr. Morrell, reader in respiratory physiology at the National Heart and Lung Institute at Imperial College in London. At each day's end, sessions will present summaries of diagnostic and management paradigms using a case-based format with review of sleep-related diagnostic testing.

The first course, PG13, will cover the neurobiology and physiology of normal sleep and will address non-pulmonary disorders, including insomnia, restless leg syndrome and the hypersomnias, Dr. Rosen said.

"This information may be particularly useful to U.S. physicians preparing for the ABIM Sleep Medicine Board Examination as a preliminary review," she said. "A solid knowledge base in both pulmonary and non-pulmonary sleep disorders is required for sleep medicine certification."

The second course, PG 28, will focus on pediatric sleep medicine and sleep-disordered breathing in adults. The pediatric sleep medicine portion will include sleep

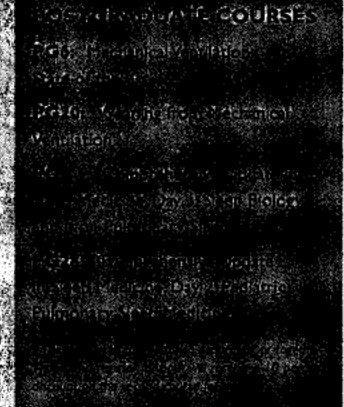
studies in children, sleep-disordered breathing in children and a review of neurologic sleep disorders manifested in children, Dr. Rosen added. The remainder of the course will address all sleep apnea diagnosis management and treatment and the interface between pulmonary disorders and sleep disorders.

"There will be something for everyone in these sleep medicine postgraduate courses from thorough reviews of sleep disorders to up-and-coming, push-the-envelope treatments," Dr. Rosen concluded.

### Mechanical Ventilation

The postgraduate courses on mechanical ventilation at the ATS International Conferences "have become classic ones," said Stefano Nava, M.D., who chairs two such courses being sponsored this year by the ATS Assembly on Critical Care. For 2009, the assembly developed "twin" postgraduate courses on mechanical ventilation and weaning to serve as a comprehensive "two-day immersion" into these topics.

"The number of mechanically ventilated patients is growing, taking up an increasing number of critical care beds in hospitals," said Dr. Nava, chief of the Respiratory Intensive Care Unit at the Fondazione S.



Maugeri Istituto Scientifico in Pavia, Italy. "Unfortunately, residents and fellows worldwide are not always ready to manage these patients because mechanical ventilation has not been a deeply explored field."

PG6: "Mechanical Ventilation: State of the Art" begins with a "back-to-the-basics" session, after which international leaders will outline the current state of knowledge, along with perspectives on how to integrate this information into clinical care.

"In addition to fundamentals, the course will be about what's new and what's hot see MECHANICAL VENTILATION, page 10

## ATS 2009 Exhibit Hall Offers Enticing New Features

"We encourage all attendees to visit the Exhibit Hall this year. Whether you want more information on a new product or service, are interested in being an investigator in new clinical trials or want to talk with patients about various pulmonary diseases, the ATS 2009 Exhibit Hall has something that can benefit everyone who attends the ATS International Conference."

*Michelle Turenne, director of ATS corporate alliances and development*

The Exhibit Hall returns to ATS 2009 with practical yet engaging enhancements and mainstay features back by popular demand. The 200-exhibitor event will be open from Sunday, May 17, through Tuesday, May 19, in Halls B1-C of the San Diego Convention Center.

New features in the Exhibit Hall this year include Product Theatres complete with complimentary box lunches; a Discovery Zone highlighting smaller exhibitors with some of the latest technology available in pulmonary, critical care and sleep medicine; and the Recruitment Pavilion, where members and attendees can talk with companies or institutions that are recruiting investigators for clinical trials or other employment opportunities.

The popular mainstays that will be returning to the Exhibit Hall include Publishers' Row, where attendees can find relevant journals and textbooks; the New Exhibitor Pavilion, which will be filled with innovative products from companies not seen before at the ATS International Conference; and the ATS Public Advisory Roundtable (ATS PAR) row, featuring the 15 member organizations that represent individuals and families affected by lung diseases, critical illnesses and sleep disorders. Collectively, ATS PAR

provides the Society's Board of Directors with strategic guidance to keep the patient and family perspectives as a central focus of all ATS activities and programs.

"We encourage all attendees to visit the Exhibit Hall this year," said Michelle Turenne, director of ATS corporate alliances and development. "Whether you want more information on a new product or service, are interested in being an investigator in new clinical trials or want to talk with patients about various pulmonary diseases, the ATS 2009 Exhibit Hall has something that can benefit everyone who attends the ATS International Conference."

Product Theatres will be held Sunday-Tuesday over lunch in the Exhibit Hall. These are promotional programs that provide the latest information on specific drugs or devices. There are three Product Theatres in the Exhibit Hall, two of which seat 250 people and one that seats 150. Boxed lunches will be available to participants while quantities last. The *ATS Daily Bulletin* will publish a Product Theatre schedule each day, complete with topics and speakers.

"When exhibitors converse one-on-one in the booth, they can only interact with so many people," said Stacy Blackshaw, CEM, associate director of meetings and events at



The Exhibit Hall is an extension of the ATS 2009 educational experience, featuring nearly 200 companies showcasing products and services supporting pulmonary, critical care and sleep medicine.

Talley Management Group, Inc., a company that works with the ATS on the conference Exhibit Hall. "These Product Theatre presentations allow exhibitors to open the dialog to a much wider audience by having content experts talk about the latest information in specific therapeutic areas."

The Discovery Zone provides an opportunity to interact with participating exhibitors in some of the smaller booths throughout the Exhibit Hall, many of which have cutting-edge products or technology. Attendees will receive game cards in their registration packets, and the cards contain questions with answers that can only be found by visiting participating booths. Once cards are filled out with all questions correctly answered, attendees may place them in designated bins for daily prize drawings.

The Exhibit Hall's Recruitment Pavilion is a centralized area where ATS members and other attendees can talk to companies that are looking to recruit investigators for clinical trials. The pavilion will be located in the 2800 aisle on the right side of the Exhibit Hall.

"Everyone involved in pulmonary research is at the ATS meeting, so this is a great way to meet with potential investigators," said Robert K. Zeldin, M.D., vice president and U.S. medical franchise head of respiratory and dermatology at Novartis Pharmaceuticals Corporation.

Another enhancement involves more Internet booths. Those have always been available outside the Exhibit Hall, but as an extended service this year, another set of  
see EXHIBIT HALL, page 8

The ATS annual Diversity Forum, which will take place from noon to 1:30 p.m. on Sunday, May 17, will highlight the importance of diversity within the fields of pulmonary, critical care and sleep medicine. The forum also serves as an opportunity to recognize the career advancement of minority group members.

This year, the forum will feature a special presentation by Wonder P. Drake, M.D., assistant professor of medicine in the Department of Infectious Diseases at Vanderbilt University School of Medicine, in Nashville. Dr. Drake will address the importance of increasing diversity within the research, academic and clinical realms to meet the needs of a diverse public.

The forum will also include the presentation of the 2009 ATS Minority Trainee Travel Awards (MTTAs). Supported by a generous grant from Merck & Co., Inc., the MTTA program recognizes junior researchers who co-authored abstracts accepted for presentation at the ATS International Conference

and who self-identify as an underrepresented minority, as defined by the National Institutes of Health. Each MTTA awardee will receive a grant, including one year's In-Training Membership, valued at \$75, and a check for \$1,425 to defray travel costs to the ATS International Conference. All past recipients are invited to attend the forum to share their experiences with the program and how it validated or changed their career paths.

Serving as Diversity Forum host will be Chadi A. Hage, M.D., assistant professor of medicine at the Veterans Administration Medical Center in Indianapolis. Dr. Hage is a member of the ATS Membership Committee, which develops the program for this annual event.

Conference badges are required for admission. Space is limited and attendance will be on a first-come, first-served basis. There is no additional fee, and a plated lunch will be served.

This event is supported by a grant from Merck & Co., Inc.

### ATS 2009

*continued from page 1*

afternoon sessions are planned for Nursing Year in Review on Monday, May 18, and for Pediatrics Year in Review on Tuesday.

This year's President's Lecture features

Jeffrey Drazen, M.D., editor-in-chief of the *New England Journal of Medicine*, whose lecture is titled "In a Sea of Information, What Can We Trust?" Dr. Drazen will provide a thought-provoking review of challenges in obtaining information from

basic, translational and clinical research and translating that information into clinical practice, Dr. Wright said. He will also offer perspectives on what it is like to be editor of the *NEJM*, a position he has held since 2000.

"Dr. Drazen has been an extremely insightful and forward-thinking leader on topics of how clinical practice is, and should be, affected by medical journals and how readers should consider concerns about conflict of interest in their reading of medical literature," Dr. Wright said. "The lecture

will challenge us to think carefully about the sources of information that we have and how we incorporate that information into our daily routines."

This is just some of the first-rate programming and activities planned for ATS 2009 in San Diego.

"When it comes to meetings in our

field, the ATS International Conference is regarded as one of the top meetings," Dr. Kraft said. "If people can only go to one meeting, they are likely to choose this one because it fulfills so many of their educational needs."

"The conference provides an outstanding blend of basic, clinical and translational science and up-to-date overviews of the state of the art in research and clinical care."

*ATS President Jo Rae Wright, Ph.D.*

## ATS PAR Symposium to Address Latest Advances in Pulmonary Fibrosis

During ATS 2009, the Society's Public Advisory Roundtable (PAR) will convene leading bench-to-bedside pulmonary fibrosis experts for its annual symposium from 1:30 to 4 p.m. on Sunday, May 17. The symposium will present basic science information, disease-specific scientific contributions, future directions for research and the patient perspective on pulmonary fibrosis.

"The idea is to bring together clinicians, researchers and patients to examine carefully the current status of our understanding with pulmonary fibrosis," said ATS Immediate-Past President David H. Ingbar, M.D., professor of medicine and director of pulmonary and critical care at the University of Minnesota in Minneapolis, who will co-chair the symposium with Donna Appell, R.N.

"This session will include short talks from patients, who will put a face on this disease and add the patient perspective to the conversation," said Ms. Appell, ATS PAR chair.

The basic science review will include discussion of new fundamental mechanisms that lead to this usually idiopathic disease, including a mixture of genetic, occupational and environmental factors, Dr. Ingbar said.

A major symposium goal is to bring together knowledge about the common idiopathic types of pulmonary fibrosis with insights learned from more rare causes of pulmonary fibrosis and from the genetics of familial pulmonary fibrosis. For example, researchers are particularly interested in pulmonary fibrosis as part of Hermansky-Pudlak Syndrome (HPS), whose causative molecular defect in the lungs is not as well understood as it is in the skin and other organs.

"The goal is to bring together the new mo-



lecular approaches, both in terms of identifying new targets for treatment based on our understandings of mechanisms and where we sit in terms of molecular diagnostics, biomarkers, proteomics and genomics," Dr. Ingbar said.

Recently, the first positive clinical trial outcome for idiopathic pulmonary fibrosis was reported using the drug pirfenidone. Now, eyes are on the pirfenidone clinical trial for HPS pulmonary fibrosis that is sponsored by the National Human Genome Research Institute (NHGRI).

"We will also talk about other clinical trials that are underway and new modalities for treatment, such as the potential application of stem cell therapy in these sets of diseases, and how they work," Dr. Ingbar continued.

Interactive discussion between speakers and the audience is a crucial feature of the ATS PAR symposium.

"It's a chance to discuss new directions in pulmonary fibrosis in a real out-of-the-box creative moment of anything new and anywhere we could head," Ms. Appell explained. "We want scientist and clinician attendees to be in the audience because we want their brilliant minds to be thinking about how to get us closer to curing pulmonary fibrosis."

Topics and speakers planned to date for this year's ATS PAR symposium include:

- "New Molecular Targets in Pulmonary Fibrosis," Peter B. Bitterman, M.D., professor of medicine and pulmonologist at the University of Minnesota in Minneapolis
- "Lessons From Pulmonary Fibrosis in Hermansky Pudlak Syndrome NHGRI," Bernadette Gochuico, M.D., pulmonary investigator at the National Human Genome Research Institute in Bethesda, Maryland
- "Genomics and Pulmonary Fibrosis," James E. Loyd, M.D., the Rudy W. Jacobson professor of medicine in the Department of Medicine/Division of Allergy, Pulmonary and Critical Care Medicine at Vanderbilt University School of Medicine in Nashville, Tennessee
- "Molecular Diagnostics and Biomarkers in IPF," Naftali Kaminski, M.D., director of the Dorothy P. and Richard P. Simmons Center for Interstitial Lung Disease in the Division of Pulmonary, Allergy and Critical Care Medicine at the University of Pittsburgh in Pennsylvania
- "Where Are We With Clinical Trials in IPF?" Paul W. Noble, M.D., chief of the Division of Pulmonary, Allergy, and Critical Care at Duke University in Durham, North Carolina
- "Novel Treatments for Pulmonary Fibrosis: Stem Cells and All That Jazz," Luis A. Ortiz, M.D., associate professor in the Division of Pulmonary, Allergy and Critical Care Medicine at the University of Pittsburgh in Pennsylvania

### Pick Up Complimentary Journals, Magazines at ATS 2009

This year, the American Thoracic Society is offering attendees an additional benefit for registering for the ATS 2009 International Conference—the opportunity to pick up copies of leading medical journals and news magazines, free-of-charge, during the conference.

The following periodicals will be available at the ATS 2009 Journal Annex, located outside of the Exhibit Hall in the San Diego Convention Center:

- *American Journal of Respiratory and Critical Care Medicine*
- *American Journal of Respiratory Cell and Molecular Biology*
- *Canadian Respiratory Journal*
- *Clinical Respiratory Journal*
- *Journal of Physiology*
- *Journal of the American Medical Association*
- *Journal of Sleep Research*
- *New England Journal of Medicine*
- *Proceedings of the American Thoracic Society*
- *Science*
- *The Lancet*
- *Thorax*

New this year, a number of leading news magazines that cover the fields of respiratory, critical care and sleep medicine will also be available at a designated area outside of the Exhibit Hall.

Attendees may pick up free copies of the following publications at the ATS 2009 Magazine Annex:

- *Advance for Managers of Respiratory Care*
- *Advance for Respiratory Care Practitioners*
- *Pulmonary Reviews*
- *RT for Decision Makers in Respiratory Care*

## ATS 2009 Offers Exceptional Programs Presented in Myriad Formats

Among the interactive courses, symposia and workshops at ATS 2009 are PG 17: "Interventional Pulmonology with Practical Demonstration: Something for Every Pulmonologist," WS1: "Endobronchial Ultrasound," A11: Fellow Case Conference: Third Edition, B12: "Fellows Symposium: Practical Tips for Transitioning to a Successful Academic Career" and WS4 "Bronchiectasis: Many Causes, Shared Challenges."

PG 17, which will take place from 8 a.m. to 4 p.m., on Saturday, May 16, will "update the audience on interventional pulmonology technologies already in use and familiarize attendees with new technologies, such as electromagnetic navigation and endobronchial ultrasound," said course chair Praveen N. Mathur, M.B.B.S., professor of clinical medicine at Indiana University School of Medicine in Indianapolis. "This course also provides a knowledge base to those pulmonologists who may want to secure more training in specific techniques and technologies. This course would cement their interest."

WS1, scheduled from noon to 1:30 p.m. on Sunday, May 17, will demonstrate how endobronchial ultrasound provides real-time feedback.

"Endobronchial ultrasound has become a very mature technology, and it has proven valuable in staging lung cancer," said workshop chair Armin Ernst, M.D., director of interventional pulmonology at Beth Israel Deaconess Medical Center in Boston. "In this session, we will discuss the applications and also provide a hands-on feature using models for participants to try out this new and exciting technology."

A11, on the other hand, "pits some of the best minds in pulmonary medicine, radiology and pathology against a series of fascinating clinical cases," said session chair John G. Mastrorade, M.D., chair of the ATS Training Committee and associate professor at Ohio State University in Columbus. "The real attraction of the Fellow Case Conference is to observe how master physicians work their way through these challenging clinical scenarios." He notes that both fellows and senior clinicians and

researchers are encouraged to attend this session, which will take place from 8:15 to 10:45 a.m. Sunday, May 17.

B12 on academic careers offers a "summary of current economic realities and opportunities and practical advice on the nuts and bolts of achieving success in academia," said course chair Robert Kempainen, M.D., associate professor of medicine at University of Minnesota School of Medicine in Minneapolis. The course, scheduled from 8:15 to 10:45 a.m., on Monday, May 18, will serve as a great supplement to the advice attendees are receiving at their home institutions.

WS4 will provide an update on the different causes of bronchiectasis and will cover the epidemiology and treatment of cystic fibrosis, primary ciliary dyskinesia, immune deficiency and infections. The workshop, which will be held from noon to 1:30 p.m., on Monday, May 18, will also address similarities and differences of effective treatments for different causes of bronchiectasis.

These courses join scores of educational



Marvin I. Schwarz, M.D., served as one of the expert panelists for last year's case-based sessions that focused on clinical pulmonologists, critical care physicians, hospitalists and trainees in pulmonary and critical care medicine.

programs addressing the most relevant topics in the field.

"This year's International Conference will offer high-quality science," said conference committee chair Monica Kraft, M.D. "We will feature the authorities in the field and provide attendees with an opportunity to interact with experts."

## Assembly Leaders Highlight Not-To-Be-Missed Presentations

The American Thoracic Society's 13 assemblies have highlighted these abstracts as some of the most interesting to be presented at ATS International Conference in San Diego. Search for full abstracts by title, author or session at [www.abstracts2view.com/ats09](http://www.abstracts2view.com/ats09) in late April.

**Assembly on Allergy, Immunology and Inflammation**  
"Deletion of Myeloid Cell I- $\kappa$ B Kinase  $\beta$  Prevents Induction of Mouse Lung Allograft Tolerance." Authors: H.J. Huang, S. Sugimoto, G.A. Patterson, A.S. Krupnick, D. Kreisel, A.E. Gelman, St. Louis, Missouri. Session: B91 "The Yin and Yang of Lung Injury: New Insights into Mechanisms of Progression and Resolution" (Mini-Symposium; 1:30 to 4 p.m., Monday, May 18, Room 3, Upper Level, San Diego Convention Center)  
"Localization and Enumeration of Human Lung Dendritic Cells from Asthmatic Patients Undergoing Anti-IgE Therapy: A Multispectral Confocal Microscopy Study." Authors: H.S. Chand, M. Schuyler, M.F. Lipscomb, Albuquerque, New Mexico. Session: C13 "Mechanisms of Disease in Human Asthma" (Mini-Symposium; 8:15 to 10:45 a.m., Tuesday, May 19, Room 33 A-C, Upper Level, SDCC)

**Assembly on Behavioral Science**  
"Improving Asthma Care for Minority Children in Head Start (HS)." Authors: A.L. Bilderback, M.N. Eakin, A.M. Butz, M.E. Bollinger, C.S. Rand, K.A. Riekert, Baltimore, Maryland. Session: B14 "Pediatric Asthma: Opportunities and Challenges to Improving Outcomes" (Mini-Symposium; 8:15 to 10:30 a.m., Monday, May 18, Room 7 A-B, Upper Level, SDCC)  
"Environmental Tobacco Smoke Exposure in Childhood Predicts Early Emphysema in Adulthood: The MESA Lung Study." Authors: G.S. Lovasi, A.V. Diez-Roux, E.A. Hoffman, R. Jiang, D.R. Jacobs, S. Kawut, R.G. Barr, Iowa City, IA, Ann Arbor, Michigan; Minneapolis, Minnesota; New York, New York. Session: C17 "Smoking Cessation" (Mini-Symposium; 8:15 to 10:45 a.m., Tuesday, May 19, Room 30 A-B, Upper Level, SDCC)

**Assembly on Clinical Problems**  
"The CAPACITY (CAP) Trials: Randomized, Double-Blind, Placebo-Controlled, Phase III Trials of Pirfenidone (PFD) in Patients with Idiopathic Pulmonary Fibrosis (IPF)." Authors: P. Noble, C. Albera, W. Bradford, U. Costabel, D. Kardatzke, T. King, Jr., S. Sahn, J. Szwarcberg, D. Valeyre, R. du Bois, Brisbane, San Francisco, California; Denver, Colorado; Durham, North Carolina; Charleston, South Carolina; Paris, France; Essen, Germany; and Italy. Session: A23 "Interstitial Lung Disease: Outcomes and Selected Clinical Issues" (Poster Discussion Session; 8:15 to 10:45 a.m., Sunday, May 17, Room 6 F, Upper Level, SDCC)  
"The (Cost)-Effectiveness of Self-Treatment of Exacerbations on the Severity of Exacerbations in COPD Patients: The COPE II-Study." Authors: T.W. Effing, H.A.M. Kerstjens, P.D.L.P.M. van der Valk, G.A. Zielhuis, J. van der Palen, Enschede, Groningen, Nijmegen, The Netherlands. Session: A39 "Chronic Obstructive Pulmonary Disease Exacerbations" (Thematic Poster Session; 8:15 a.m. to 4 p.m., Sunday, May 17, Area K, Sails Pavilion, Upper Level, SDCC)

**Assembly on Critical Care**  
"Effect of Race on the Incidence of Acute Lung Injury." Authors: S.E. Erickson, C.R. Cooke, M.D. Eisner, G.S. Martin, Atlanta, Georgia; Seattle, Washington; San Francisco, California. Session: C92 "Acute Lung Injury/Acute Respiratory Distress Syndrome: Outcomes and Predictors of Failure" (Mini-Symposium; 1:30 to 4 p.m., Tuesday, May 19, Room 30 C-E, Upper Level, SDCC)  
"Plateau Pressure: A Lung-Specific Predictor of Hospital Mortality in Patients with Acute Lung Injury (ALI)." Authors: W. Checkley, D. Hager, R. Brower, Baltimore, Maryland. Session: C92 "Acute Lung Injury/Acute Respiratory Distress Syndrome: Outcomes and Predictors of Failure" (Mini-Symposium; 1:30 to 4 p.m., Tuesday, May 19, Room 30 C-E, Upper Level, SDCC)

**Assembly on Environmental & Occupational Health**  
"A Carbon Nanotube Model of Pulmonary Granuloma in Wild-Type and PPAR $\gamma$  Knock Out (KO) Mice." Authors: D. Brescia, L. Dobbs, C.J. Wingard, B.P. Barna, A.J. Mccoy, A. Malur, C. Kukoly, M.S. Kavuru, M.J. Thomassen, Greenville, North Carolina. Session: C105 "Nanomaterials: Little Particles, Big Impact" (Poster Discussion Session; 1:30 to 4 p.m., Tuesday, May 19, San Diego Ballroom B, North Tower, Lobby Level, San Diego Marriott Hotel And Marina)  
"A High Fat, High Energy Food Challenge Induces an Exaggerated Inflammatory Response in Asthma." Authors: L.G. Wood, M.L. Garg, A. Wood, J. Smart, P.G. Gibson, Newcastle, Australia. Session: A94 "Asthma as a Systemic Disease: The Role of Co-Morbidities" (Mini-Symposium; 1:30 to 4 p.m., Sunday, May 17, Room 6 C, Upper Level, SDCC)

**Assembly on Microbiology, Tuberculosis & Pulmonary Infections**  
"Extensively Drug-Resistant Tuberculosis—A Threat to Health Care Workers." Authors: J.M. Jarand, M. Loveday, K. Shean, P. Willcox, K. Dheda, Calgary, Canada, Cape Town, Western Cape, South Africa. Session: A96 "Tuberculosis: Assessing Transmission and Risk" (Mini-Symposium; 1:30 to 4 p.m., Sunday, May 17, Room 33 A-C, Upper Level, SDCC)  
"Zinc Supplementation Restores GM-CSF Signaling in the Alveolar Macrophage and Facilitates Clearance of Klebsiella Pneumoniae in the Lungs of Alcohol-Fed Rats." Authors: A.J. Mehta, P.C. Joshi, X. Fan, D.M. Guidot, Atlanta, Georgia. Session: A15 "Pulmonary Infections: Modulating Host Defenses" (Mini-Symposium; 8:15 to 10:45 a.m., Sunday, May 17, Room 11 A-B, Upper Level, SDCC)

**Assembly on Nursing**  
"Effect of Oral Corticosteroid Addiction in Treatment of Controlled Asthma Patients: A Randomized Clinical Trial." Authors: A.A. Araruna, M.M. Amorim, L.B. Caetano,

I.L. Santoro, A.L.G. Fernandes, São Paulo, Brazil. Session: A16 "Asthma Management/Monitoring Chronic Obstructive Pulmonary Disease" (Mini-Symposium; 8:15 to 10:45 a.m., Sunday, May 17, Room 3, Upper Level, SDCC)  
"Environmental Tobacco Smoke Exposure in Childhood Predicts Early Emphysema in Adulthood: The MESA Lung Study." Authors: G.S. Lovasi, A.V. Diez-Roux, E.A. Hoffman, R. Jiang, D.R. Jacobs, S. Kawut, R.G. Barr, Iowa City, IA, Ann Arbor, MI, Minneapolis, MN, New York, NY. Session: C17 "Smoking Cessation" (Mini-Symposium; 8:15 to 10:45 a.m., Tuesday, May 19, Room 30 A-B, Upper Level, SDCC)

**Assembly on Pediatrics**  
"Immune Response Varies by TLR4 Genotype After RSV Infection." Authors: T.W. Guilbert, S.A. Sund, M.D. Evans, C. Ober, J.E. Gern, R.F. Lemanske, Jr., Madison, Wisconsin; Chicago, Illinois. Session: C94 "Viral Infections in Childhood Respiratory Disease" (Mini-Symposium; 1:30 to 4 p.m., Tuesday, May 19, Room 3, Upper Level, SDCC)

"Anti-IL-5 Treatment Attenuates the Asthma Phenotype in Infant Monkeys, But Also Affects Normal Lung Development." Authors: L.A. Miller, J.E. Gerriets, R.O. Fishman, E.D. Wallis, K.P. Maniar, J.H. Fontaine, E.S. Schelegle, Davis, California. Session: A97 "Best in Pediatrics" (Mini-Symposium; 1:30 to 4 p.m., Sunday, May 17, Marriott Hall 3, SDMHM)

**Assembly on Pulmonary Circulation**  
"A Primary Role of Activated CD8 $^{+}$ T-Cells in the Pathogenesis of Pulmonary Arterial Hypertension." Authors: G. Sutendra, S. Bonnet, P. Dromparis, S. McMurtry, A. Haromy, C. Bleackley, E.D. Michelakis, Edmonton, Canada. Session: A106 "Role of Inflammation in Pulmonary Vascular Remodeling and Injury" (Poster Discussion Session; 1:30 to 4 p.m., Sunday, May 17, Room 8, Upper Level, SDCC)

"Prevalence and Mechanism of Pulmonary Hypertension in Sickle Cell Disease: A Prospective Multicentre French Study." Authors: F. Parent, D. Bachir, F. Lionnet, J. Inamo, F. Driss, L. Savale, G. Loko, A. Elmazouzi, A. Leterrier, R. Girot, F. Galacteros, G. Simonneau, Clamart, France. Session: B27 "From Alpha to Omega: Assessment and Outcomes in Pulmonary Hypertension" (Poster Discussion Session; 8:15 to 10:45 a.m., Monday, May 18, Room 31 A-C, Upper Level, SDCC)

**Assembly on Pulmonary Rehabilitation**  
"Cost-Effectiveness of a 24-Month INTERdisciplinary COMMunity-Based COPD Management Program (INTERCOM) in Patients with Less Advanced Airflow Obstruction." Authors: C.R. van Wetering, M. Hoogenboom, D.R. De Munck, M.P. Rutten-van Molken, A.M. Schols, Veldhoven, Rotterdam, Maastricht, The Netherlands. Session: D16 "Outcomes in Pulmonary Rehabilitation" (Mini-Symposium; 8:15 to 10:45 a.m., Wednesday, May 20, Room 6 E, Upper Level, SDCC)

"Contractile Muscle Fatigue is Associated with Effectiveness of Exercise Training in COPD." Authors: C. Burtin, D. Saey, D. Langer, M. Saglam, R. Gosselink, M. Decramer, T. Troosters, Leuven, Belgium. Session: A18 "Pulmonary Rehabilitation: Adding Muscle to Therapy for Patients with Respiratory Disease" (Mini-Symposium; 8:15 to 10:45 a.m., Sunday, May 17, Room 30 C-E, Upper Level, SDCC)

**Assembly on Respiratory Cell and Molecular Biology**  
"On the TRAIL of a Killer: TRAIL-Expressing Mesenchymal Stem Cells are Able to Target and Eliminate Lung Metastases." Authors: M.R. Loebinger, S.M. Janes, London, England. Session: C96 "Lung Tumorigenesis: Insights from Animal Models" (Mini-Symposium; 1:30 to 4 p.m., Tuesday, May 19, Marriott Hall 5-6, SDMHM)  
"Dimethylarginine Dimethylaminohydrolase 2 in Idiopathic Pulmonary Fibrosis." Authors: S.S. Pullamsetti, R. Savai, R. Dumitrascu, M. Konigshoff, H.A. Ghofrani, N. Weissmann, F. Grimminger, O. Eickelberg, A. Guenther, J. Leiper, W. Seeger, R.T. Schermuly, Giessen, Bad Nauheim, Germany, London, England. Session: D17 "Fibroblasts, Progenitor Cells and Models of Interstitial Fibrosis that Reveal Mechanisms of Disease" (Mini-Symposium; 8:15 to 10:45 a.m., Wednesday, May 20, Marriott Hall 4, SDMHM)

**Assembly on Respiratory Structure and Function**  
"Allogeneic Human Mesenchymal Stem Cells Improve Endothelial Barrier Integrity Across Human Lung Microvascular Endothelial Cells Following an Inflammatory Insult." Authors: J.W. Lee, J. Howard, M.A. Matthay, San Francisco, California. Session: B97 "Mesenchymal Stem Cells in the Lung: Recruitment, Retention and Performance" (Mini-Symposium; 1:30 to 4 p.m., Monday, May 18, Room 30 A-B, Upper Level, SDCC)  
"Non-Destructive Morphometric Assessment of Murine Airway Via Hi-Res microCT." Authors: D.M. Vasilescu, D. Chon, T. Fong, J. Heverhagen, M. Ochs, E.R. Weibel, E.A. Hoffman, Concord, CA, Iowa City, IA, Marburg, Germany, Bern, Switzerland. Session: A19 "Imaging the Distal Lung: Advances in Technique and Application" (Mini-Symposium; 8:15 to 10:45 a.m., Sunday, May 17, Room 1 A-B, Upper Level, SDCC)

**Assembly on Sleep and Respiratory Neurobiology**  
"Intermittent Hypoxia Alters Endothelial Cell Barrier Function: Role of ROS and MAP Kinases." Authors: M.M. Lee, V. Makarenko, J. Nanduri, P. Usatyuk, V. Natarajan, N.R. Prabhakar, Chicago, Illinois. Session: A20 "Physiological Responses to Intermittent Hypoxia" (Mini-Symposium; 10:15 to 10:45 a.m., Sunday, May 17, Marriott Hall 4, San Diego Marriott Hotel and Marina)  
"Obesity, Leptin and Upper Airway Collapsibility in Mice." Authors: A.S. Elsayed-Ahmed, L.E. Pichard, H. Schneider, P.L. Smith, V. Polotsky, A.R. Schwartz, Baltimore, Maryland. Session: D19 "Upper Airway: State of the Art 2009" (Mini-Symposium; 8:15 to 10:45 a.m., Wednesday, May 20, Room 11 A-B, Upper Level, SDCC)

FOR PULMONARY  
ARTERIAL HYPERTENSION  
(PAH) NYHA CLASS II

# SECOND WIND<sup>®</sup> IN PAH

**Ventavis is the only PAH therapy proven to improve**

- ✓ **Significant improvement** in clinical outcomes ( $p=0.002$ ).<sup>1,2</sup>
- ✓ **Significant improvement** in NYHA functional class ( $p=0.002$ ),<sup>2,3</sup> and
- ✓ **Significant improvement** in exercise capacity ( $p=0.01$ ).<sup>4</sup>

**AN PROSTALINAM** Randomized, double-blind, multicenter, placebo-controlled trial to evaluate the efficacy and safety of Ventavis as monotherapy in the treatment of PAH NYHA Class II or III (n=348). Clinical outcomes defined as a 25% increase in 6MWD, improvement in NYHA functional class, and lack of clinical deterioration or death.

**IMPORTANT SAFETY INFORMATION:**

In clinical studies, common adverse reactions due to Ventavis included vasodilation (flushing), cough, headache, tremor, and insomnia. Serious adverse events reported at a rate of less than 3% included congestive heart failure, chest pain, supraventricular tachycardia, dyspnea, peripheral edema, and kidney failure. Vital signs should be monitored while initiating Ventavis. Ventavis should not be initiated in patients with systolic blood pressure less than 85 mm Hg. Stop Ventavis immediately if signs of pulmonary edema occur; this may be a sign of pulmonary venous hypertension.

Please see brief summary of prescribing information on following page.



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# Forum Honors Women Researchers and Clinicians



Cynthia S. Rand, Ph.D., professor of medicine at Johns Hopkins University, in Baltimore, will present at this year's Women's Forum.

The Women's Forum will take place from noon to 1:30 p.m. on Monday, May 18, at ATS 2009. This annual event formally recognizes the advancement of women in research, translational science and clinical care within the fields of pulmonary, critical care and sleep medicine. This year, the forum will feature a special presentation from Cynthia S. Rand, Ph.D., professor of medicine at Johns Hopkins University, in Baltimore. An active and accomplished ATS member, Dr. Rand will discuss her professional and personal journey to become a prominent leader in her field. She will specifically address "Climbing Ladders,

Juggling Monkeys and the Work-Life Balancing Act: Thoughts on Gender and Life in the Academic Medicine Circus."

The forum will also feature the presentation of the 2009 Elizabeth A. Rich, M.D., Award to Patricia W. Finn, M.D., chief of pulmonary and critical care medicine at the University of California, San Diego. Each year, the ATS Membership Committee presents this award to a female member who has demonstrated leadership in her field, has made major achievements in pulmonary, critical care or sleep medicine, and has been a mentor to her juniors in the profession.

Serving as forum moderator will be ATS

Membership Committee Chair Serpil C. Erzurum, M.D., chair of the Department of Pathobiology at the Cleveland Clinic Foundation's Lerner Research Institute in Ohio. She is a leading researcher in the areas of asthma and pulmonary arterial hypertension, with additional interests in lung biology and physiology and exhaled markers of lung disease.

Conference badges are required for admission. Space is limited and admittance will be on a first-come, first-served basis. There is no additional fee, and a plated lunch will be served.

This event is supported by a grant from Merck & Co, Inc.



### KEY MESSAGE

The following is a summary of the Full Prescribing Information for Ventovis (quetiapine fumarate). Please refer to the Full Prescribing Information for prescribing Ventovis.

### INDICATIONS AND USAGE

Ventovis is indicated for the treatment of primary and secondary prevention of stroke in patients with atrial fibrillation. Ventovis is not indicated for the treatment of stroke in patients with atrial fibrillation. Ventovis is not indicated for the treatment of stroke in patients with atrial fibrillation. Ventovis is not indicated for the treatment of stroke in patients with atrial fibrillation.

### CONTRAINDICATIONS

Ventovis is contraindicated in patients with known hypersensitivity to quetiapine fumarate or any of its components.

### WARNINGS

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### PRECAUTIONS

#### General

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Patients should be advised that they may have a fall in blood pressure with Ventovis, so they may become dizzy or even faint. They should always drive when they get out of a chair or bed. If taking this drug, patients should avoid alcohol. Patients should avoid alcohol.

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Table 1. Adverse Events in Phase 3 Clinical Trial

Adverse Event	Quetiapine (n=100)	Placebo (n=100)	Relative Risk (%)
Headache	15	10	1.5
Dizziness	12	8	1.5
Nausea	10	7	1.4
Constipation	8	5	1.6
Fatigue	7	5	1.4
Blurred vision	6	4	1.5
Weight gain	5	3	1.7
Orthostatic hypotension	4	2	2.0
Diarrhea	3	2	1.5
Insomnia	2	1	2.0
Abnormal ECG	1	0	1.0
Stroke	1	0	1.0
Death	1	0	1.0

Stroke was the most common adverse event in the phase 3 clinical trial. The relative risk of stroke was 1.0 for the quetiapine group compared to the placebo group. The absolute risk of stroke was 1.0% for the quetiapine group and 0% for the placebo group.

Other adverse events included dizziness, headache, and constipation. The relative risk of these events was 1.5 for the quetiapine group compared to the placebo group. The absolute risk of these events was 1.5% for the quetiapine group and 1.0% for the placebo group.

Patients should be advised that they may have a fall in blood pressure with Ventovis, so they may become dizzy or even faint. They should always drive when they get out of a chair or bed. If taking this drug, patients should avoid alcohol. Patients should avoid alcohol.

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## EXHIBIT HALL

continued from page 4

Internet booths will also be placed inside the Exhibit Hall, Ms. Turenne said.

One challenge for attendees is that there is so much to do and see in the Exhibit Hall that it can be a bit overwhelming. Many companies send out pre-mailers to let attendees know what they will be talking about at their booths. If you get pre-mailers that interest you, pop them in the folder with your itinerary and hotel confirmation numbers so you can visit the booth onsite. Additionally, the ATS recommends that attendees do their homework before they reach the hall by reviewing the ATS Exhibit Guide carefully to select key exhibits they will want to visit.

"The ATS Exhibit Guide will help attendees navigate the floor and make their Exhibit Hall experience more productive," Ms. Blackshaw said. "Also, take time to walk the aisles and meet exhibitors. You never know when you are going to come across some interesting product in an exhibit that you hadn't planned to visit."

And with many individuals having less opportunity to interact with sales representatives, staying current in new products can be challenging. "For many physicians and researchers these days, the ATS Exhibit Hall is the only forum where they can engage in discussions with company representatives about their products," Ms. Turenne said.

While significantly fewer giveaways will be available for ATS 2009 because of compliance with the new PhRMA Code, not all exhibitors are pharmaceutical or device companies, so those companies will be eligible to provide giveaway products to attendees. Still, what all companies will certainly provide is the latest information about the products and services that support pulmonary, critical care and sleep medicine.

"Visiting the Exhibit Hall allows attendees to collect additional information that will be helpful in their practice or their labs," Ms. Blackshaw said. "The Exhibit Hall provides attendees with a venue to immediately compare the many types of products and services that could be relevant for a condition or treatment."

"It is also important because the participation of these more than 200 companies in the Exhibit Hall does support the ATS International Conference as a whole," Ms. Turenne noted. "There really are a lot of exciting companies on the floor this year, and we want them to come back again next year."

RESEARCHER: Y. Okazaki, M. Saito, M. Goto, et al. Clinical Impact for severe pulmonary hypertension. *N Engl J Med*. 2009;361:222-232. N. Ventovis (quetiapine fumarate) information. Astellas Pharmaceuticals US, Inc. 2009.

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July 2009  
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## Meet Future Clinicians, Researchers, Educators at Exchange

The Fellow and Junior Professional Exchange is an annual networking event at the ATS International Conference for pulmonary, critical care and sleep medicine fellows, internal medicine and pediatric residents and other trainees, as well as for those transitioning to professional careers. The 2009 exchange will take place from 7 to 8 p.m. on Sunday, May 17. This informal, resource-filled event allows trainees and others at the beginning of their careers to network with peers and leaders in their fields. This year, the exchange will feature career pathway experts who will discuss their professional journeys in pulmonary, critical care and sleep medicine from a variety of perspectives at the "bench and bedside"—including research, academia, administration and clinical practice.

ATS leaders, program directors, national public health experts and decision-makers look forward to this exchange as an opportunity to meet and greet future clinicians, researchers and educators.

Each year, this event is jointly developed and hosted by the ATS Membership Committee, Training Committee and Members In-Transition and Training Committee.

Conference badges are required for admission. Space is limited and admittance will be on a first-come, first-served basis. There is no additional fee. Cocktails and hors d'oeuvres will be served.

### RESEARCH continued from page 1

findings for the audience to understand what we have found to date about factors that contribute to the development of allergy and wheezing disease in inner-city infants."

Hear how NASA is in a unique position to contribute to pulmonary science during the session "Moon Dust and Pollen: Initial Results of Exploratory Research with NASA" from noon to 1 p.m. on Monday, May 18. The NASA-sponsored session will address recent research on the hazards of the super-fine moon dust and opportunities to track by satellite seasonal concentrations of pollen.

"I hope attendees will learn that this is another way to understand the distribution of pollen and areas of asthma exposure, and to realize that longer moon explorations will result in more danger from moon dust to astronauts and the need to protect them from that," said session co-chair William C. Bailey, M.D., professor of medicine at the University of Alabama at Birmingham. "I also hope attendees will make contacts with NASA researchers to learn more about opportunities to participate in such research."

During the "Long-Term Outcomes from the Inhaled Nitric Oxide Trials in Neonates" session from noon to 1 p.m. on Sunday, May 17, the results of two NHLBI-funded trials and of one industry-sponsored trial will be presented. All examined long-term outcomes of chronic lung disease, cost effectiveness and neurodevelopmental disability one to four years after treatment.

"The indications, benefits and risks of iNO therapy in preterm infants are important and may lead to changes in the way neonatologists manage preterm infants at risk of bronchopulmonary dysplasia, or BPD, as well as influence the long-term

outcomes of these infants as evaluated by pulmonologists, pediatricians and neurologists," said session co-chair Carol J. Blaisdell, M.D., medical officer of Lung Developmental Biology and Pediatric Pulmonary Diseases in the Division of Lung Diseases at the NHLBI. "The results from these studies will contribute to the evidence base to develop practice guidelines for treating the preterm infant with iNO."

To promote pulmonary research efforts, the ATS Assembly on Nursing will sponsor a research session on "National Institute of Nursing Research (NINR): Funding Opportunities and Priorities" from noon to 1 p.m. on Sunday, May 17.

The ATS International Conference attracts many nurse researchers who have been funded by the NINR or other NIH institutes and those who are in a position to apply for grants and funding, said session chair Lynn B. Reinke, Ph.D., A.R.N.P., a research fellow in Health Services R&D and advance practice nurse at the Department of Veterans Affairs in Seattle.

"This venue is a perfect opportunity for NINR program officers to personally convey the NIH agenda and funding priorities," Dr. Reinke said. "The funding opportunities from NINR often focus on methods to improve clinical care for patients with lung disease. Hence, the majority of research conducted by nurse investigators directly translates to good quality patient-care outcomes."

### Other noteworthy research topics at ATS 2009 will be presented during the following times and days:

**Noon to 1 p.m., Sunday, May 17**  
L2: "Update on Training and Use of Spirometry in Occupational Settings"  
L4: "NHLBI Asthma Clinical Research Network (ACRN) and Chronic Obstructive Pulmonary Disease Clinical Research

Network (CCRN): New Findings"  
L6: "The Biology of Asthma Disparities: Findings from the NHLBI Centers for Reducing Asthma Disparities"

### Noon to 1 p.m., Monday, May 18

L9: "The Coronary Artery Risk Development in Young Adults (CARDIA) Study: Insights into Lung Disease and Lung Function in Young Adults"  
L10: "Using Genetic and Genomic Technologies to Better Understand Asthma: New Findings from the NHLBI Clinical Research Programs"  
L11: "Acute Respiratory Distress Syndrome Network (ARDSNet): Results of the Albuterol for the Treatment of Acute Lung Injury (ALTA) Trial"  
L12: "Cardiovascular and Other Health Consequences of Sleep-Disordered Breathing and Hypoxia in Older Men"

### Noon to 1 p.m., Wednesday, May 20

L13: "Chronic Obstructive Pulmonary Disease Outcomes Based Network for Clinical Effectiveness and Research Translation (CONCERT Consortium)"  
L14: "Clinical Implications of Acid Reflux: Therapy and Rhinosinusitis in Asthma: Results from the ALA Asthma Clinical Research Centers"  
L15: "Update from the CDC's Tuberculosis Trails and Tuberculosis Epidemiological Studies Consortium"  
L16: "Translational Research Efforts on Pulmonary Disease and Genetic Susceptibility to Air Pollution"  
L17: "Idiopathic Pulmonary Fibrosis Network: New Insights into IPF Pathogenesis and Therapy"  
L18: "The Multi-Ethnic Study of Atherosclerosis: Investigation of Cardiopulmonary Interactions in Adults"  
L19: "NHLBI Cultural Competence and Health Disparity Academic Award Program for Pulmonary Medicine"

### Fully Paid Registrants May Access ATS 2009 Webcasts

As a benefit of registering for the American Thoracic Society's 2009 International Conference, the ATS is again offering 12 months of free access to ATS 2009 IC Webcasts. Fully paid conference registrants will have post-meeting access to more than 200 hours of ATS 2009 presentations, reflecting the diverse topic areas of the conference at no extra charge.

The "Best of ATS Conferences" Webcasts provide full audio and slides, synchronized and searchable. More details will be provided in the ATS International Conference final program and onsite materials.

Free access is limited to paid conference registrants in full conference categories (including in-training). One-day registrants, other attendees and non-attendees may pay for this 12-month access by placing orders at designated pricing levels to be announced in the final program onsite.



# SAVE THE DATE

INAUGURAL BENEFIT DINNER FOR THE ATS RESEARCH PROGRAM

SATURDAY, MAY 16, 2009, 7 PM

SAN DIEGO, CALIFORNIA  
MANCHESTER GRAND HYATT

To register for the International Conference and Dinner, visit <http://foundation.thoracic.org/web/ats-research-program-dinner.html>

Call (212) 315-6464 for more information

Inaugural Gala Benefactor:  
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## Tours: Take in San Diego's Exceptional Attractions

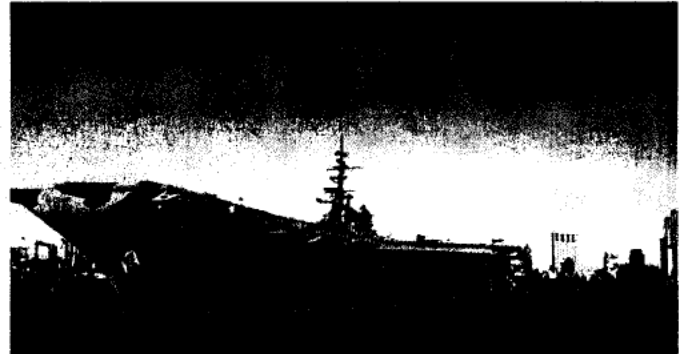
San Diego consistently ranks as one of the top travel destinations in North America because of its picture-perfect landscape and exceptional attractions. The region is home to 33 beaches, and plenty of scenic stops offer breath-taking views of the Pacific Ocean's blue waters. Each day, tourists flock to San Diego's scenic locales, museums and distinctive shops and boutiques. Enjoy the best San Diego has to offer by taking a tour during the American Thoracic Society's 2009 International Conference. For more information about these tours or to register online, visit [www.thoracic.org/go/international-conference](http://www.thoracic.org/go/international-conference).

- The **San Diego Orientation** tour will provide an overview of not-to-be missed attractions at no charge. (Friday, May 15, 9:30 to 10 a.m.)
- The **San Diego City Tour with Harbor Cruise** will begin at Balboa Park, the horticultural wonder in the heart of San Diego. Guests will then take a 21-mile cruise on San Diego Bay, one of the most beautiful natural harbors in the world. (10 a.m. to 3 p.m., Friday, May 15, and Tuesday, May 19; \$43/person)



Torrey Pines Golf Course

- The **La Jolla Tour** takes visitors to this scenic seaside village, located on seven spectacular miles of sandy beaches and stunning cliffs. La Jolla is home to upscale boutiques, chic restaurants, the Stephen Birch Aquarium & Museum and the San Diego Museum of Contemporary Art. (11 a.m. to 3 p.m., Friday, May 15, and 1 to 5 p.m., Sunday, May 17; \$26/person)
- The **Midway Tour with Harbor Cruise** begins with exploring this former U.S. Navy aircraft carrier, which has been converted into a multi-dimensional museum. Next guests embark upon a 21-mile cruise of scenic waterways, including Harbor and Shelter Islands, Point Loma (home of the Cabrillo Monument), the magnificent Coronado Bay Bridge and the U.S. Pacific Naval Fleet. (10 a.m. to 3 p.m. Saturday, May 16, and Wednesday, May 20; \$62/person)
- The **Shopping in Del Mar and Solana Beach** tour includes a special afternoon of browsing lovely shops at Del Mar Plaza and the neighboring area—and then goes on to



Midway Museum

- the shops of the Cedros Design District in Solana Beach, which is known for antiques and designer and specialty items. (10:30 a.m. to 3:30 p.m., Saturday, May 16; \$30/person)
- The **Coronado Walking Tour** begins at the clock tower of the famous, century-old Hotel del Coronado. From "The Dell," the tour then continues to some of the island's magnificent celebrity homes. Depending on interests, guests may later visit either quaint shops, cafes and galleries or stroll along the sandy Coronado Beach, the best seashell beach in San Diego. (1 to 5 p.m., Saturday, May 16, and 10 a.m. to 2 p.m., Monday, May 18; \$45/person)
- The **Wild Animal Park Tour** takes visitors to the 2,100-acre sanctuary, where animals roam freely in settings similar to their native African and North American habitats. The park features a special open-air tram with an informative guide describing the park's animals. (11 a.m. to 4 p.m., Sunday, May 17, and Tuesday, May 19; \$64/person)
- The **Southern California Wine Tour** includes a visit and tasting at one winery and a tasting at a second winery in the wine-famous Temecula Valley. Temecula Valley has become renowned for producing everything from vintage sherry to award-winning champagne. (9 a.m. to 3 p.m., Monday, May 18; \$75/person)
- The **Aolani Catamaran Cruise** offers the smoothest ride on the San Diego Bay, with spectacular scenery of the San Diego skyline and the bay's majestic waters. The 31-foot catamaran accommodates up to 30 people, and guests can walk freely around the boat. (1 to 5 p.m., Monday, May 18; \$113/person)
- The **Trekking in Torrey Pines** tour features an invigorating day of hiking in the scenic Torrey Pines State Reserve, perched high atop the bluffs overlooking the Pacific Ocean. The reserve offers breathtaking views, superb trails and gnarled, twisted, rugged Torrey pine trees. (1 to 5 p.m., Tuesday, May 19; \$47/person)

### MECHANICAL VENTILATION

continued from page 3

in mechanical ventilation," said Niall D. Ferguson, M.D., M.S.C., who co-chairs the PG6 course. "It will also include an extensive discussion on non-invasive ventilation (NIV), a rapidly expanding technology about which clinicians want to learn more."

The course will additionally address the latest innovations in three modes of ventilation—proportional assist ventilation, neurally adjusted ventilatory assistance and high-frequency ventilation, said Dr. Ferguson, director of clinical research in critical care medicine at the University of Toronto. It will end with disease-specific discussion on pediatric patients, airway obstruction in asthma and COPD, acute lung injury and acute respiratory distress syndrome.

PG20: "Weaning from Mechanical Ventilation" will cover the pathophysiology of weaning failure and the role of respiratory muscles, the potential use of the various weaning predictors, the role of weaning protocols and the utility of

automated weaning techniques, the role of non-invasive ventilation in weaning failure, and post-extubation failure and the clinical approach to managing the difficult to wean patient. Dr. Nava also co-chairs this course with Franco Laghi, M.D., professor of medicine, pulmonary and critical care medicine at Ed Hines Jr., VA Hospital and Loyola University Medical Center, in Hines, Ill., and Theodoros Vassilakopoulos, M.D., of the Department of Critical Care and Pulmonary Services at the University of Athens Medical School and Evangelismos Hospital in Greece.

"There are still so many differences around the world regarding the practice of mechanical ventilation and weaning," Dr. Nava said. For example, weaning protocols are popular in the U.S., but not so popular in Europe. Nevertheless, "overall our clinical success is very similar."

It may be easier to convince a physician to change their prescribing practices of a drug than to change modes of ventilation that they are comfortable with, he said.

"Honestly, very few drugs influence



Two sleep medicine clinicians conduct a study on sleep tracing used to diagnose sleep disorders. Sleep disorders and sleep neurobiology and physiology will be addressed during the sleep medicine postgraduate courses.

outcomes on patients as much as a well-applied ventilatory strategy," Dr. Nava said. "By reviewing the most recent advances

and guidelines, these courses will be helpful in driving our colleagues toward new attitudes."



# CURRENT AND EMERGING THERAPIES FOR PAIN

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**Evening Program  
Sessions**

**May 17, 2008**

**San Diego, California**

**Dinner – 5:30pm**

**Program – 7:00-9:00pm**

**Manchester Grand Hyatt Hotel**

**Carlsbad Ballroom E-1**

**Session Code – E1**



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# Current Controversies in Pulmonary Arterial Hypertension: **PRO-CON DEBATES**



✓ E7

## PROGRAM

### 7:30 pm **PRO: Existing and Pending PAH**

**Are Therapies and Adequately  
Sean P. Galis, MD, PhD  
Mater Misericordiae  
University Hospital  
University College Dublin  
Dublin, Ireland**

### 7:35 pm **CON: Traditional End Points in PAH**

**Trials Are Not Adequate. We Need to Set  
End Points Such as Long-term Mortality  
and Morbidity  
Victor E. Topson, MD  
Duke University Medical Center  
Durham, North Carolina**

### 7:38 pm **GENERAL DISCUSSION**

### 7:40 pm **PRO: Combination Therapy is Effective and Recommended**

**for Most PAH Patients  
Valerie V. McLaughlin, MD  
University of Michigan  
Health System  
Ann Arbor, Michigan**

### 7:55 pm **CON: There is Still Inadequate Data to Routinely Recommend Combination**

**Therapy for the Treatment of PAH  
David B. Badesch, MD  
University of Colorado Health  
Sciences Center  
Aurora, Colorado**

### 8:18 pm **GENERAL DISCUSSION**

### 8:30 pm **PRO: Oral and Inhaled PAH**

**Therapies Are Highly Effective for  
Most Patients, Preventing the Need  
for Parenteral Therapy  
Lewis J. Rubin, MD  
UCSD School of Medicine  
La Jolla, California**

### 8:35 pm **CON: Oral and Inhaled PAH Therapies Are**

**Inadequate for Many Patients. First-Line  
Parenteral Prostaglandin Therapy Should Be  
Used More Often  
Robyn J. Barst, MD  
Columbia University College of  
Physicians and Surgeons  
New York, New York**

### 8:58 pm **GENERAL DISCUSSION**

(b) (5)



**From:** Cheng, Helen  
**To:** Susan Hintz  
**Cc:** Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: SUPPORT Summary Tables  
**Date:** Friday, February 05, 2010 1:06:52 AM  
**Attachments:** Table6\_04feb.doc

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Hi Susan,

Attached is table 6. I'll modify it as necessary per your answers re: the unilateral and normal measures.

Please let me know if you have any questions.

Thanks,  
Helen

---

**From:** Cheng, Helen  
**Sent:** Thursday, February 04, 2010 8:07 PM  
**To:** 'Susan Hintz'  
**Cc:** Das, Abhik; Rosemary Higgins  
**Subject:** SUPPORT Summary Tables

Hi Susan,

Attached please find five of the six updated ultrasound tables. Note that in tables 2 and 3, variables that were adjusted for site correlation are bolded.

I will send the updated table 6 tomorrow. Per your e-mail on 13 Jan, the number of ppts in the denominator for each row will be the number of ppts who meet the criteria at the early CUS. Also, per your note on the table, the definition for meeting the criteria at the late finding will be 'relaxed' in that if a ppt experiences grade 1 on the right at early, and at late, experiences no vent enlargement on the right, but experiences vent enlargement on the left, this will be considered a case of progressing from 'grade ½' to 'any vent enlargement'.

Your note on the table re: the 'unilateral' rows was cut off. Were there specific instructions for these variables? Given that the only progressions you are interested in are to 'normal', side shouldn't be an issue since I am using A.9 (normal reading) to satisfy that requirement.

Helen

**Table 6. Progression of findings – EARLY CUS to LATE CUS**

(Qing – for these analyses to make sense, I think we will need to define "EARLY" and "LATE" findings more globally; in other words, abnormalities on EITHER or BOTH sides. Does that make sense and seem correct to you? So, that is why I am asking for you to include the n/N, % in the central reader results column – I believe for these more "global" definitions of findings, we have not yet seen the numbers in the previous tables.) **The exception is where I specify UNILATERAL or BILATERAL findings. "Bilateral" is pretty clear. "Unilateral" - .**

Early CUS finding	Late CUS finding	Central reader #1 (n/N, %)	Central reader #2 (n/N, %)
Normal	Normal	332 / 411 (81%)	336 / 410 (82%)
Normal	Any vent enlarge	11 / 411 (3%)	11 / 410 (3%)
Normal	Mod-severe vent enlarge	6 / 411 (1%)	5 / 410 (1%)
Normal	Cystic PVL	4 / 411 (1%)	5 / 410 (1%)
Grade 1 or 2	Normal	46 / 81 (57%)	39 / 70 (56%)
Grade 1 or 2	Any vent enlargement	7 / 81 (9%)	3 / 70 (4%)
Grade 1 or 2	Mod-severe vent enlarge	4 / 81 (5%)	1 / 70 (1%)
Grade 1 or 2	Cystic PVL	2 / 81 (2%)	1 / 70 (1%)
Grade 1 or 2	Porencephalic cyst	3 / 81 (4%)	2 / 70 (3%)
Grade 1 or 2	Shunt	1 / 81 (1%)	1 / 70 (1%)
<b>UNILATERAL 1 or 2</b>	<b>Normal</b>	32 / 49 (65%)	26 / 45 (58%)
<b>BILATERAL 1 or 2</b>	<b>Normal</b>	14 / 23 (61%)	10 / 19 (53%)
Grade 3 or 4	Normal	4 / 39 (10%)	12 / 55 (22%)
Grade 3 or 4	Any vent enlargement	24 / 39 (62%)	29 / 55 (53%)
Grade 3 or 4	Mod-severe vent enlarge	19 / 39 (49%)	19 / 55 (35%)
Grade 3 or 4	Cystic PVL	3 / 39 (8%)	1 / 55 (2%)
Grade 3 or 4	Porencephalic cyst	10 / 39 (26%)	14 / 55 (25%)
Grade 3 or 4	Shunt	7 / 39 (18%)	13 / 55 (24%)
<b>UNILATERAL 3 or 4</b>	<b>Normal</b>	3 / 13 (23%)	4 / 15 (27%)
<b>BILATERAL 3 or 4</b>	<b>Normal</b>	1 / 18 (6%)	5 / 34 (15%)

**From:** Cheng, Helen  
**To:** Susan Hintz  
**Cc:** Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** SUPPORT Summary Tables  
**Date:** Thursday, February 04, 2010 11:07:12 PM  
**Attachments:** [Table1a\\_1b\\_04feb.doc](#)  
[Table2a\\_2b\\_04feb.doc](#)  
[Table3a\\_3b\\_04feb.doc](#)  
[Table4a\\_4b\\_04feb.doc](#)  
[Table5\\_04feb.doc](#)

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Hi Susan,

Attached please find five of the six updated ultrasound tables. Note that in tables 2 and 3, variables that were adjusted for site correlation are bolded.

I will send the updated table 6 tomorrow. Per your e-mail on 13 Jan, the number of ppts in the denominator for each row will be the number of ppts who meet the criteria at the early CUS. Also, per your note on the table, the definition for meeting the criteria at the late finding will be 'relaxed' in that if a ppt experiences grade 1 on the right at early, and at late, experiences no vent enlargement on the right, but experiences vent enlargement on the left, this will be considered a case of progressing from 'grade ½' to 'any vent enlargement'.

Your note on the table re: the 'unilateral' rows was cut off. Were there specific instructions for these variables? Given that the only progressions you are interested in are to 'normal', side shouldn't be an issue since I am using A.9 (normal reading) to satisfy that requirement.

Helen

**Table 1a: Demographic and perinatal clinical characteristics of CUS cohort by ventilation and oxygenation randomized groups.**

	VENTILATION STRATEGY		OXYGENATION STRATEGY	
	CPAP	Surfactant	High sat	Low sat
N	282/572 (49%)	290/572 (51%)	302/572 (53%)	270/572 (47%)
BW (grams) (mean (SD))	851 (186)	845 (193)	838 (194)	859 (185)
EGA (weeks) (mean (SD))	25.9 (1.03)	25.8 (1.02)	25.9 (1.03)	25.8 (1.01)
% 24 -25 weeks	107/282 (38%)	113/290 (39%)	120/302 (40%)	100/270 (37%)
Multiple gestation	64/282 (23%)	70/290 (24%)	73/302 (24%)	61/270 (23%)
Race				
Non-hispanic Black	86/282 (30%)	88/289 (30%)	77/301 (26%)	97/270 (36%)
Non-hispanic White	122/282 (43%)	122/289 (42%)	136/301 (45%)	108/270 (40%)
Hispanic	63/282 (22%)	65/289 (22%)	73/301 (24%)	55/270 (20%)
Other	11/282 (4%)	14/289 (5%)	15/301 (5%)	10/270 (4%)
Male	149/282 (53%)	170/290 (59%)	174/302 (58%)	145/270 (54%)
Any antenatal steroids	273/282 (97%)	273/290 (94%)	286/302 (95%)	260/270 (96%)
Maternal hypertension	68/282 (24%)	76/290 (26%)	75/302 (25%)	69/270 (26%)
ROM >24 hours	107/282 (38%)	95/290 (33%)	110/302 (36%)	92/270 (34%)
Cesarean section	187/282 (66%)	205/290 (71%)	207/302 (69%)	185/270 (69%)
Apgar <3 at 5 minutes	8/282 (3%)	9/290 (3%)	11/302 (4%)	6/270 (2%)
Epinephrine or chest compressions in DR	15/282 (5%)	19/290 (7%)	19/302 (6%)	15/270 (6%)

**Table 1b: In hospital morbidities and characteristics of CUS cohort by ventilation and oxygenation randomized groups**

	VENTILATION STRATEGY		OXYGENATION STRATEGY	
	CPAP	Surfactant	High sat	Low sat
N	282/572 (49%)	290/572 (51%)	302/572 (53%)	270/572 (47%)
On ANY ventilator at any time	234/280 (84%)	289/289 (100%)	279/301 (93%)	244/268 (91%)
On high-frequency ventilation at any time	93/282 (33%)	115/290 (40%)	120/302 (40%)	88/270 (33%)
Surfactant treatment	195/282 (69%)	285/290 (98%)	257/302 (85%)	223/270 (83%)
PDA diagnosed	139/282 (49%)	150/290 (52%)	158/302 (52%)	131/270 (49%)
Surgery for PDA	36/282 (13%)	34/290 (12%)	35/302 (12%)	35/270 (13%)
Sepsis Early Late	9/282 (3%)	10/290 (3%)	11/302 (4%)	8/270 (3%)
NEC (definite) diagnosed	89/282 (32%)	102/290 (35%)	107/302 (35%)	84/270 (31%)
Surgery for NEC (lap OR drain)	27/282 (10%)	18/290 (6%)	23/302 (8%)	22/270 (8%)
ROP stage 3 or greater with plus	11/282 (4%)	8/290 (3%)	11/302 (4%)	8/270 (3%)
Surgery for PDA or NEC or ROP	20/281 (7%)	21/285 (7%)	33/298 (11%)	8/268 (3%)
Postnatal steroids	55/282 (20%)	60/290 (21%)	67/302 (22%)	48/270 (18%)
Oxygen use at 36 weeks PMA	20/282 (7%)	34/290 (12%)	29/302 (10%)	25/270 (9%)
BPD (physiologic definition)	105/282 (37%)	112/290 (39%)	122/302 (40%)	95/270 (35%)



**Table 2 a. Central reader diagnostic assignments for EARLY CUS by VENTILATION STRATEGY randomized groups; p value for association between randomized groups and findings.** Note – where p value box is shadowed, you don't need to provide. Note that variables in **bold** were adjusted for in separate output

Ventilation strategy→	CENTRAL READER #1			CENTRAL READER #2		
	CPAP	Surfactant	P value	CPAP	Surfactant	P value
<b>Normal reading (MRI04, A.9 = yes)</b>	<b>199/282 (71%)</b>	<b>213/290 (73%)</b>	<b>.443</b>	<b>194/282 (69%)</b>	<b>216/290 (74%)</b>	<b>.131</b>
<b>**For these items in BLUE are hemisphere-specific, so the N will be #CUS x 2; for Grades, see section F..</b>						
Grade 1	16/564 (3%)	16/580 (3%)		39/564 (7%)	42/580 (7%)	
Grade 2	40/564 (7%)	32/580 (6%)		1/564 (0%)	7/580 (1%)	
Grade 3	21/564 (4%)	15/580 (3%)		41/564 (7%)	30/580 (5%)	
Grade 4	12/564 (2%)	9/580 (2%)		11/564 (2%)	7/580 (1%)	
<b>**For the remaining rows, the findings are on either or both sides, so the N= # of CUS</b>						
<b>Any hemorrhage (Grade 1 - 4)</b>	<b>64/282 (23%)</b>	<b>48/290 (17%)</b>	<b>.064</b>	<b>63/282 (22%)</b>	<b>56/290 (19%)</b>	<b>.372</b>
Grade 1 or 2	44/282 (16%)	37/290 (13%)	.329	33/282 (12%)	37/290 (13%)	.700
<b>Grade 3 or 4</b>	<b>24/282 (9%)</b>	<b>15/290 (5%)</b>	<b>.113</b>	<b>32/282 (11%)</b>	<b>23/290 (8%)</b>	<b>.166</b>
Echolucent PVL (C.1.b =yes)	2/282 (1%)					
<b>Grade 3 or 4 or cystic PVL</b>	<b>26/282 (9%)</b>	<b>15/290 (5%)</b>	<b>.061</b>	<b>32/282 (11%)</b>	<b>23/290 (8%)</b>	<b>.166</b>
Any ventricular enlargement (E.1.a = yes for mild or moderate or severe)	28/282 (10%)	23/290 (8%)	.402	41/282 (15%)	33/290 (11%)	.260
Mod-severe ventricular	16/282	10/290	.201	16/282	10/290	.201

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enlarge (E.1.a = yes for moderate or severe)	(6%)	(3%)		(6%)	(3%)	
BILATERAL grade 1 or 2 (left and right = yes)	12/282 (4%)	11/290 (4%)	.778	7/282 (2%)	12/290 (4%)	.269
BILATERAL grade 3 or 4	9/282 (3%)	9/290 (3%)	.952	20/282 (7%)	14/290 (5%)	.252
BILATERAL grade 3 or 4 or cPVL	10/282 (4%)	9/290 (3%)	.768	20/282 (7%)	14/290 (5%)	.252
Grade 1/2 on one side, NO hemorrhage on other (F.1 =no on other side)	27/282 (10%)	22/290 (8%)	.396	24/282 (9%)	21/290 (7%)	.573
Grade 3/4 on one side, Grade 1/2 on other side	4/282 (1%)	4/290 (1%)	.968	2/282 (1%)	4/290 (1%)	.432
Grade 3 or 4 on one side, NO Hemorrhage on other	11/282 (4%)	2/290 (1%)	.010	10/282 (4%)	5/290 (2%)	.173

**Table 2 b. Central reader diagnostic assignments for EARLY CUS by OXYGENATION STRATEGY randomized groups: p value for association between randomized groups and findings.** Note – where p value box is shadowed, you don't need to provide. Note that variables in **bold** were adjusted for in separate output

	CENTRAL READER #1			CENTRAL READER #2		
Oxygenation strategy→	High	Low	P value	High	Low	P value
<b>Normal reading (MRI04, A.9 = yes)</b>	<b>221/302 (73%)</b>	<b>191/270 (71%)</b>	<b>.517</b>	<b>218/302 (72%)</b>	<b>192/270 (71%)</b>	<b>.776</b>
<b>**For these items in BLUE are hemisphere-specific, so the N will be #CUS x 2; for Grades, see section F.</b>						
Grade 1	20/604 (3%)	12/540 (2%)		40/604 (7%)	41/540 (8%)	
Grade 2	35/604 (6%)	37/540 (7%)		4/604 (1%)	4/540 (1%)	
Grade 3	19/604 (3%)	17/540 (3%)		37/604 (6%)	34/540 (6%)	
Grade 4	10/604 (2%)	11/540 (2%)		11/604 (2%)	7/540 (1%)	
<b>**For the remaining rows, the findings are on either or both sides, so the N= # of CUS</b>						
<b>Any hemorrhage (Grade 1 - 4)</b>	<b>57/302 (19%)</b>	<b>55/270 (20%)</b>	<b>.653</b>	<b>60/302 (20%)</b>	<b>59/270 (22%)</b>	<b>.559</b>
Grade 1 or 2	42/302 (14%)	39/270 (14%)	.854	34/302 (11%)	36/270 (13%)	.450
<b>Grade 3 or 4</b>	<b>20/302 (7%)</b>	<b>19/270 (7%)</b>	<b>.844</b>	<b>29/302 (10%)</b>	<b>26/270 (10%)</b>	<b>.991</b>
Echolucent PVL (C.1.b =yes)		2/270 (1%)				
<b>Grade 3 or 4 or cystic PVL</b>	<b>20/302 (7%)</b>	<b>21/270 (8%)</b>	<b>.593</b>	<b>29/302 (10%)</b>	<b>26/270 (10%)</b>	<b>.991</b>
Any ventricular enlargement (E.1.a = yes for mild or moderate or severe)	27/302 (9%)	24/270 (9%)	.983	37/302 (12%)	37/270 (14%)	.605

Mod-severe ventricular enlarge (E.1.a = yes for moderate or severe)	13/302 (4%)	13/270 (5%)	.770	14/302 (5%)	12/270 (4%)	.913
BILATERAL grade 1 or 2 (left and right = yes)	13/302 (4%)	10/270 (4%)	.715	10/302 (3%)	9/270 (3%)	.988
BILATERAL grade 3 or 4	9/302 (3%)	9/270 (3%)	.809	19/302 (6%)	15/270 (6%)	.710
BILATERAL grade 3 or 4 or cPVL	9/302 (3%)	10/270 (4%)	.630	19/302 (6%)	15/270 (6%)	.710
Grade 1/2 on one side, NO hemorrhage on other (F.1 =no on other side)	23/302 (8%)	26/270 (10%)	.390	21/302 (7%)	24/270 (9%)	.391
Grade 3/4 on one side, Grade 1/2 on other side	5/302 (2%)	3/270 (1%)	.580	3/302 (1%)	3/270 (1%)	.890
Grade 3 or 4 on one side, NO Hemorrhage on other	6/302 (2%)	7/270 (3%)	.627	7/302 (2%)	8/270 (3%)	.630

**Table 3 a. Central reader diagnostic assignments for LATE CUS by VENTILATION STRATEGY randomized groups; p value for association between randomized groups and findings.**

Note that variables in **bold** were adjusted for in separate output

Ventilation strategy→	CENTRAL READER #1			CENTRAL READER #2		
	CPAP	Surfactant	P value	CPAP	Surfactant	P value
<b>Normal reading (MRI04, A.9 = yes)</b>	<b>188/281 (67%)</b>	<b>216/290 (74%)</b>	<b>.047</b>	<b>184/282 (65%)</b>	<b>220/290 (76%)</b>	<b>.005</b>
Normal or mild ventricular enlargement (E.1.a = yes for mild on either or both sides)	263/281 (94%)	281/290 (97%)	.063	266/282 (94%)	282/290 (97%)	.082
Echolucent PVL (C.1.b = yes)	5/281 (2%)	4/290 (1%)	.701	4/282 (1%)	2/290 (1%)	.392
Porencephalic cyst (C.1.c = yes)	8/281 (3%)	4/290 (1%)	.222	12/282 (4%)	3/290 (1%)	.016
ANY ventricular enlargement (E.1.a = yes for mild, moderate or severe)	26/281 (9%)	18/290 (6%)	.172	33/282 (12%)	15/290 (5%)	.005
<b>Moderate or severe ventricular enlargement (E.1.a = yes for moderate or severe)</b>	<b>17/281 (6%)</b>	<b>8/290 (3%)</b>	<b>.055</b>	<b>16/282 (6%)</b>	<b>8/290 (3%)</b>	<b>.082</b>
Shunt (G.2 = yes on either or both sides)	7/281 (2%)	2/290 (1%)	.084	11/282 (4%)	4/290 (1%)	.059
<b>EcholucentPVL/P-cyst/mod-sev enlargement/shunt</b>	<b>26/281 (9%)</b>	<b>11/290 (4%)</b>	<b>.008</b>	<b>27/282 (10%)</b>	<b>11/290 (4%)</b>	<b>.006</b>
BILATERAL ANY ventricular enlargement - (left & right = yes for mild, moderate or severe)	22/281 (8%)	14/290 (5%)	.140	23/282 (8%)	13/290 (4%)	.071
BILATERAL <b>moderate or severe</b> ventricular enlargement	15/281 (5%)	8/290 (3%)	.117	15/282 (5%)	8/290 (3%)	.119
BILATERAL echolucent PVL (C.1.b)	3/281 (1%)	2/290 (1%)	.628	1/282 (0%)	1/290 (0%)	.984

BILATERAL porencephalic cyst (C.1.c)		1/290 (0%)	.325		1/290 (0%)	.324
BILATERAL echolucent PVL <b>OR</b> porencephalic cyst <b>OR</b> moderate to severe ventricular enlargement <b>OR</b> shunt	19/281 (7%)	9/290 (3%)	.043	16/282 (6%)	9/290 (3%)	.133

**Table 3 b. Central reader diagnostic assignments for LATE CUS by OXYGENATION STRATEGY randomized groups; p value for association between randomized groups and findings.**

Note that variables in **bold** were adjusted for in separate output

Oxygenation strategy→	CENTRAL READER #1			CENTRAL READER #2		
	High	Low	P value	High	Low	P value
<b>Normal reading (MRI04, A.9 = yes)</b>	<b>206/301 (68%)</b>	<b>198/270 (73%)</b>	<b>.199</b>	<b>213/302 (71%)</b>	<b>191/270 (71%)</b>	<b>.956</b>
Normal or mild ventricular enlargement (E.1.a = yes for mild on either or both sides)	285/301 (95%)	259/270 (96%)	.485	288/302 (95%)	260/270 (96%)	.579
Echolucent PVL (C.1.b = yes)	4/301 (1%)	5/270 (2%)	.616	1/302 (0%)	5/270 (2%)	.075
Porencephalic cyst (C.1.c = yes)	6/301 (2%)	6/270 (2%)	.849	6/302 (2%)	9/270 (3%)	.314
ANY ventricular enlargement (E.1.a = yes for mild, moderate or severe)	21/301 (7%)	23/270 (9%)	.490	25/302 (8%)	23/270 (9%)	.918
<b>Moderate or severe ventricular enlargement (E.1.a = yes for moderate or severe)</b>	<b>14/301 (5%)</b>	<b>11/270 (4%)</b>	<b>.737</b>	<b>14/302 (5%)</b>	<b>10/270 (4%)</b>	<b>.579</b>
Shunt (G.2 = yes on either or both sides)	5/301 (2%)	4/270 (1%)	.863	7/302 (2%)	8/270 (3%)	.630
<b>EcholucentPVL/P-cyst/mod-sev enlargement/shunt</b>	<b>19/301 (6%)</b>	<b>18/270 (7%)</b>	<b>.864</b>	<b>18/302 (6%)</b>	<b>20/270 (7%)</b>	<b>.488</b>
BILATERAL ANY ventricular enlargement - (left & right = yes for mild, moderate or severe)	17/301 (6%)	19/270 (7%)	.495	18/302 (6%)	18/270 (7%)	.728
BILATERAL <b>moderate or severe</b> ventricular enlargement	12/301 (4%)	11/270 (4%)	.958	14/302 (5%)	9/270 (3%)	.429
BILATERAL echolucent PVL (C.1.b)	1/301 (0%)	4/270 (1%)	.141		2/270 (1%)	.134

BILATERAL porencephalic cyst (C.1.c)		1/270 (0%)	.291		1/270 (0%)	.290
BILATERAL echolucent PVL <b>OR</b> porencephalic cyst <b>OR</b> moderate to severe ventricular enlargement <b>OR</b> shunt	14/301 (5%)	14/270 (5%)	.768	14/302 (5%)	11/270 (4%)	.743



Table 4a. Other Central Reader diagnostic assignments – **EARLY CUS** - Findings thought to be “incidental” or “mild” or “isolated”

<b>EARLY CUS FINDING</b>	<b>Central reader #1 (n/N, %)</b>	<b>Central reader #2 (n/N, %)</b>
Caudate echodensity <u>only</u> (MRI04, B.1.a.1 = yes, either or both sides) -> nothing else = “yes” in parts B -G	2/572 (0.3%)	1/572 (0.2%)
LS Branching <u>only</u> (D.1.f. = yes, either or both sides) -> nothing else = “yes” in parts B -G	2/572 (0.3%)	1/572 (0.2%)
Choroid cyst <u>only</u> (E. 2.a. = yes, either or both sides) -> nothing else = “yes” in B -G	13/572 (2.3%)	5/572 (0.9%)
Choroid hemorrhage <u>only</u> (E.2.b. = yes, either or both sides) -> nothing else = “yes” in B -G	2/572 (0.3%)	0/572 (0.0%)
Intracerebral echodensity <u>isolated and UNILATERAL</u> (B.1.d, any or several of 1 through 6 = yes on ONE SIDE ONLY) -> <u>nothing</u> else marked “yes” in B -G <b>except</b> Grade IV <i>may be yes</i> on same side (F.1.a, Grade IV)	0/572 (0.0%)	0/572 (0.0%)
Intracerebral echodensity <u>isolated and BILATERAL</u> (B.1.d, any or several of 1 through 6 = yes, BOTH SIDES) -> <u>nothing</u> else marked “yes” in B -G <b>except</b> Grade IV <i>may be yes</i>	1/572 (0.2%)	0/572 (0.0%)
Cerebellar echodensity <u>isolated and UNILATERAL</u> (B.1.d.6.a = yes, on ONE SIDE ONLY) -> nothing else = “yes” in parts B -G <b>except</b> Grade IV <i>may be yes</i> on same side (F.1.a, Grade IV)	0/572 (0.0%)	0/572 (0.0%)
Cerebellar echodensity <u>isolated and BILATERAL</u> (B.1.d.6.a = yes, on BOTH SIDES) -> nothing else = “yes” in parts B -G <b>except</b> Grade IV <i>may be yes</i>	1/572 (0.2%)	0/572 (0.0%)

Table 4b. Other Central Reader diagnostic assignments – **LATE CUS** - Findings thought to be “incidental” or “mild” or “isolated”

<b>LATE CUS FINDING</b>	<b>Central reader #1 (n/N, %)</b>	<b>Central reader #2 (n/N, %)</b>
Choroid cyst <u>only</u> (E. 2.a. = yes, either or both sides) -> nothing else marked “yes” in parts B -G	24/571 (4.2%)	14/572 (2.4%)
Cerebellar echodensity <u>isolated and UNILATERAL</u> (B.1.d.6.a = yes, on ONE SIDE ONLY) -> nothing else = “yes” in parts B -G <b>except</b> Grade IV <i>may be yes</i> on same side (F.1.a, Grade IV)	0/571 (0.0%)	0/572 (0.0%)
Cerebellar echodensity <u>isolated and BILATERAL</u> (B.1.d.6.a = yes, on BOTH SIDES) -> nothing else = “yes” in parts B -G <b>except</b> Grade IV <i>may be yes</i>	0/571 (0.0%)	0/572 (0.0%)
Cortical atrophy <u>only</u> (D.1.c=yes, either or both sides) -> nothing else marked yes B-G	0/571 (0.0%)	0/572 (0.0%)

Revised 10/28/09: See items in RED – these are new or revised items

**Table 5. Interobserver reliability for major findings**

	N (positive agreement)	Kappa	95% CI	% positive agreement/%negative agreement
<b>EARLY CUS</b>				
Normal vs. abnormal (MRI04 A.9 = yes vs. no)	383	0.76	(0.70, 0.82)	67.0% / 23.3%
Grade 1 or 2	54	0.52	(0.43, 0.61)	4.72% / 87.9%
Grade 3 or 4	54	0.72	(0.64, 0.81)	4.72% / 92.0%
Grade 3 or 4 or PVL	54	0.71	(0.62, 0.79)	4.72% / 91.7%
<b>LATE CUS</b>				
Normal vs. abnormal	363	0.66	(0.59, 0.73)	63.6% / 22.2%
Echolucent PVL	5	0.45	(0.19, 0.71)	0.44% / 98.5%
Porencephalic cyst	11	0.76	(0.58, 0.93)	0.96% / 98.4%
ANY ventricular enlargement	73	0.88	(0.83, 0.94)	6.39% / 92.0%
Moderate-severe ventricular enlargement	43	0.90	(0.84, 0.97)	3.77% / 95.5%
Shunt	7	0.53	(0.30, 0.77)	0.61% / 98.3%

Items in BLUE are hemisphere-specific, so the N will be #CUS x 2

**From:** Das, Abhik  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: SUPPORT revision progress  
**Date:** Wednesday, February 03, 2010 10:48:39 AM

---

Yes, he did, (b) (6). It was quite a personal setback for me, because Nabil was a great friend and mentor!

Thanks

Abhik

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Wednesday, February 03, 2010 10:45 AM  
**To:** Das, Abhik  
**Subject:** RE: SUPPORT revision progress

This is terrible. I believe (b) (6), right??

Rose

---

**From:** Das, Abhik [mailto:adas@rti.org]  
**Sent:** Wednesday, February 03, 2010 10:24 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** FW: SUPPORT revision progress

FYI, the RTI PI for the DC Initiative (Dr. Nabil El-Khorazaty) died after a 6 year battle with multiple myeloma. Marie was recently named co-PI for that study but nobody thought that Nabil's decline would be so sudden (he used to come to work daily right until 2 weeks before his passing). That study will be winding down this Spring.

Thanks

Abhik

---

**From:** Gantz, Marie  
**Sent:** Wednesday, February 03, 2010 10:15 AM  
**To:** 'Finer, Neil'; 'Wally Carlo, M.D.'  
**Cc:** Das, Abhik; Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** SUPPORT revision progress

Hi Neil and Wally,

I wanted to let you know that I will be responding to your requests for the NEJM revisions later this week. Just to fill you in, I've been made PI of one of our other DCC projects following the recent death of one of our RTI colleagues, and I've been in the Rockville office this week taking care of some urgent issues for that project. But I know the NEJM revisions are very high priority, and I will be working on them tomorrow and Friday.

Marie

**Marie Gantz, Ph.D.**  
**Research Statistician**  
**RTI International**  
**mgantz@rti.org**  
**828-254-6255**

**From:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**To:** ["wacarlo@uab.edu"](mailto:wacarlo@uab.edu)  
**Subject:** O2 Sats NEJM Response 1 27 10  
**Date:** Tuesday, February 02, 2010 2:06:00 PM  
**Attachments:** [O2 Sats NEJM Response 1 27 10.doc](#)

---

Here are my suggestions

Rose

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January 30, 2010

Caren G. Solomon, M.D.  
Michael F. Greene, M.D.  
New England Journal of Medicine  
10 Shattuck Street  
Boston, MA 02115

RE: 09-11781 - The SUPPORT Trial: Randomized Trial of Oxygen Saturation Targets in Extremely Premature Infants

Dear Drs. Solomon and Greene:

Enclosed is a revised version of the manuscript that addresses the editors' and reviewers' comments. A point-by-point response is provided below.

We have addressed the concerns raised by the statistical reviewer regarding the (b) (4)

(unless additional space can be granted).

The Copyright Transfer Agreement and Universal Disclosure forms are being completed by each author.

I have prepared a "Disclosure" following your instructions and samples of recent *New England Journal of Medicine* publications.

I designed the study, assisted by Neil Finer, M.D. (the second author), and the Neonatal Research Network (NRN) Steering Committee members (included as authors). The research coordinators of the NRN gathered the data. The authors from Research Triangle International analyzed the data and vouch for it and its analysis. I wrote the paper, assisted by the NRN Steering Committee members. The NRN Steering Committee members decided that the manuscript

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should be published. The Massimo Company provided the altered pulse oximeters at the usual oximeter cost to the network, but did not sponsor the trial or have any other role in it. Abhik Das, PhD., Principal Investigator of the grant at Research Triangle Institute International, takes responsibility for the data and analysis. {There are agreements concerning confidentiality of the data. What does this mean???}

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I wrote the first full draft of the manuscript. Writing assistance was not provided.

The manuscript includes a full, accurate, and up-to-date report of adverse events.

The article nor any part has been published or will be submitted elsewhere before appearing in the *New England Journal of Medicine*.

We do not have other manuscripts by me or the co-authors addressing similar or related research questions in preparation or under consideration at other journals. Studies on growth, neuroimaging, and follow up at 18-22 months corrected age are underway.

Sincerely,

Wally Carlo, M.D.  
Edwin M. Dixon Professor of Pediatrics  
University of Alabama at Birmingham  
PI for the Oxygen Saturation Trial of the SUPPORT Trial

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Response to Reviewers' Comments

RE: 09-11781 - The SUPPORT Trial: Randomized Trial of Oxygen Saturation Targets in Extremely Premature Infants

Each of the comments of the reviewers (**in bold**) and a point-by-point response is provided.

Reviewer: 1

Comments for the Author

**(b) (4)** [Redacted]

Thanks

**Several clarifications/modifications would improve the manuscript:**

**(b) (4)** [Redacted]

[Redacted]

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(b) (4)

[Redacted]

[Redacted]

The reviewer is correct that (b) (4)

[Redacted]

(b) (4)

[Redacted] per the  
American Academy of Pediatrics Policy Statement enclosed. (b) (4)

(b) (4)

The sentence has been rewritten.

(b) (4)

[Redacted]

[Redacted]

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Reviewer: 2

**Comments for the Author**

**1. General Comments:**

(b) (4)

Thanks

(b) (4)

We agree (b) (4)

**2. Specific Comments:**

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(b) (4) [Redacted]

[Redacted]

Thanks. (b) (4) [Redacted]

(b) (4) [Redacted]

[Redacted]

[Redacted]

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(b) (4)

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--	--	---

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(b) (4)

[Redacted text block]

**Discussion:**

(b) (4)

[Redacted text block]

[Redacted text block]

Statistical Reviewer: 1

**Comments for the Author:**

(b) (4)

[Redacted text block]

[Redacted text block]

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(b) (4)

[Redacted text block]

[Redacted text block]

[Redacted text block]

[Redacted text line]

(Marie: Was this done?)

ADDITIONAL COMMENTS OF THE EDITORS

Title should be shortened to no more than 75 characters.

Done

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--	--	---

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(b) (4) [Redacted] . This is now stated.

(b) (4) [Redacted]  
(Marie: Help)

(b) (4) [Redacted]  
(Marie: Help)

Please rephrase : (b) (4) [Redacted]  
The sentence has been (b) (4) [Redacted]

(b) (4) [Redacted]

(b) (4) [Redacted]



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(b) (4)



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**From:** Eastman, Diane  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Bell, Edward  
**Cc:** Johnson, Karen; Acarregui, Michael  
**Subject:** Support trial twins  
**Date:** Tuesday, February 02, 2010 11:52:08 AM

---

We will go to their community and do their exams on 3/1. Keep your fingers crossed that by then the weather is better and we'll get there!! Diane

*Diane Eastman, ARNP  
High Risk Infant Followup Program  
Children's Hospital of Iowa  
319-353-6880*

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Eastman, Diane"; "Bell, Edward"  
**Cc:** "Johnson, Karen"  
**Subject:** RE: NRN support appts  
**Date:** Tuesday, February 02, 2010 10:58:00 AM

---

Sorry to hear that the weather is NOT cooperating!!  
Good luck  
Rose

---

**From:** Eastman, Diane [mailto:diane-eastman@uiowa.edu]  
**Sent:** Tuesday, February 02, 2010 10:54 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Bell, Edward  
**Cc:** Johnson, Karen  
**Subject:** NRN support appts

Rose,

Once again, Mother Nature messed up our plans for today. The support trial twins we've been rescheduling for months now are not coming today d/t the snow we got yesterday & today. We'll work on scheduling a trip there to get them done, hopefully in the next few weeks. Diane

*Diane Eastman, ARNP*

*High Risk Infant Followup Program*

*Children's Hospital of Iowa*

*319-353-6880*

**From:** Das, Abhik  
**To:** Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu; Gantz, Marie  
**Subject:** RE: SUPPORT paper  
**Date:** Monday, February 01, 2010 10:36:11 AM  
**Attachments:** Q2 Sats NEJM Response 1 27 10 adrev.doc

---

Wally:

Please see my suggested changes and comments on the response to the editor (changes tracked).

Thanks

Abhik

---

**From:** Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]  
**Sent:** Saturday, January 30, 2010 4:59 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu; Das, Abhik; Gantz, Marie  
**Cc:** Wally Carlo, M.D.  
**Subject:** SUPPORT paper

Dear Rose, Neil, Abhik, and Marie:

Enclosed is the draft of the letter to the editor and the revised manuscript. I would appreciate all of your comments.

From Marie I need the following.

1. Data on multiple birth for Table 1.
2. Confirm whether the Cox Regression was adjusted for clustering.
3. The 98% CIs for the primary outcomes.
4. The P value for the interaction between oxygen saturation and ventilatory support.

I will be in meetings Monday through Thursday next week but will have internet access at night and can respond to emails throughout the day.

I have not added the data of adjudication of ROP outcomes. What should we do about these data?

The figures, legends, and Appendix tables are attached separately. Only Table 1 had changes.

Thanks  
Wally

Wally Carlo, M.D.  
Edwin M. Dixon Professor of Pediatrics  
University of Alabama at Birmingham  
Director, Division of Neonatology  
Director, Newborn Nurseries  
Phone: 205 934 4680  
FAX: 205 934 3100  
Cell: 205 266 (b)

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January 30, 2010

Caren G. Solomon, M.D.  
Michael F. Greene, M.D.  
New England Journal of Medicine  
10 Shattuck Street  
Boston, MA 02115

RE: 09-11781 - The SUPPORT Trial: Randomized Trial of Oxygen Saturation Targets in Extremely Premature Infants

Dear Drs. Solomon and Greene:

Enclosed is a revised version of the manuscript that addresses the editors' and reviewers' comments. A point-by-point response is provided below.

We have addressed the concerns raised by the statistical reviewer regarding (b) (4)

The Copyright Transfer Agreement and Universal Disclosure forms are being completed by each author.

I have prepared a "Disclosure" following your instructions and samples of recent *New England Journal of Medicine* publications.

I designed the study, assisted by Neil Finer, M.D. (the second author), and the Neonatal Research Network (NRN) Steering Committee members (included as authors). The research coordinators of the NRN gathered the data. The authors from Research Triangle International analyzed the data and vouch for it and its analysis. I wrote the paper, assisted by the NRN Steering Committee members. The NRN Steering Committee members decided that the manuscript should be published. The Massimo Company provided the altered pulse oximeters, but did not

1

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sponsor the trial or have any other role in it. Abhik Das, PhD., Principal Investigator, and Marie Gantz, Ph.D., Statistician, of from the grant-NRN Data Coordinating Center at Research TriangleRTI International, takes responsibility for the data and analysis. There are agreements in place concerning confidentiality of the data.

I wrote the first full draft of the manuscript. Writing assistance was not provided.

The manuscript includes a full, accurate, and up-to-date report of adverse events.

This article nor any part has been published or will be submitted elsewhere before appearing in the *New England Journal of Medicine*.

We do not have other manuscripts by me or the co-authors addressing similar or related research questions in preparation or under consideration at other journals. Secondary studies on growth, neuroimaging, and neurodevelopmental follow up at 18-22 months corrected age are underway.

Sincerely,

Wally Carlo, M.D.  
Edwin M. Dixon Professor of Pediatrics  
University of Alabama at Birmingham  
PI for the Oxygen Saturation Trial of the SUPPORT Trial

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Response to Reviewers' Comments

RE: 09-11781 - The SUPPORT Trial: Randomized Trial of Oxygen Saturation Targets in Extremely Premature Infants

Each of the comments of the reviewers (**in bold**) and a point-by-point response is provided.

Reviewer: 1

Comments for the Author

(b) (4)

Thanks

Several clarifications/modifications would improve the manuscript:

(b) (4)

[Redacted text block]

[Redacted text block]

[Redacted text block]

**Comment [AD1]:** Do you need to elaborate?  
Feedback was only provided based on pooled data and not by group. The DSMC was the only body that looked at such data by treatment group while the trial was ongoing.

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(b) (4)

[Redacted]

[Redacted]

The reviewer is correct (b) (4)

[Redacted]

(b) (4)  
American Academy of Pediatrics Policy Statement enclosed. (b) (4)

(b) (4)

The sentence has been rewritten.

(b) (4)

[Redacted]

**Comment [AD2]:** Neil's response seems to take a different tack; should we be consistent? There, we

(b) (4)



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Reviewer: 2

**Comments for the Author**

**1. General Comments:**

(b) (4)

Thanks

(b) (4)

**2. Specific Comments:**

(b) (4)

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Thanks

(b) (4)

Thanks. (b) (4)

(b) (4)

(b) (4)

(b) (4)

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(b) (4)

[Redacted text block]

(b) (4)

[Redacted text block]

(b) (4)

(Rose and team: I need help to phrase this carefully)

(b) (4)

Comment [AD3]: Are they asking about the  
(b) (4)

[Redacted text block]

(b) (4)

[Redacted text block]

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(b) (4)

Comment [AP4]: Is this correct for (b) (4) Marie will need to confirm.

(b) (4)

**Discussion:**

(b) (4)

Statistical Reviewer: 1

**Comments for the Author:**

(b) (4)

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(b) (4)

1

1

(b) (4)

(Marie: Was this done?)

#### ADDITIONAL COMMENTS OF THE EDITORS

**Title should be shortened to no more than 75 characters.**

Done

(b) (4)

. This is now stated.

#### Results:

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(b) (4)  
),  
(Marie: Help)

(b) (4)  
(Marie: Help)

(b) (4)  
The sentence has been (b) (4)

(b) (4)

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(b) (4)

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## **Higgins, Rosemary (NIH/NICHD) [E]**

---

**From:** Finer, Neil <nfiner@ucsd.edu>  
**Sent:** Saturday, January 30, 2010 11:06 PM  
**To:** Wally Carlo, M.D.  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Rich, Wade  
**Subject:** RE: SUPPORT paper

Wally

I think that I would not include the adjudication data. This paper has sailed through and the adjudication has not added anything of substance – In addition we did not pre-specify such an adjudication  
In the letter of response I would prefer if you indicated that this study was designed and approved by the SUPPORT Subcommittee. No single person fully designed it – it was repeatedly revised, with input from every member, and as the PI I think that this is a more appropriate statement. I would probably also indicate that the skew in the oximeters was developed by the investigators in conjunction with Masimo.

Thanks for all your efforts  
Neil

---

**From:** Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]  
**Sent:** Saturday, January 30, 2010 1:59 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; adas@rti.org; Gantz, Marie  
**Cc:** Wally Carlo, M.D.  
**Subject:** SUPPORT paper

Dear Rose, Neil, Abhik, and Marie:

Enclosed is the draft of the letter to the editor and the revised manuscript. I would appreciate all of your comments.

From Marie I need the following.

1. Data on multiple birth for Table 1.
2. Confirm whether the Cox Regression was adjusted for clustering.
3. The 98% CIs for the primary outcomes.
4. The P value for the interaction between oxygen saturation and ventilatory support.

I will be in meetings Monday through Thursday next week but will have internet access at night and can respond to emails throughout the day.

I have not added the data of adjudication of ROP outcomes. What should we do about these data?

The figures, legends, and Appendix tables are attached separately. Only Table 1 had changes.

Thanks  
Wally

Wally Carlo, M.D.  
Edwin M. Dixon Professor of Pediatrics  
University of Alabama at Birmingham



Director, Division of Neonatology  
Director, Newborn Nurseries  
Phone: 205 934 4680  
FAX: 205 934 3100  
Cell: 205 266 (b)

## Higgins, Rosemary (NIH/NICHD) [E]

---

**From:** Finer, Neil <nfiner@ucsd.edu>  
**Sent:** Saturday, January 30, 2010 7:55 PM  
**To:** Wally Carlo, M.D.  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]; adas@rti.org; Gantz, Marie; Wally Carlo, M.D.  
**Subject:** Re: SUPPORT paper

Great work Wally!!!  
I will get a response back ASAP  
Neil

Sent from my iPhone

On Jan 30, 2010, at 1:59 PM, "Wally Carlo, M.D." <WCarlo@peds.uab.edu> wrote:

> Dear Rose, Neil, Abhik, and Marie:  
>  
> Enclosed is the draft of the letter to the editor and the revised  
> manuscript. I would appreciate all of your comments.  
>  
> From Marie I need the following.  
>  
> 1. Data on multiple birth for Table 1.  
> 2. Confirm whether the Cox Regression was adjusted for clustering.  
> 3. The 98% CIs for the primary outcomes.  
> 4. The P value for the interaction between oxygen saturation and  
> ventilatory support.  
>  
> I will be in meetings Monday through Thursday next week but will have  
> internet access at night and can respond to emails throughout the day.  
>  
> I have not added the data of adjudication of ROP outcomes. What  
> should we do about these data?  
>  
> The figures, legends, and Appendix tables are attached separately.  
> Only Table 1 had changes.  
>  
> Thanks  
> Wally  
>  
>  
> Wally Carlo, M.D.  
> Edwin M. Dixon Professor of Pediatrics University of Alabama at  
> Birmingham Director, Division of Neonatology Director, Newborn  
> Nurseries  
> Phone: 205 934 4680  
> FAX: 205 934 3100  
> Cell: 205 266 (b)

- >
- > <O2.Sats.NEJM.Response.1.27.10.doc>
- > <Figure 1,2,3 NEJM.12.01.09.doc>
- > <Appendix Table 1 and 2.FINAL NEJM.doc>
- > <Legends.FINAL.NEJM.12.01.09.doc> <SUPPORT
- > O2.1.30.10.TRACKED.FINAL.NEJM.doc>

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Paoliaro, Susan (NIH/NICHD) [E]  
**Subject:** FW: Iowa SUPPORT Follow-up pt has moved to Maryland  
**Date:** Friday, January 29, 2010 4:37:00 PM

---

Can you send me the info for Christiana for FU?  
Contact person, neuro and bayley examiner??

---

**From:** Zaterka-Baxter, Kristin [mailto:kzaterka@rti.org]  
**Sent:** Friday, January 29, 2010 11:29 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: Iowa SUPPORT Follow-up pt has moved to Maryland

Hi,

Karen sent an email to this person but does not have any other contacts; do you happen to have a phone number? When I talked with her yesterday she had not gotten an email response.

Thanks,  
Kris

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Friday, January 29, 2010 10:49 AM  
**To:** Newman, Jamie; Vohr, Betty  
**Cc:** Zaterka-Baxter, Kristin; Johnson, Karen  
**Subject:** RE: Iowa SUPPORT Follow-up pt has moved to Maryland

Do they also have a certified neuro examiner as part of their FU? Also, Iowa can pay the site (from their grant) for seeing the child. The forms get keyed from the Iowa site.

Let me know if there are other questions  
Rose

---

**From:** Newman, Jamie [mailto:newman@rti.org]  
**Sent:** Thursday, January 28, 2010 5:21 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Vohr, Betty  
**Cc:** Zaterka-Baxter, Kristin; Johnson, Karen  
**Subject:** Iowa SUPPORT Follow-up pt has moved to Maryland

Karen Johnson, coordinator from Iowa, called us today and she has a SUPPORT Follow-up pt that has moved to Maryland. They have found someone in Philly that can do Bayley exam (certified examiner). How do you suggest we handle payment for the examiner? Also, the person that does Bayley is probably a psychologist and will not be able to do a neuro exam. Do you have any suggestions for seeing this child?

Thanks, Jamie

Jamie E. Newman, PhD, MPH  
Statistics and Epidemiology  
RTI International

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Telephone: (919) 485-5719  
Fax: (919) 485-7762  
[newman@rti.org](mailto:newman@rti.org)

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Newman, Jamie"; "Johnson, Karen"; "Vohr, Betty"  
**Cc:** "Zaterka-Baxter, Kristin"  
**Subject:** RE: Iowa SUPPORT Follow-up pt has moved to Maryland  
**Date:** Friday, January 29, 2010 4:13:00 PM

---

I am trying to get some additional contact info

Thanks  
Rose

---

**From:** Newman, Jamie [mailto:newman@rti.org]  
**Sent:** Friday, January 29, 2010 11:40 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Johnson, Karen; Vohr, Betty  
**Cc:** Zaterka-Baxter, Kristin  
**Subject:** RE: Iowa SUPPORT Follow-up pt has moved to Maryland

Iowa could do the following forms over the phone:

NF03-SES at 18 months

NF04 – Medical History form (and NF04A Readmission Form if applicable)

NF13 – BITSEA, if applicable (Note: the BITSEA is only be administered at the 18 month follow-up visit for infants less than or equal to 26 completed weeks GA (up to and including 26 6/7 weeks).

The Bayley examiner in Philly would complete the NF09A form and send it to Iowa for keying (What network is this person with? Does this Network also have 18 mo neuro examiners?). It may be a good idea for you to obtain a copy of this patient's original Bayley score forms for the child's file at Iowa. Does this patient need the Object Permanence Ancillary form completed (MRI09A)? I have not seen the pt's Network number or else I could tell you.

You're done with the Autism pilot so no need to the the NF15.

So all there is left is the Neuro exam NF05 (Infant examination form). Would it be possible for the child's regular physician (or the Bayley examiner) to complete part of this form? If yes, what questions are reasonable to expect to receive accurate data given the person completing these select questions would not be an NRN certified neuro examiner? In terms of how to complete the Status Form (NF10) for this type of scenario, without the neuro exam (NF05) the child would need to be coded as "Child seen but incomplete visit (code 6)".

I hope this helps. Please do not hesitate to let us know if you have additional questions.

Thanks, Jamie

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Friday, January 29, 2010 11:12 AM  
**To:** 'Johnson, Karen'; Newman, Jamie; Vohr, Betty  
**Cc:** Zaterka-Baxter, Kristin  
**Subject:** RE: Iowa SUPPORT Follow-up pt has moved to Maryland

Yes

---

**From:** Johnson, Karen [mailto:karen-johnson@uiowa.edu]  
**Sent:** Friday, January 29, 2010 11:11 AM

**To:** Higgins, Rosemary (NIH/NICHD) [E]; Newman, Jamie; Vohr, Betty  
**Cc:** Zaterka-Baxter, Kristin  
**Subject:** RE: Iowa SUPPORT Follow-up pt has moved to Maryland

So, we would get the entire capitation and would then pay them, right?  
Karen

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Friday, January 29, 2010 9:49 AM  
**To:** 'Newman, Jamie'; Vohr, Betty  
**Cc:** Zaterka-Baxter, Kristin; Johnson, Karen  
**Subject:** RE: Iowa SUPPORT Follow-up pt has moved to Maryland

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Let me know if there are other questions  
Rose

---

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**Sent:** Thursday, January 28, 2010 5:21 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Vohr, Betty  
**Cc:** Zaterka-Baxter, Kristin; Johnson, Karen  
**Subject:** Iowa SUPPORT Follow-up pt has moved to Maryland

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Thanks, Jamie

Jamie E. Newman, PhD, MPH  
Statistics and Epidemiology  
RTI International  
Telephone: (919) 485-5719  
Fax: (919) 485-7762  
[newman@rti.org](mailto:newman@rti.org)

**From:** Michael Cotten  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** Re: CONFIDENTIAL:New England Journal of Medicine 09-11783 and 09-11781  
**Date:** Friday, January 29, 2010 12:50:42 PM

---

HI again..sorry to bug you..but is the oxygen manuscript 09-11783? or 11781?

thanks

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: 919-681-6024  
fax: 919-681-6065  
email: cotte010@mc.duke.edu

"Higgins, Rosemary (NIH/NICHD) [E]"  
<higginsr@mail.nih.gov>

01/26/2010 05:06 PM

To "Wally Carlo, M.D." <WCarlo@peds.uab.edu>, "Michele Walsh" <mcw3@case.edu>, "Finer, Neil" <nfiner@ucsd.edu>, "Abbot Laptook" <ALaptook@wihri.org>, "Rich, Wade" <wrich@ucsd.edu>, "Gantz, Marie" <mgantz@rti.org>, "Roger Faix" <Roger.Faix@hsc.utah.edu>, "Bradley Yoder" <Bradley.Yoder@hsc.utah.edu>, "Das, Abhik" <adas@rti.org>, "Poole Kenneth (E-mail)" <poo@rti.org>, "Kurt Schibler" <Kurt.Schibler@cchmc.org>, "Nancy Newman" <nxs5@case.edu>, "Ambal (ambal@uab.edu)" <ambal@uab.edu>, "Frantz, Ivan" <ifrantz@tuftsmedicalcenter.org>, "Pablo Sanchez@UTSouthwestern.edu" <Pablo.Sanchez@UTSouthwestern.edu>, "Anthony Piazza (Anthony.Piazza@oz.ped.emory.edu)" <Anthony.Piazza@oz.ped.emory.edu>, "(b) (6)", "Laroia, Nirupama" <Nirupama\_Laroia@URMC.Rochester.edu>, "Phelps, Dale" <Dale\_Phelps@URMC.Rochester.edu>, "bpoindex@iupui.edu" <bpoindex@iupui.edu>, "Michael Cotten" <cotte010@mc.duke.edu>, "Krisa Van Meurs" <vanmeurs@stanford.edu>, "Duara, Shahnaz" <SDuara@med.miami.edu>, Vivek Narendran <Vivek.Narendran@cchmc.org>, "Sood, Beena" <bsood@med.wayne.edu>, "Michael O' Shea" <moshea@wfubmc.edu>, "Bell, Edward" <edward-bell@uiowa.edu>, "Richard Ehrenkranz" <richard.ehrenkranz@yale.edu>, "kwaterberg@salud.unm.edu" <kwaterberg@salud.unm.edu>, "Ed Donovan" <edward.donovan@cchmc.org>, "(susie.buchter@oz.ped.emory.edu)" <susie.buchter@oz.ped.emory.edu>, "vineet.bhandari@yale.edu" <vineet.bhandari@yale.edu>

cc "Archer, Stephanie (NIH/NICHD) [E]" <archerst@mail.nih.gov>, "Cunningham, Meg" <mcunningham@rti.org>, "Zaterka-Baxter, Kristin" <kzaterka@rti.org>, "Huitema, Carolyn Petrie" <petrie@rti.org>

Subject CONFIDENTIAL:New England Journal of Medicine 09-11783 and 09-11781



Hi,  
Both Wally and Neil got news today from the NEJM. Revisions are requested for both papers and the subcommittee will work on these. Please fill out the attached forms and return them to NICHD @ 301-496-3790 (FAX).

Also included in the reviews are the following statements:

Please note that we are also inviting a revised version of the companion manuscript. If/when both manuscripts are satisfactorily revised, we would anticipate publishing them back to back. This is an important clinical trial. The study was well designed and was conducted at centers with excellent research credentials. The paper is clear and succinctly written. The results demonstrating substantial reduction in severe ROP but increased in-hospital mortality in the lower saturation target group are noteworthy with the potential to change clinical practice. This is a timely topic that is the source of great clinical controversy and practice variation. Contemporary, well designed clinical investigations to enlighten the debate are long overdue. This large RCT in such a difficult area is a fantastic achievement and you need to be congratulated.

We will need the attached forms once the papers are revised.

Please keep the information on review and status confidential. The New England journal has a strict embargo policy.

Thanks to everyone for all of the effort for this important study!!

Best regards

Rose

[attachment "NEJM-CTA-2009.pdf" deleted by Michael Cotten/Pediatrics/mc/Duke] [attachment "NEJM-inst-for-ICMJE-form.pdf" deleted by Michael Cotten/Pediatrics/mc/Duke] [attachment "ICMJE-Disclosure-Form-102309.pdf" deleted by Michael Cotten/Pediatrics/mc/Duke]

**From:** Michael Cotten  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** Re: CONFIDENTIAL:New England Journal of Medicine 09-11783 and 09-11781  
**Date:** Friday, January 29, 2010 12:40:34 PM

---

Hi Rose..just making sure.....is Neil corresponding on one and Wally on the other (for the ICMJE form)?

thanks

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: 919-681-6024  
fax: 919-681-6065  
email: cotte010@mc.duke.edu

"Higgins, Rosemary (NIH/NICHD) [E]"  
<higginsr@mail.nih.gov>

01/26/2010 05:06 PM

To "Wally Carlo, M.D." <WCarlo@peds.uab.edu>, "Michele Walsh" <mcw3@case.edu>, "Finer, Neil" <nfiner@ucsd.edu>, "Abbot Laptook" <ALaptook@wihri.org>, "Rich, Wade" <wrich@ucsd.edu>, "Gantz, Marie" <mgantz@rti.org>, "Roger Faix" <Roger.Faix@hsc.utah.edu>, "Bradley Yoder" <Bradley.Yoder@hsc.utah.edu>, "Das, Abhik" <adas@rti.org>, "Poole Kenneth (E-mail)" <poo@rti.org>, "Kurt Schibler" <Kurt.Schibler@cchmc.org>, "Nancy Newman" <nxs5@case.edu>, "Ambal (ambal@uab.edu)" <ambal@uab.edu>, "Frantz, Ivan" <ifrantz@tuftsmedicalcenter.org>, "Pablo Sanchez@UTSouthwestern.edu" <Pablo.Sanchez@UTSouthwestern.edu>, "Anthony Piazza (Anthony.Piazza@oz.ped.emory.edu)" <Anthony.Piazza@oz.ped.emory.edu>, "(b) (6)", "(b) (6)", "Laroia, Nirupama" <Nirupama\_Laroia@URMC.Rochester.edu>, "Phelps, Dale" <Dale\_Phelps@URMC.Rochester.edu>, "bpoindex@iupui.edu" <bpoindex@iupui.edu>, "Michael Cotten" <cotte010@mc.duke.edu>, "Krisa Van Meurs" <vanmeurs@stanford.edu>, "Duara, Shahnaz" <SDuara@med.miami.edu>, Vivek Narendran <Vivek.Narendran@cchmc.org>, "Sood, Beena" <bsood@med.wayne.edu>, "Michael O'Shea" <moshea@wfubmc.edu>, "Bell, Edward" <edward-bell@uiowa.edu>, "Richard Ehrenkranz" <richard.ehrenkranz@yale.edu>, "kwatterberg@salud.unm.edu" <kwatterberg@salud.unm.edu>, "Ed Donovan" <edward.donovan@cchmc.org>, "(susie.buchter@oz.ped.emory.edu)" <susie.buchter@oz.ped.emory.edu>, "vineet.bhandari@yale.edu" <vineet.bhandari@yale.edu>

cc "Archer, Stephanie (NIH/NICHD) [E]" <archerst@mail.nih.gov>, "Cunningham, Meg" <mcunningham@rti.org>, "Zaterka-Baxter, Kristin" <kzaterka@rti.org>, "Huitema, Carolyn Petrie" <petrie@rti.org>

Subject CONFIDENTIAL:New England Journal of Medicine 09-11783 and 09-11781

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Both Wally and Neil got news today from the NEJM. Revisions are requested for both papers and the

This document is provided for reference purposes only. Persons with disabilities having difficulty accessing information in this document should e-mail NICHD FOIA Office at NICHDFOIARequest@mail.nih.gov for assistance.

subcommittee will work on these. Please fill out the attached forms and return them to NICHD @ 301-496-3790 (FAX).

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Please note that we are also inviting a revised version of the companion manuscript. If/when both manuscripts are satisfactorily revised, we would anticipate publishing them back to back. This is an important clinical trial. The study was well designed and was conducted at centers with excellent research credentials. The paper is clear and succinctly written. The results demonstrating substantial reduction in severe ROP but increased in-hospital mortality in the lower saturation target group are noteworthy with the potential to change clinical practice. This is a timely topic that is the source of great clinical controversy and practice variation. Contemporary, well designed clinical investigations to enlighten the debate are long overdue. This large RCT in such a difficult area is a fantastic achievement and you need to be congratulated.

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Thanks to everyone for all of the effort for this important study!!

Best regards

Rose

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**From:** [Das, Abhik](#)  
**To:** [Finer, Neil](#); [Wally Carlo, M.D.](#); [Higgins, Rosemary \(NIH/NICHHD\)](#) [E]  
**Cc:** [Gantz, Marie](#)  
**Subject:** SUPPORT CPAP paper response  
**Date:** Friday, January 29, 2010 10:50:39 AM  
**Attachments:** [Neil Letter to Editor - Revision1 28 10 adrev.doc](#)

---

Attached please find my suggested changes appended to the revisions from Rose. The statistical responses incorporate some input I got from Ken. Marie can add stuff in as well. Please let me know whether you think the NEJM will find these adequate.

Thanks

Abhik

**Abhik Das, PhD**  
**Senior Research Statistician**  
**Statistics and Epidemiology Unit**  
**RTI International**  
**6110 Executive Blvd., Suite 902**  
**Rockville, MD 20852**

**Phone: (301) 770-8214**  
**e-mail: [adas@rti.org](mailto:adas@rti.org)**

Caren G. Solomon, MD Deputy Editor  
Michael F. Greene, MD Associate Editor  
New England Journal of Medicine  
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Boston, MA 02115  
(617) 734-9800  
Fax: (617) 739-9864  
<http://www.nejm.org>

Dear Drs Solomon and Green

Thank you for your response to our submission "Early CPAP versus Surfactant in Very Preterm Infants: The SUPPORT Trial". We have examined all the critiques by reviewers and the editors and below we have outlined our response to each query and the changes made to manuscript as a result of each.

Reviewer # 1

We thank this reviewer for the detailed and helpful comments.

Introduction:

1. (b) (4) [Redacted]

[Redacted]

2. (b) (4) [Redacted]

I can't find this??

Methods:

3. (b) (4) [Redacted]

[Redacted]

4. (b) (4) [Redacted]

(b) (4)

5. (b) (4)

[Redacted]

6. (b) (4)

[Redacted]

Original Manuscript)

7. (b) (4)

[Redacted]

8. (b) (4)

[Redacted]

Results:

9. (b) (4)

Comment [AD1]: Let's not say that we powered on another outcome; the y may want us to adjust the Type I error further for that then!

Comment [AD2]: I agree that providing some data on this may be useful.

Formatted: Highlight

(b) (4)

10. (b) (4) [Redacted]

[Redacted]

11. (b) (4) [Redacted]

[Redacted] ( Marie can you provide??  
Thanks)

12. (b) (4) [Redacted]

[Redacted]

Thanks

13. (b) (4) [Redacted]

[Redacted]

14. (b) (4) [Redacted]

[Redacted]

(b) (4)

Reviewer: 2

We thank this reviewer for the detailed and helpful comments.

<b>Comments for the Author</b>

(b) (4)

Abstract

Comments

1. (b) (4)

2. (b) (4)

We agree and (b) (4)

3. (b) (4)

(b) (4)

Introduction

Comments

1. (b) (4)

This is correct - (b) (4)



2. (b) (4) [Redacted]

[Redacted]

3. (b) (4) [Redacted]

Thank you - We have corrected this

4. (b) (4) [Redacted]

The reviewer is correct and (b) (4) [Redacted]

5. (b) (4) [Redacted]

[Redacted]

(b) (4)

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Methods

Comments

1. (b) (4)

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(b) (4)

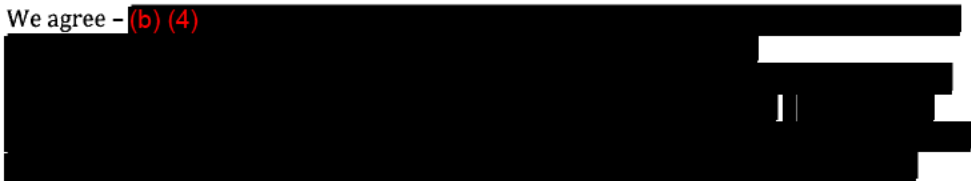
A very large rectangular area of the document is completely redacted with black ink.

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2. (b) (4)

A rectangular area of the document is completely redacted with black ink.

We agree - (b) (4)

A rectangular area of the document is completely redacted with black ink.

(b) (4)

3. (b) (4)

4. (b) (4)

5. (b) (4)

6. (b) (4)

(b) (4)

7. (b) (4)

We are happy to (b) (4)

8. (b) (4)

Either one

9. (b) (4)

(b) (4)  
- Marie do we know this??

10. (b) (4)

(b) (4)

11. (b) (4)

(b) (4)  
- Marie do we have any such information??

12. (b) (4)

(b) (4)

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13. (b) (4)

Please see (b) (4)

14. (b) (4)

(b) (4)

( Abhik – feel free to weigh in here!!) (Ken may also wish to weigh in as

he (b) (4)

15. (b) (4)

(b) (4)

(b) (4)

(Abhik - knock yourself out!!) (b) (4)

Results  
Comments

(b) (4)

(b) (4)

2. (b) (4)

We agree. (b) (4)

3. (b) (4)

(b) (4)

4. (b) (4)

(b) (4)

5. (b) (4)

Thanks

6. (b) (4)

Please see (b) (4)

(b) (4)

Marie please verify for me - Thanks

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7. (b) (4)

We agree - (b) (4)

Discussion  
Comments

1. (b) (4)

(b) (4)

2. (b) (4)

(b) (4)

3. (b) (4)

(b) (4)

Comment [AD3]: I understand your point; but do you want to phrase the response more diplomatically?

Thanks

3. (b) (4) [Redacted]

We agree - (b) (4) [Redacted]

Conclusion  
Comments

1. (b) (4) [Redacted]

We have changed this to read as follows:

(b) (4) [Redacted]

Comment [AD4]: Do you want to start by first saying flat out that (b) (4) [Redacted] This may appease them.

2. (b) (4) [Redacted]

Please see response to previous comment and our revised Conclusion

References

1. (b) (4) [Redacted]

We have corrected this

Statistical Reviewer: 1  
Comments for the Author:



(b) (4)

[Redacted text block]

[Redacted text block]

Abhik - Please write an appropriate reply - Good luck!!

(b) (4)

[Redacted text block]

[Redacted text block]

[Redacted text block]

[Redacted text block]

(b) (4)

[REDACTED]

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(b) (4)

[REDACTED]

[REDACTED]

(b) (4)

[Redacted text block]

Editorial Comments:

(b) (4)

[Redacted text block]

We have revised (b) (4) and believe that we have addressed these issues.

ADDITIONAL COMMENTS OF THE EDITORS

Title: should be no more than 75 characters.

The current Title is 71 characters including spaces.

Abstract:

(b) (4)

[Redacted text block]

(b) (4)

[Redacted text block]

Introduction:

(b) (4)

[Redacted text block]

(b) (4)

[Redacted text block]

[Redacted text line]

Methods:

(b) (4)

[Redacted text block]

[Redacted text block]

Results:

(b) (4)

[Redacted text block]

This has been done

(b) (4)

[Redacted text line]

Marie - Please supply - Thanks

(b) (4)

[Redacted text line]

Marie - Please supply - Thanks

(b) (4)

[Redacted text block]

[Redacted text block]

(b) (4)

Discussion:

(b) (4)

[Redacted]

[Redacted]

*Abhik I will let you write this area - I note that the editor has indicated* (b) (4)

(b) (4)

(b) (4)

[Redacted]

[Redacted]

**Comment [AD5]:** I am actually not sure what they want us to do here. Do they want us to reinstate something like the statements below that were in a previous draft?

(b) (4)

*We have so clarified*

(b) (4)

[Redacted]

[Redacted]

*Marie - Please redo as requested. - Thanks*

*We hope that revised manuscript and Tables are now acceptable for publication in the NEJM. We thank you and your reviewers for their constructive comments and suggestions.*

*Yours Truly*

*Neil Finer MD - Principal Investigator - SUPPORT Study*

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Hale, Ellen"  
**Subject:** RE: SUPPORT FU  
**Date:** Friday, January 29, 2010 8:46:00 AM

---

AWESOME!!  
THNAKS  
ROSE

-----Original Message-----

From: Hale, Ellen [mailto:ehale@emory.edu]  
Sent: Thursday, January 28, 2010 7:20 PM  
To: Higgins, Rosemary (NIH/NICHD) [E]  
Subject: RE: SUPPORT FU

Rose,  
Mission accomplished. Eyes are good and follow-up visit for both she and her brother are complete. Now if I can just find a few more. We will keep trying.  
Ellen

Ellen Hale, RN, BS, CCRC  
Neonatal Research Network  
Emory University School of Medicine  
Department of Pediatrics - Division of Neonatology  
Office: 404-778-1679  
Fax: 404-778-1467

---

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]  
Sent: Wednesday, January 27, 2010 12:11 PM  
To: Hale, Ellen  
Subject: RE: SUPPORT FU

THANKS

---

From: Hale, Ellen [mailto:ehale@emory.edu]  
Sent: Wednesday, January 27, 2010 12:06 PM  
To: Higgins, Rosemary (NIH/NICHD) [E]  
Subject: RE: SUPPORT FU

Rose,  
I have completed the NF12/SF12 on the 2 babies below.  
Surprise! One of our lost children for an eye appointment is coming into clinic tomorrow for 18 month visit. Good news is that eye clinic is open tomorrow so will see if we can keep mom long enough to get eye exam done. This is (b) (6) Keep you fingers crossed.  
Ellen

Ellen Hale, RN, BS, CCRC  
Neonatal Research Network  
Emory University School of Medicine  
Department of Pediatrics - Division of Neonatology  
Office: 404-778-1679  
Fax: 404-778-1467

---

From: Higgins, Rosemary (NIH/NICHD) [E] [higginsr@mail.nih.gov]

Sent: Wednesday, January 20, 2010 3:18 PM  
To: Hale, Ellen; Adams-Chapman, Ira; Barbara Stoll; Ellen Hale  
Cc: 'Gantz, Marie'  
Subject: SUPPORT FU  
Hi,

We are missing a few outcomes for the SUPPORT FU. Let us know how you are doing.

CENTER

NETWORK

FU\_message

9

(b)

Infant is lost to FU per NF10/SF10 but NF12/SF12 has not been completed.

9

(b)

Infant is lost to FU per NF10/SF10 but NF12/SF12 has not been completed.

Thanks for all the effort!!  
Rose

Rosemary D. Higgins, MD

Program Scientist for the Neonatal Research Network

Pregnancy and Perinatology Branch



Center for Developmental Biology and Perinatal Medicine

Eunice Kennedy Shriver National Institute of Child Health and Human Development

National Institutes of Health

6100 Executive Blvd., Room 4B03

MSC 7510

Bethesda, MD 20892

For overnight delivery use Rockville, MD 20852

301-496-5575

301-496-3790 (FAX)

[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)<<mailto:higginsr@mail.nih.gov>>

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## **Higgins, Rosemary (NIH/NICHD) [E]**

---

**From:** Finer, Neil <nfiner@ucsd.edu>  
**Sent:** Thursday, January 28, 2010 6:38 PM  
**To:** Wally Carlo, M.D.  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik; Rich, Wade  
**Subject:** RE: O2 saturation abstract

Hi Wally

I was also surprised when I opened your email I am totally lost as to how one of the studies is epidemiology and the other in Clinical Trials. I was hoping to have them both at the same session Maybe you will Chair my session!! Do you want to query this? - I wouldn't know who to ask If you do query it please include me as I totally agree We will get a different audience but in reality your presentation will draw the entire house!!!!

Either way

-its great to present both  
Thanks for everything Wally  
Neil

-----Original Message-----

**From:** Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]  
**Sent:** Thursday, January 28, 2010 3:06 PM  
**To:** Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]; das@rti.org; Gantz, Marie; Rich, Wade  
**Subject:** RE: O2 saturation abstract

Congratulations, Neil.

I was disappointed that the O2 one was put in an epidemiology session. I wonder what was the logic.

Any ideas? Could it be an error?

Wally

Wally Carlo, M.D.  
Edwin M. Dixon Professor of Pediatrics  
University of Alabama at Birmingham  
Director, Division of Neonatology  
Director, Newborn Nurseries  
619 South 20th Street  
525 New Hillman Building  
Birmingham, AL 35233-7335  
Phone: 205 934 4680  
FAX: 205 934 3100  
Cell: 205 266 (b)

-----Original Message-----

**From:** Finer, Neil [mailto:nfiner@ucsd.edu]  
**Sent:** Thursday, January 28, 2010 5:01 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.; das@rti.org; Gantz, Marie; Rich, Wade

Subject: RE: O2 saturation abstract

Here is the acceptance for CPAP Surf

Neil Finer

Department of Pediatrics, Division of Neonatology, UCSD School of Medicine and Medical Center  
402 Dickinson St., MPF 1-140  
San Diego Ca 92103-8774

RE: The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants – The SUPPORT Trial (Abstract #: 751689) Dear Dr. Neil Finer:

The abstract listed below has been selected for a PLATFORM PRESENTATION at the 2010 Pediatric Academic Societies' Annual Meeting in Vancouver, BC, Canada, May 1-4. On behalf of the PAS Program Committee, we would like to thank you for your submission and extend our congratulations!

ABSTRACT TITLE: The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants – The SUPPORT Trial FIRST AUTHOR: Neil Finer PUBLICATION NUMBER: 1670.1

SESSION\*\*: 1670—Neonatal Medicine: Clinical Trials I SESSION DATE & TIME: Saturday, May 1, 2010, 2:45 pm–4:45 pm

ROOM: West Ballroom A (Vancouver Convention Centre) PRESENTATION TIME: 2:45 pm (10-minute oral presentation followed by 5 minutes of discussion) -----Original Message-----

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]

Sent: Thursday, January 28, 2010 1:20 PM

To: 'Wally Carlo, M.D.'; Finer, Neil; das@rti.org; Gantz, Marie; Rich, Wade

Subject: RE: O2 saturation abstract

congratulations!!

Rosemary D. Higgins, MD

Program Scientist for the Neonatal Research Network

-----Original Message-----

From: Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]

Sent: Thursday, January 28, 2010 4:17 PM

To: Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; das@rti.org; Gantz, Marie; Rich, Wade

Subject: O2 saturation abstract

Congratulations! Another one accepted.

Wally

Wally Carlo, M.D.

Edwin M. Dixon Professor of Pediatrics

University of Alabama at Birmingham

Director, Division of Neonatology

Director, Newborn Nurseries

619 South 20th Street

525 New Hillman Building

Birmingham, AL 35233-7335

Phone: 205 934 4680

FAX: 205 934 3100

Cell: 205 266 (b)

**From:** Susan Hintz  
**To:** [adas@rti.org](mailto:adas@rti.org)  
**Cc:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Subject:** statistician to work on CUS analysis  
**Date:** Thursday, January 28, 2010 1:05:54 PM

---

Hi Abhik

Thank you for the information regarding the transition in statistical support for the CUS analysis. I have no doubt that Helen is fantastic - I have been consistently impressed by everyone at RTI with whom I have worked, so I am sure Helen will be excellent as well. It will be a real pleasure to have someone in my time zone - I might even drive up to SF to see her face to face sometime!

I hope that (b) (6) - will she be leaving RTI altogether, or taking a leave? Please give her my best.

Do you have a sense of when we will be seeing any further analysis? I am sorry to be inpatient, just want to have enough time to digest and consider the findings.

Thanks

Susan

--

Susan R. Hintz, M.D., M.S. Epi  
Associate Professor of Pediatrics  
Division of Neonatal and Developmental Medicine  
Stanford University School of Medicine  
750 Welch Road, Suite 315  
Palo Alto, CA 94304  
ph: 650-723-5711  
fax: 650-725-8351

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Finer, Neil"; "Gantz, Marie"; "wcarlo@peds.uab.edu"; "Das, Abhik"; "Rich, Wade"  
**Subject:** RE: New England Journal of Medicine 09-11783  
**Date:** Thursday, January 28, 2010 9:31:00 AM  
**Attachments:** Letter to Editor - Revision1.28.10.doc

---

Neil

This is excellent - my comments are in track changes and highlighted in green.

Let me know when you want it to go to the subcommittee.

Thanks

Rose

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network

-----Original Message-----

From: Finer, Neil [mailto:nfiner@ucsd.edu]

Sent: Wednesday, January 27, 2010 8:51 PM

To: Finer, Neil; 'Gantz, Marie'; Higgins, Rosemary (NIH/NICHD) [E]; 'wcarlo@peds.uab.edu'; 'Das, Abhik'; Rich, Wade

Subject: RE: New England Journal of Medicine 09-11783

Hello Everyone

I have now attempted to respond to each query and include a response and make manuscript changes.

Please review. I have identified some areas for Abhik and Marie to reply.

Please look at everything and let me know what you think. I now need a break from this.

Look forward to your thoughts and suggestions

Be well

Neil

Caren G. Solomon, MD Deputy Editor  
Michael F. Greene, MD Associate Editor  
New England Journal of Medicine  
10 Shattuck Street  
Boston, MA 02115  
(617) 734-9800  
Fax: (617) 739-9864  
<http://www.nejm.org>

Dear Drs Solomon and Green

Thank you for your response to our submission "Early CPAP versus Surfactant in Very Preterm Infants: The SUPPORT Trial". We have examined all the critiques by reviewers and the editors and below we have outlined our response to each query and the changes made to manuscript as a result of each.

Reviewer # 1

We thank this reviewer for the detailed and helpful comments.

Introduction:

1. (b) (4)  
[Redacted]

[Redacted]

2. (b) (4)  
I can't find this??

Methods:

3. What methods were used in the NICU to provide CPAP?

(b) (4)  
[Redacted]

(b) (4)

5. (b) (4)

[Redacted]

6. (b) (4)

[Redacted]

Original Manuscript)

7. (b) (4)

[Redacted]

8. (b) (4)

[Redacted]

Results:

9. When infants in the "CPAP" arm of the study were intubated in the delivery room (b) (4)

[Redacted]

(b) (4)

Formatted: Highlight

10. (b) (4) [Redacted]

[Redacted]

11. (b) (4) [Redacted]

[Redacted] ( Marie can you provide??  
Thanks)

12. (b) (4) [Redacted]

[Redacted]

Thanks

13. (b) (4) [Redacted]

(b) (4)

Formatted: Highlight

14. (b) (4) [Redacted]

[Redacted]



(b) (4)

Reviewer: 2

We thank this reviewer for the detailed and helpful comments.

<b>Comments for the Author</b>

(b) (4)

Abstract

Comments

1. (b) (4)

(b) (4)

2. (b) (4)

We agree and (b) (4)

3. (b) (4)

(b) (4)

Introduction

Comments

1. (b) (4)

This is correct - (b) (4)

2. (b) (4) [Redacted]

[Redacted]

3. (b) (4) [Redacted]

Thank you – We have corrected this

4. (b) (4) [Redacted]

The reviewer is correct and (b) (4) [Redacted]

5. (b) (4) [Redacted]

[Redacted]

(b) (4)



Methods

Comments

1. (b) (4)



(b) (4)




Formatted: Highlight

2. (b) (4)



We agree - (b) (4)



3. (b) (4) [Redacted]

[Redacted]

4. (b) (4) [Redacted]

[Redacted]

5. (b) (4) [Redacted]

(b) (4) [Redacted]

6. (b) (4) [Redacted]

We can state these - (b) (4) [Redacted]

7. (b) (4)

We are happy to (b) (4).

8. (b) (4)

Either one

9. Intubation for low blood pressure or pressor support is unusual. The criteria (b) (4)

(b) (4)  
Marie do we know this??

10. (b) (4)

(b) (4)

11. (b) (4)

(b) (4)

- Marie do we have any such information??

12. (b) (4)

(b) (4)



13. (b) (4) [Redacted]

Please see the answer to question (b) (4) [Redacted]

14. (b) (4) [Redacted]

[Redacted] (Abhik - feel free to weigh in here!!) (Ken may also wish to weigh in a (b) (4) [Redacted]

15. (b) (4) [Redacted]

[Redacted] (Abhik - knock yourself out!!) (b) (4) [Redacted]

Results  
Comments

1. (b) (4) [Redacted]

[Redacted]

2. I (b) (4) [Redacted]

We agree. (b) (4) [Redacted]

3. (b) (4) [Redacted]

[Redacted]

4. (b) (4) [Redacted]

[Redacted]

5. (b) (4) [Redacted]

[Redacted]. Marie - can you discuss and decide what you want here? Thanks

6. (b) (4) [Redacted]

Please see the answer to (b) (4) [Redacted]

Marie please verify for me - Thanks

7. (b) (4) [Redacted]

We agree - (b) (4) [Redacted]

Discussion  
Comments

1. (b) (4) [Redacted]

I believe that I have answered this in response to (b) (4)

2. (b) (4)

(b) (4)

3. (b) (4)

(b) (4)

(b) (4) Marie - please obtain for me so that we can make this point Thanks

3. (b) (4)

We agree - We would like to include such a paragraph - (b) (4)

(b) (4)

Conclusion  
Comments



1. (b) (4) [Redacted]

We have changed this to read as follows :

(b) (4) [Redacted]

2. (b) (4) [Redacted]

Please see response to previous comment and our revised Conclusion

References

1. (b) (4) [Redacted]

We have corrected this

Statistical Reviewer: 1

Comments for the Author:

(b) (4) [Redacted]

[Redacted]

(b) (4) [Redacted]

(b) (4) [Redacted]

Abhik - Please write an appropriate reply - Good luck!!

(b) (4) [Redacted]

(b) (4) [Redacted]

Editorial Comments:

(b) (4)  
[Redacted]

We have revised (b) (4) and believe that we have addressed these issues.

ADDITIONAL COMMENTS OF THE EDITORS

Title: should be no more than 75 characters.

The current Title is 71 characters including spaces.

Abstract:

(b) (4)  
[Redacted]

Introduction:

(b) (4)  
[Redacted]

This now reads as follows:

(b) (4) [Redacted]

[Redacted]

(b) (4) [Redacted] ?

[Redacted]

(b) (4) [Redacted]

This has been done

(b) (4) [Redacted]

Marie - Please supply - Thanks

(b) (4) [Redacted]

Marie - Please supply - Thanks

(b) (4) [Redacted]

[Redacted]

[Redacted]

[Redacted]

(b) (4)

**Abhik I will let you write this area -**

(b) (4)

(b) (4)

**We have so clarified**

(b) (4)

**Marie - Please redo as requested. - Thanks**

**We hope that revised manuscript and Tables are now acceptable for publication in the NEJM. We thank you and your reviewers for their constructive comments and suggestions.**

**Yours Truly**

**Neil Finer MD - Principal Investigator - SUPPORT Study**

**From:** [Buchter, Susie](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Subject:** RE: CONFIDENTIAL:New England Journal of Medicine 09-11783 and 09-11781  
**Date:** Wednesday, January 27, 2010 5:06:26 PM

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Thanks.

SB

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**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Wednesday, January 27, 2010 5:05 PM  
**To:** Buchter, Susie  
**Subject:** RE: CONFIDENTIAL:New England Journal of Medicine 09-11783 and 09-11781

Neil's ends in 83

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**From:** Buchter, Susie [mailto:dbuchte@emory.edu]  
**Sent:** Wednesday, January 27, 2010 5:00 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: CONFIDENTIAL:New England Journal of Medicine 09-11783 and 09-11781

Rose—

Which number is which paper.

Is 09-11783 Neil's paper or Wally's.

Since I am author on only one, I want to be sure to do the numbers right.

Thanks.

SB

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Tuesday, January 26, 2010 5:11 PM  
**To:** Buchter, Susie; Higgins, Rosemary (NIH/NICHD) [E]; 'wcarlo@peds.uab.edu'; 'mcw3@case.edu'; 'nfiner@ucsd.edu'; 'alaptook@WIHRI.org'; 'wrich@ucsd.edu'; 'mgantz@rti.org'; 'Roger.Faix@hsc.utah.edu'; 'Bradley.yoder@hsc.utah.edu'; 'adas@rti.org'; 'poo@rti.org'; 'kurt.schibler@cchmc.org'; 'nxs5@case.edu'; 'ambal@uab.edu'; 'ifrantz@tuftsmedicalcenter.org'; 'Pablo.Sanchez@UTSouthwestern.edu'; Anthony Piazza; (b) (6); 'Nirupama\_Laroya@URMC.Rochester.edu'; 'dale\_phelps@urmc.rochester.edu'; 'bpoindex@iupui.edu'; 'cotte010@mc.duke.edu'; 'vanmeurs@stanford.edu'; 'SDuara@med.miami.edu';

'Vivek.Narendran@cchmc.org'; 'bsood@med.wayne.edu'; 'moshea@wfubmc.edu'; 'edward-bell@uiowa.edu'; 'richard.ehrenkranz@yale.edu'; 'kwatterberg@salud.unm.edu'; 'edward.donovan@cchmc.org'; Susie Buchter; 'vineet.bhandari@yale.edu'  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; 'mcunningham@rti.org'; 'kzaterka@rti.org'; 'petrie@rti.org'  
**Subject:** Re: CONFIDENTIAL:New England Journal of Medicine 09-11783 and 09-11781

We need one form for each paper (so if you co-authored both, we need 2 sets of forms)

Rose

----- Original Message -----

From: Higgins, Rosemary (NIH/NICHD) [E]  
To: Wally Carlo, M.D. <WCarlo@peds.uab.edu>; 'Michele Walsh' <mcw3@case.edu>; 'Finer, Neil' <nfiner@ucsd.edu>; 'Abbot Laptook' <ALaptook@wihri.org>; Rich, Wade <wrich@ucsd.edu>; Gantz, Marie <mgantz@rti.org>; 'Roger Faix' <Roger.Faix@hsc.utah.edu>; 'Bradley Yoder' <Bradley.Yoder@hsc.utah.edu>; 'Das, Abhik' <adas@rti.org>; Poole Kenneth (E-mail) <poo@rti.org>; 'Kurt Schibler' <Kurt.Schibler@cchmc.org>; 'Nancy Newman' <nxs5@case.edu>; Ambal (ambal@uab.edu) <ambal@uab.edu>; 'Frantz, Ivan' <ifrantz@tuftsmedicalcenter.org>; Pablo.Sanchez@UTSouthwestern.edu <Pablo.Sanchez@UTSouthwestern.edu>; Anthony Piazza (Anthony.Piazza@oz.ped.emory.edu) <Anthony.Piazza@oz.ped.emory.edu>; (b) (6) Laroia, Nirupama <Nirupama\_Laroia@URMC.Rochester.edu>; 'Phelps, Dale' <Dale\_Phelps@URMC.Rochester.edu>; bpoindex@iupui.edu <bpoindex@iupui.edu>; 'Michael Cotten' <cotte010@mc.duke.edu>; 'Krisa Van Meurs' <vanmeurs@stanford.edu>; 'Duara, Shahnaz' <SDuara@med.miami.edu>; Vivek Narendran <Vivek.Narendran@cchmc.org>; 'Sood, Beena' <bsood@med.wayne.edu>; 'Michael O'Shea' <moshea@wfubmc.edu>; Bell, Edward <edward-bell@uiowa.edu>; 'Richard Ehrenkranz' <richard.ehrenkranz@yale.edu>; kwatterberg@salud.unm.edu <kwatterberg@salud.unm.edu>; 'Ed Donovan' <edward.donovan@cchmc.org>; (susie.buchter@oz.ped.emory.edu) <susie.buchter@oz.ped.emory.edu>; 'vineet.bhandari@yale.edu' <vineet.bhandari@yale.edu>  
Cc: Archer, Stephanie (NIH/NICHD) [E]; Cunningham, Meg <mcunningham@rti.org>; Zaterka-Baxter, Kristin <kzaterka@rti.org>; Huitema, Carolyn Petrie <petrie@rti.org>  
Sent: Tue Jan 26 17:05:52 2010  
Subject: CONFIDENTIAL:New England Journal of Medicine 09-11783 and 09-11781

Hi.

Both Wally and Neil got news today from the NEJM. Revisions are requested for both papers and the subcommittee will work on these. Please fill out the attached forms and return them to NICHD @ 301-496-3790 (FAX).

Also included in the reviews are the following statements:

Please note that we are also inviting a revised version of the companion manuscript. If/when both manuscripts are satisfactorily revised, we would anticipate publishing them back to back.  
This is an important clinical trial. The study was well designed and was conducted at centers with excellent research credentials. The paper is clear and succinctly written.  
The results demonstrating substantial reduction in severe ROP but increased in-hospital mortality in the lower saturation target group are noteworthy with the potential to change clinical practice. This is a timely topic that is the source of great clinical controversy and practice variation. Contemporary, well designed clinical investigations to enlighten the debate are long overdue.  
This large RCT in such a difficult area is a fantastic achievement and you need to be congratulated.

We will need the attached forms once the papers are revised.

Please keep the information on review and status confidential. The New England journal has a strict embargo

policy.

Thanks to everyone for all of the effort for this important study!!

Best regards

Rose

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**From:** Susan Hintz  
**To:** Newman, Jamie  
**Cc:** petrie@rti.org; Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: DRAFT: SUPPORT MRI School Age FU forms  
**Date:** Wednesday, January 27, 2010 1:48:59 PM

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You guys are great. Thanks for the clarification - I will take a deep breath and dive in soon.

Susan

Hi Susan,

Just to clarify - Carolyn and I had some time to devote to this but there is no rush in you reviewing these. I hear through the grapevine that you are on service and are meeting some other NRN deadlines. Feel free to file these away and review them when your current storm of deadlines/obligations blows over.

Thanks, Jamie

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**From:** Newman, Jamie  
**Sent:** Wednesday, January 27, 2010 12:46 PM  
**To:** 'srhintz@stanford.edu'; 'Bethany Ball'  
**Cc:** Huitema, Carolyn Petrie; Hammond, Jane  
**Subject:** DRAFT: SUPPORT MRI School Age FU forms

Susan,

Attached are 4 more DRAFT SUPPORT MRI School Age Follow-up forms for your review:

- WISC-IV: drafted from Hypo Ext Follow-up form HEF16
- GMFCS: drafted from Hypo Ext Follow-up form HEF08B
- Bimanual Fine Motor Function: drafted from Hypo Ext Follow-up form HEF08C

- **SES at School Age:** (includes living arrangement) drafted from Hypo Ext Follow-up form HEF02
- **Medical History:** drafted from Hypo Ext Follow-up form HEF03 - I realize that relevant medical history may be quite different between these two studies but I thought this would give you a good template/starting point for making revisions for your study.

Question: Hypo Ext Follow-up also has a Cerebral Palsy Worksheet (form HEF08A). Will this be needed for SUPPORT MRI School Age Follow-up as well?

Once you have had a chance to review these forms, perhaps you, Carolyn, and I can have a brief call to discuss.

Thanks, Jamie

---

**From:** Newman, Jamie  
**Sent:** Monday, January 25, 2010 3:03 PM  
**To:** 'srhintz@stanford.edu'; 'Bethany Ball'  
**Cc:** Huitema, Carolyn Petrie; Hammond, Jane  
**Subject:** DRAFT: SUPPORT MRI School Age FU forms

Susan,

We have started drafting the SUPPORT MRI School Age Follow-up forms. Attached are a few of them along with several questions I have for you:

-Social Communication Questionnaire (SCQ): Do you anticipate wanting to look at the individual item responses or are you only interested in the total score? The AutoScore Form has a carbon copy (between the front and back sides of the questionnaire) that assists the examiner with determining the total score. If you are only interested in using the total score, then I suggest we have examiners use the manufacturer's AutoScore form and only key sections A, C, and D (in other

words, remove section B from this form).

-Movement ABC. Relevant Not Done codes will need to be developed.

-Questionnaire for Identifying Children with Chronic Conditions-Revised (QuICCC-R). Note: The child is identified as likely to have a chronic or disabling condition if any of the items highlighted in gray are checked.

-BRIEF - Centers 9, 14, 16, 19, 23, 24 previously indicated that they administer the BRIEF. I'd like for someone who is accustomed to administering the BRIEF to 'pilot' this form by completing the NRN form using one of their previously completed BRIEF assessments. Do you have anything to add for this form before I ask one of the centers mentioned above to do this?

Thanks, Jamie

Jamie E. Newman, PhD, MPH

Statistics and Epidemiology

RTI International

Telephone: (919) 485-5719

Fax: (919) 485-7762

[newman@rti.org](mailto:newman@rti.org)

**From:** Walsh, Michele  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: CONFIDENTIAL:New England Journal of Medicine 09-11783 and 09-11781  
**Date:** Wednesday, January 27, 2010 11:49:34 AM

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uploaded originals to site as directed in cover letter. mw

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**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Tue 1/26/2010 5:10 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; 'wcarlo@peds.uab.edu'; 'mcw3@case.edu'; 'nfiner@ucsd.edu'; 'alaptook@WIHRI.org'; 'wrich@ucsd.edu'; 'mgantz@rti.org'; 'Roger.Faix@hsc.utah.edu'; 'Bradley.yoder@hsc.utah.edu'; 'adas@rti.org'; 'poo@rti.org'; 'kurt.schibler@cchmc.org'; 'nxs5@case.edu'; 'ambal@uab.edu'; 'ifrantz@tuftsmedicalcenter.org'; 'Pablo.Sanchez@UTSouthwestern.edu'; 'Anthony.Piazza@oz.ped.emory.edu'; (b) (6)  
'Nirupama\_Laroia@URMC.Rochester.edu'; 'dale\_phelps@urmc.rochester.edu'; 'bpoindex@iupui.edu'; 'cotte010@mc.duke.edu'; 'vanmeurs@stanford.edu'; 'SDuara@med.miami.edu'; 'Vivek.Narendran@cchmc.org'; 'bsood@med.wayne.edu'; 'moshea@wfubmc.edu'; 'edward-bell@uiowa.edu'; 'richard.ehrenkranz@yale.edu'; 'kwatterberg@salud.unm.edu'; 'edward.donovan@cchmc.org'; 'susie.buchter@oz.ped.emory.edu'; 'vineet.bhandari@yale.edu'  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; 'mcunningham@rti.org'; 'kzaterka@rti.org'; 'petrie@rti.org'  
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Rose

----- Original Message -----

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Wally Carlo, M.D. <WCarlo@peds.uab.edu>; 'Michele Walsh' <mcw3@case.edu>; 'Finer, Neil' <nfiner@ucsd.edu>; 'Abbot Laptook' <ALaptook@wihri.org>; Rich, Wade <wrich@ucsd.edu>; Gantz, Marie <mgantz@rti.org>; 'Roger Faix' <Roger.Faix@hsc.utah.edu>; 'Bradley Yoder' <Bradley.Yoder@hsc.utah.edu>; 'Das, Abhik' <adas@rti.org>; Poole Kenneth (E-mail) <poo@rti.org>; 'Kurt Schibler' <Kurt.Schibler@cchmc.org>; 'Nancy Newman' <nxs5@case.edu>; 'Ambal (ambal@uab.edu) <ambal@uab.edu>; 'Frantz, Ivan' <ifrantz@tuftsmedicalcenter.org>; Pablo.Sanchez@UTSouthwestern.edu <Pablo.Sanchez@UTSouthwestern.edu>; Anthony Piazza (Anthony.Piazza@oz.ped.emory.edu) <Anthony.Piazza@oz.ped.emory.edu>; (b) (6) Laroia, Nirupama <Nirupama\_Laroia@URMC.Rochester.edu>; 'Phelps, Dale' <Dale\_Phelps@URMC.Rochester.edu>; bpoindex@iupui.edu <bpoindex@iupui.edu>; 'Michael Cotten' <cotte010@mc.duke.edu>; 'Krisa Van Meurs' <vanmeurs@stanford.edu>; 'Duara, Shahnaz' <SDuara@med.miami.edu>; Vivek Narendran <Vivek.Narendran@cchmc.org>; 'Sood, Beena' <bsood@med.wayne.edu>; 'Michael O`Shea' <moshea@wfubmc.edu>; Bell, Edward <edward-bell@uiowa.edu>; 'Richard Ehrenkranz' <richard.ehrenkranz@yale.edu>; kwatterberg@salud.unm.edu <kwatterberg@salud.unm.edu>; 'Ed Donovan' <edward.donovan@cchmc.org>; (susie.buchter@oz.ped.emory.edu) <susie.buchter@oz.ped.emory.edu>; 'vineet.bhandari@yale.edu' <vineet.bhandari@yale.edu>  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; Cunningham, Meg <mcunningham@rti.org>; Zaterka-Baxter, Kristin <kzaterka@rti.org>; Huitema, Carolyn Petrie <petrie@rti.org>  
**Sent:** Tue Jan 26 17:05:52 2010  
**Subject:** CONFIDENTIAL:New England Journal of Medicine 09-11783 and 09-11781

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Thanks to everyone for all of the effort for this important study!!

Best regards  
Rose

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**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Phelps, Dale"  
**Subject:** RE: SUPPORT and retinopathy  
**Date:** Wednesday, January 27, 2010 10:52:00 AM

---

This sounds like a good plan.

(b) (6)

Rose

---

**From:** Phelps, Dale [mailto:Dale\_Phelps@URMC.Rochester.edu]  
**Sent:** Wednesday, January 27, 2010 10:47 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: SUPPORT and retinopathy

Hi Rose,  
Things are settling down at bit here\*\*, and the PLAN is to write, now that INS-2 is launched. I want an INS-2 manuscript to be vetted by the Subcommittee before we present the poster (hopefully) at PAS. That would mean the cross sectional paper should get done too.

Dale

(b) (6)

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**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Wednesday, January 27, 2010 6:50 AM  
**To:** Phelps, Dale  
**Subject:** RE: SUPPORT and retinopathy

Dale

These sound like great ideas. One item to consider that I previously failed to mention— we will need a draft of the pending papers that you have prior to allowing further statistical analyses as per our policies. Do you have a time frame for the scavenged sample and the INS-1 paper??

Thanks

Rose

---

**From:** Phelps, Dale [mailto:Dale\_Phelps@URMC.Rochester.edu]  
**Sent:** Saturday, January 23, 2010 8:11 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Kennedy, Kathleen A  
**Cc:** Bell, Edward  
**Subject:** RE: SUPPORT and retinopathy

Hi all,

Here is the outline of what I'd propose. This is what I'm most interested in, but it does appear that we are all interested in 'epidemiology' of ROP in some manner. Not really incidence, but how to wrap our arms around who should be examined and when do we give up.

Rose, it looks like we could have a writing group with Kathleen, Ed, probably Neil and myself plus one or two of the ophthalmologists.

I know David Wallace thinks a lot about these issues. Gary Markowitz worries about them, but has not been writing papers... but he gave excellent co-authorship feedback during the initial writing up of the ETROP study. Although I know names of Sarah Friedman and Amy Hutchinson well, I have not worked with them personally.

I could query these for their interest and availability....?

I will be at the Pediatric Ophthalmologist's annual meeting in April. Maybe I could meet with interested ophthal then--have a writing session ? Kathleen, Ed and I could do prep work/ plans at the Network meeting in Feb.

Thoughts all ?

Dale

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]

**Sent:** Thursday, January 21, 2010 10:26 AM

**To:** 'Kennedy, Kathleen A'; Phelps, Dale

**Cc:** Bell, Edward

**Subject:** RE: SUPPORT and retinopathy

We had 4 ophthalmologists who have done a SUPPORT ROP adjudication. They are:

David Wallace – Duke

Sarah Friedman – Duke

Gary Markowitz (Rochester)

Amy Hutchinson (Emory)

Ed Bell was also interested in ROP and growth rate, so I have copied him on the email

Rose

---

**From:** Kennedy, Kathleen A [mailto:Kathleen.A.Kennedy@uth.tmc.edu]

**Sent:** Wednesday, January 20, 2010 8:15 PM

**To:** Phelps, Dale; Higgins, Rosemary (NIH/NICHD) [E]

**Subject:** RE: SUPPORT and retinopathy

I think this is where the paper trail on that ended. It wasn't real clear to me where to go from here and I haven't had time to ponder it since then. I am still interested in it and it seems like Dale thinks it would be worthwhile. I think we really need an ophthalmologist to participate in this. I haven't been able to get Helen Hittner's attention since she's been immersed in her Avastin study. Do you know of any other ophthalmologists in the Network sites who might be interested? I'll be off service in February and I should have some more time to think about this then.

Kathleen A. Kennedy, MD, MPH

Richard W. Mithoff Professor of Pediatrics

Director, Division of Neonatal-Perinatal Medicine

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, March 31, 2009 4:00 PM  
**To:** Kennedy, Kathleen A; higginsr@mail.nih.gov  
**Cc:** nfiner@ucsd.edu  
**Subject:** RE: SUPPORT and retinopathy

Hi Kathleen, and all,

Thank you for forwarding your original plan. It is extremely interesting, would be of value for the literature and I am very interested and feel I would have much to offer. I can respond to some of the questions you asked Helen (and will below). I would enjoy working on this with you and the SUPPORT team.

I actually had a different question in mind, but it would nicely fold into the analyses you propose.

That is:

If ROP examinations cease following hospital discharge (back-transfer), what proportion of infants go on to reach the criteria for surgery after discharge home (or back-transfer)? Are there identifying characteristics of these infants that could predict this outcome?

Dale

Your questions:

Would treatment initiated after 45 weeks PMA not be beneficial?

I do not believe there are data to answer this question. In part you need to know if the ROP JUST reached criteria later, or if it had been smoldering at criteria before hand. Also, you are in the zone at 45 weeks PMA where aggressive treatment of early retinal detachments are being performed by some ophthalmologists, so you have the combination of the early treatment phase trailing off and the aggressive later treatment beginning.

In the SUPPORT study, 55 weeks PMA was used for the "give up" time.

I believe onset of disease (as various stages) in the first eye would be sufficient. However, if the paper turns up a little thin, we could add the second eye analyses... ophthalmologists who delve into pathogenesis are always interested in this oddity.

---

**From:** Kennedy, Kathleen A [mailto:Kathleen.A.Kennedy@uth.tmc.edu]  
**Sent:** Tuesday, March 31, 2009 4:16 PM  
**To:** Phelps, Dale; higginsr@mail.nih.gov  
**Cc:** nfiner@ucsd.edu  
**Subject:** RE: SUPPORT and retinopathy

I wrote a brief proposal for this in Oct 2007 after Dale and I discussed it (attached). I really thought it



needed some input from an ophthalmologist (see questions in red) so I sent it Helen Hittner (our ophthalmologist). She had initially expressed interest and then never responded (got busy with the Avastin study). I also got the impression that Dale wasn't very interested so I let it drop. I'd be happy to pick it up and do most of the work if Dale and Neil are interested. Maybe Dale could answer the questions that I posed to Helen in the attachment.

Kathleen A. Kennedy, MD, MPH  
Richard W. Mithoff Professor of Pediatrics  
Director, Division of Neonatal-Perinatal Medicine  
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:** Monday, March 30, 2009 12:40 PM  
**To:** higginsr@mail.nih.gov; Kennedy, Kathleen A  
**Cc:** nfiner@ucsd.edu  
**Subject:** Re: SUPPORT and retinopathy

I remain very interested in this. However I can not work on it until INS-2 is launched.  
Dale

---

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** Kathleen.A.Kennedy@uth.tmc.edu ; Phelps, Dale  
**Cc:** nfiner@ucsd.edu  
**Sent:** Mon Mar 30 11:58:07 2009  
**Subject:** SUPPORT and retinopathy  
Dale and Kathleen

The SUPPORT subcommittee met today to discuss data analysis. I recall that there was some discussion with the two of you regarding a "natural history" analysis of the ROP exams. Let me know if there is still interest in this as we had not received any secondary proposal to perform this analysis.

Thanks  
Rose

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network  
Pregnancy and Perinatology Branch  
Center for Developmental Biology and Perinatal Medicine  
Eunice Kennedy Shriver National Institute of Child Health and Human Development  
National Institutes of Health  
6100 Executive Blvd., Room 4B03  
MSC 7510  
Bethesda, MD 20892  
For overnight delivery use Rockville, MD 20892  
301-496-5575  
301-496-3790 (FAX)  
higginsr@mail.nih.gov

**From:** Edward Bell  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.; "Michele Walsh"; "Finer, Neil"; "Abbot Laptook"; Rich, Wade; Gantz, Marie; "Roger Faix"; "Bradley Yoder"; "Das, Abhik"; Poole Kenneth(E-mail); "Kurt Schibler"; "NancyNewman"; Ambal (ambal@uab.edu); "Frantz,Ivan"; Pablo.Sanchez@UTSouthwestern.edu; Anthony Piazza(Anthony.Piazza@oz.ped.emory.edu); (b) (6) Laroia, Nirupama; "Phelps, Dale"; bpoindex@iupui.edu; "Michael Cotten"; "Krisa Van Meurs"; "Duara, Shahnaz"; VivekNarendran; "Sood, Beena"; "Michael O' Shea"; "Richard Ehrenkranz"; kwatterberg@salud.unm.edu; "Ed Donovan"; (susie.buchter@oz.ped.emory.edu); "vineet.bhandari@yale.edu"  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; Cunningham,Meg; Zaterka-Baxter, Kristin; Huitema, Carolyn Petrie  
**Subject:** Re: CONFIDENTIAL:New England Journal of Medicine 09-11783 and 09-11781  
**Date:** Wednesday, January 27, 2010 12:51:05 AM

---

Neil, Wally, and others, CONGRATULATIONS on a monumental accomplishment, from start to finish. Rose, I assume you will share the editor's comments with the coordinators at the appropriate time.

Ed

Sent from my phone

-----Original Message-----

From: "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov>

Date: Tue, 26 Jan 2010 17:05:52

To: Wally Carlo, M.D.<WCarlo@peds.uab.edu>; 'Michele Walsh'<mcw3@case.edu>; 'Finer, Neil'<nfiner@ucsd.edu>; 'Abbot Laptook'<ALaptook@wihri.org>; Rich, Wade<wrich@ucsd.edu>; Gantz, Marie<mgantz@rti.org>; 'Roger Faix'<Roger.Faix@hsc.utah.edu>; 'Bradley Yoder'<Bradley.Yoder@hsc.utah.edu>; 'Das, Abhik'<adas@rti.org>; Poole Kenneth(E-mail)<poo@rti.org>; 'Kurt Schibler'<Kurt.Schibler@cchmc.org>; 'NancyNewman'<nxs5@case.edu>; Ambal (ambal@uab.edu) <ambal@uab.edu>; 'Frantz,Ivan'<ifrantz@tuftsmedicalcenter.org>; Pablo.Sanchez@UTSouthwestern.edu<Pablo.Sanchez@UTSouthwestern.edu>; Anthony Piazza(Anthony.Piazza@oz.ped.emory.edu)<Anthony.Piazza@oz.ped.emory.edu>; (b) (6) Laroia, Nirupama<Nirupama\_Laroia@URMC.Rochester.edu>; 'Phelps, Dale'<Dale\_Phelps@URMC.Rochester.edu>; bpoindex@iupui.edu<bpoindex@iupui.edu>; 'Michael Cotten'<cotte010@mc.duke.edu>; 'Krisa Van Meurs'<vanmeurs@stanford.edu>; 'Duara, Shahnaz'<SDuara@med.miami.edu>; VivekNarendran<Vivek.Narendran@cchmc.org>; 'Sood, Beena'<bsood@med.wayne.edu>; 'Michael O' Shea'<moshea@wfulmc.edu>; Bell, Edward<edward-bell@uiowa.edu>; 'Richard Ehrenkranz'<richard.ehrenkranz@yale.edu>; kwatterberg@salud.unm.edu<kwatterberg@salud.unm.edu>; 'Ed Donovan'<edward.donovan@cchmc.org>; (susie.buchter@oz.ped.emory.edu)<susie.buchter@oz.ped.emory.edu>; 'vineet.bhandari@yale.edu'<vineet.bhandari@yale.edu>  
Cc: Archer, Stephanie (NIH/NICHD) [E]<archerst@mail.nih.gov>; Cunningham,Meg<mcunningham@rti.org>; Zaterka-Baxter, Kristin<kzaterka@rti.org>; Huitema, Carolyn Petrie<petrie@rti.org>  
Subject: CONFIDENTIAL:New England Journal of Medicine 09-11783 and 09-11781

Hi,

Both Wally and Neil got news today from the NEJM. Revisions are requested for both papers and the subcommittee will work on these. Please fill out the attached forms and return them to NICHD @ 301-496-3790 (FAX).

Also included in the reviews are the following statements:

Please note that we are also inviting a revised version of the companion manuscript. If/when both manuscripts are satisfactorily revised, we would anticipate publishing them back to back.

This is an important clinical trial. The study was well designed and was conducted at centers with excellent research credentials. The paper is clear and succinctly written.

The results demonstrating substantial reduction in severe ROP but increased in-hospital mortality in the lower saturation target group are noteworthy with the potential to change clinical practice. This is a timely topic that is the source of great clinical controversy and practice variation. Contemporary, well designed clinical investigations to enlighten the debate are long overdue.

This large RCT in such a difficult area is a fantastic achievement and you need to be congratulated.

We will need the attached forms once the papers are revised.

Please keep the information on review and status confidential. The New England journal has a strict embargo policy.

Thanks to everyone for all of the effort for this important study!!

Best regards  
Rose

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "kwatterberg@salud.unm.edu"  
**Subject:** Re: CONFIDENTIAL:New England Journal of Medicine 09-11783 and 09-11781  
**Date:** Tuesday, January 26, 2010 6:09:18 PM

---

83 is the cpap paper and 81 is the oximetry paper.  
Grant support needs to be acknowledged.

Thanks - this is terrific!  
Rose

---

**From:** Kristi Watterberg <KWatterberg@salud.unm.edu>  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Sent:** Tue Jan 26 18:06:41 2010  
**Subject:** Re: CONFIDENTIAL:New England Journal of Medicine 09-11783 and 09-11781

Hi, Rose, this is wonderful news! The form is more complex by the day - this one appears to ask if we received ANY support, not just commercial, so I figure I should say yes, Grant, NICHD?

Also, which ID number goes with which manuscript?

thanks, Kristi

>>> "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> 1/26/2010 3:05 PM >>>

Hi,

Both Wally and Neil got news today from the NEJM. Revisions are requested for both papers and the subcommittee will work on these. Please fill out the attached forms and return them to NICHD @ 301-496-3790 (FAX).

Also included in the reviews are the following statements:

Please note that we are also inviting a revised version of the companion manuscript. If/when both manuscripts are satisfactorily revised, we would anticipate publishing them back to back. This is an important clinical trial. The study was well designed and was conducted at centers with excellent research credentials. The paper is clear and succinctly written. The results demonstrating substantial reduction in severe ROP but increased in-hospital mortality in the lower saturation target group are noteworthy with the potential to change clinical practice. This is a timely topic that is the source of great clinical controversy and practice variation. Contemporary, well designed clinical investigations to enlighten the debate are long overdue. This large RCT in such a difficult area is a fantastic achievement and you need to be congratulated.

We will need the attached forms once the papers are revised.

Please keep the information on review and status confidential. The New England journal has a strict embargo policy.

Thanks to everyone for all of the effort for this important study!!

Best regards  
Rose

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "alaptook@WIHRI.org"  
**Subject:** Re: CONFIDENTIAL FW: New England Journal of Medicine 09-11783  
**Date:** Tuesday, January 26, 2010 5:38:31 PM

---

It was attached  
I can resend

----- Original Message -----

From: Laptook, Abbot <ALaptook@WIHRI.org>  
To: Higgins, Rosemary (NIH/NICHD) [E]  
Sent: Tue Jan 26 17:28:11 2010  
Subject: RE: CONFIDENTIAL FW: New England Journal of Medicine 09-11783

I don't see the review and number for the pulse oximeter paper. AL

-----Original Message-----

From: Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
Sent: Tuesday, January 26, 2010 4:48 PM  
To: 'Finer, Neil'; Wally Carlo, M.D.; 'Michele Walsh'; 'Bradley Yoder'; 'Roger Faix'; 'Kurt Schibler'; 'Nancy Newman'; Rich, Wade; Gantz, Marie; 'Das, Abhik'; Laptook, Abbot  
Cc: Cunningham, Meg; Archer, Stephanie (NIH/NICHD) [E]; Zaterka-Baxter, Kristin  
Subject: CONFIDENTIAL FW: New England Journal of Medicine 09-11783  
Importance: High

To the SUPPORT Subcommittee:

First, thanks to all of you for the incredible work - we are getting close.  
The reviews are below and attached. Neil and Wally are revising the manuscripts and we should have updated versions in the very near future.

Again, thanks for all the hard work!!!  
Rose

-----Original Message-----

From: Finer, Neil [mailto:nfiner@ucsd.edu]  
Sent: Tuesday, January 26, 2010 10:47 AM  
To: Higgins, Rosemary (NIH/NICHD) [E]; wcarlo@peds.uab.edu  
Cc: Rich, Wade; 'mgantz@rti.org'; 'adas@rti.org'  
Subject: FW: New England Journal of Medicine 09-11783

Good Morning

Here is the NEJM response. There are a number of statistical issues that we will need to address - I will need Abhik and Marie to help - ie 98% CIs - do we do this?? This p=.02 is an issue Please have a look and I will begin the basic process.

Rose I don't know if you want this more widely circulated - I think we should deal with the queries and then perhaps send out a final version I will await your reply Be well Neil

-----Original Message-----

From: onbehalfof+editorial+nejm.org@manuscriptcentral.com  
[mailto:onbehalfof+editorial+nejm.org@manuscriptcentral.com] On Behalf Of editorial@nejm.org  
Sent: Tuesday, January 26, 2010 5:58 AM  
To: Finer, Neil  
Subject: New England Journal of Medicine 09-11783

Dear Dr. Finer:

Your manuscript, "Early CPAP versus Surfactant in Very Preterm Infants: The SUPPORT Trial," has been evaluated by outside reviewers and by the editors. Although it is not acceptable for publication in its present form, we would be pleased to consider a revised version that responds to the enclosed comments of the outside reviewers and to the editors' points noted below. Please understand that we cannot commit to publication until we have evaluated a revised version.

We ask that you attend in particular to the comments of the statistical reviewer regarding (b) (4)

Please note that we are also inviting a revised version of the companion manuscript. If/when both manuscripts are satisfactorily revised, we would anticipate publishing them back to back. The companion manuscript should be cited in your report, and overlap kept to a minimum.

When you send in your revised manuscript, please provide a point-by-point response to the editors' and reviewers' comments in a covering letter and return two copies of the revision, one in which the changes you have made are highlighted and the other a clean copy. Please include a word count for the text. Any changes in authorship must be made in writing, signed by all authors.

To revise your manuscript, log into <http://mc.manuscriptcentral.com/nejm> and enter For Authors, where you will find a button to "Submit a Revision."

Journal policy dictates that we must have on file a signed Copyright Transfer Agreement from each author before a manuscript can be accepted. Please ask all authors to sign and fax back the enclosed form as soon as possible to (781) 207-6529. This will eliminate unnecessary delays in the event that your manuscript is accepted.

The Universal Disclosure form is also attached. Each author must complete it. After you have filled in the appropriate information in the spaces provided, you may either e-mail your completed form to [editorial@nejm.org](mailto:editorial@nejm.org) or upload it to your Author Dashboard of ScholarOne Manuscripts. It is essential that you return the forms as soon as possible, because we cannot process your manuscript without them. Please be aware that in the event of publication, each author's submitted disclosure form will be posted on the web (with any dollar amounts redacted).

We ask that you, as the corresponding author, prepare a financial disclosure statement for publication with the manuscript. The statement should describe the relationships of all authors with companies that make products relevant to the manuscript. The statement should specify the type of relationship (e.g., consulting, paid speaking, grant support, equity, patents, royalties) each author has with each company. The information should be consistent with the authors' signed financial disclosure forms. The statement should be inserted before the Acknowledgment section of the text and labeled "Disclosure." If you have nothing relevant to disclose, please indicate this.

We also ask that you make clear in your cover letter who designed the study, who gathered the data, who analyzed the data, who vouches for the data and the analysis, who wrote the paper, and who decided to publish the paper. If there was an industry sponsor, please include in the Methods section of the manuscript a statement on the role of the industry sponsor in each of these activities; an investigator should be named who takes responsibility for the data and analyses. Please state as well if there were any agreements concerning confidentiality of the data between the sponsor and the authors or the institutions named in the credit lines. (see the editorial in the September 13, 2001, issue of the Journal).

In addition, please indicate who wrote the first draft of your manuscript. If it was not one of the authors, please name the person or persons and indicate who paid them. If any writing assistance other than copy editing was provided, please name the person or persons and indicate who paid them.

We expect your revised manuscript to include full, accurate, and up-to-date reporting of adverse events. In general, this should be in the form of a table containing descriptions of all serious adverse events and all other common or important adverse events. The abstract should contain a statement regarding adverse events.

Please recall that the Journal requires that neither an article under consideration nor any part of its essential substance, tables, or figures has been or will be published or submitted elsewhere before appearing in the Journal.

If you have not done so already, 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.

If you have any questions about compliance with these policies, please contact the editorial office for clarification.

Although we cannot commit to publication of your revised manuscript until we have had the opportunity to evaluate it, we look forward to receiving it and assure you of a prompt evaluation when it arrives. Please submit your revised manuscript no later than February 16th, 2010.

Thank you for sending us your work.

Sincerely,

Caren G. Solomon, MD  
Deputy Editor

Michael F. Greene, MD  
Associate Editor

New England Journal of Medicine  
10 Shattuck Street  
Boston, MA 02115  
(617) 734-9800  
Fax: (617) 739-9864  
<http://www.nejm.org>

Reviewer: 1

<b>Comments for the Author</b>

(b) (4)  
[Redacted]

Introduction:

1. (b) (4)  
[Redacted]

2. (b) (4)  
[Redacted]

(b) (4)  
[Redacted]

(b) (4)

Reviewer: 2

<b>Comments for the Author</b>

(b) (4)

Abstract

Comments

1. (b) (4)

Introduction

Comments

1. (b) (4)

Methods

Comments

1. (b) (4)



(b) (4)

[Redacted text block]

Results

Comments

1. (b) (4)
- [Redacted text block]

Discussion

Comments

1. (b) (4)
- [Redacted text block]

Conclusion

Comments

1. (b) (4)
- [Redacted text block]

(b) (4)

References

1. (b) (4)

Statistical Reviewer: 1

Comments for the Author:

(b) (4)

[Redacted]

[Redacted]

[Redacted]

Editorial Comments:

(b) (4)

ADDITIONAL COMMENTS OF THE EDITORS

Title: should be no more than 75 characters.

Abstract:

(b) (4)

Introduction:

(b) (4)  
[Redacted text block]

Methods:

(b) (4)  
[Redacted text block]

Results:

(b) (4)  
[Redacted text block]

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## Higgins, Rosemary (NIH/NICHD) [E]

---

**From:** Finer, Neil <nfiner@ucsd.edu>  
**Sent:** Tuesday, January 26, 2010 5:11 PM  
**To:** Wally Carlo, M.D.  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]; Abhik Das; Marie Gantz; Rich, Wade  
**Subject:** Re: New England Journal of Medicine 09-11781

Nice work Wally

You and should start to respond to the individual queries and get Abhik and Marie to assist Be well Neil

Sent from my iPhone

On Jan 26, 2010, at 11:17 AM, "Wally Carlo, M.D."  
<WCarlo@peds.uab.edu> wrote:

>  
>  
> Wally Carlo, M.D.  
> Edwin M. Dixon Professor of Pediatrics University of Alabama at  
> Birmingham Director, Division of Neonatology Director, Newborn  
> Nurseries  
> 619 South 20th Street  
> 525 New Hillman Building  
> Birmingham, AL 35233-7335  
> Phone: 205 934 4680  
> FAX: 205 934 3100  
> Cell: 205 266 (b)

> -----Original Message-----

> From: Wally Carlo, M.D.  
> Sent: Tuesday, January 26, 2010 12:47 PM  
> To: Marsha Sumner  
> Cc: Wally Carlo, M.D.  
> Subject: FW: New England Journal of Medicine 09-11781

>  
>  
>  
> Wally Carlo, M.D.  
> Edwin M. Dixon Professor of Pediatrics University of Alabama at  
> Birmingham Director, Division of Neonatology Director, Newborn  
> Nurseries  
> 619 South 20th Street  
> 525 New Hillman Building  
> Birmingham, AL 35233-7335  
> Phone: 205 934 4680  
> FAX: 205 934 3100  
> Cell: 205 266 (b)

> -----Original Message-----

> From: Wally Carlo, M.D.  
> Sent: Tuesday, January 26, 2010 8:29 AM  
> To: 'Higgins, Rosemary (NIH/NICHD) [E]'; 'Finer, Neil'; Das, Abhik;  
> Gantz, Marie  
> Subject: FW: New England Journal of Medicine 09-11781  
>  
> Dear Rose, Neil, Abhik, Marie and Abhik:  
>  
> This is outstanding. BOTH ACCEPTED!!! I think we should try to respond  
> to each of the comment and compromise with their requests as much as  
> possible as long as the revisions do not compromise the integrity of  
> the message.  
>  
> How do we proceed to include the rest of the authors in the review  
> process?

> Wally

>  
> Wally Carlo, M.D.  
> Edwin M. Dixon Professor of Pediatrics University of Alabama at  
> Birmingham Director, Division of Neonatology Director, Newborn  
> Nurseries  
> 619 South 20th Street  
> 525 New Hillman Building  
> Birmingham, AL 35233-7335  
> Phone: 205 934 4680  
> FAX: 205 934 3100  
> Cell: 205 266 (b)

> -----Original Message-----

> From: onbehalfof+editorial+nejm.org@manuscriptcentral.com  
> [mailto:onbehalfof+editorial+nejm.org@manuscriptcentral.com] On Behalf  
> Of editorial@nejm.org  
> Sent: Tuesday, January 26, 2010 8:07 AM  
> To: Wally Carlo, M.D.  
> Subject: New England Journal of Medicine 09-11781

>  
> Re: 09-11781 - The SUPPORT Trial: Randomized Trial of Oxygen  
> Saturation Targets in Extremely Premature Infants

> Dear Dr. Carlo:

>  
> Your manuscript, "The SUPPORT Trial: Randomized Trial of Oxygen  
> Saturation Targets in Extremely Premature Infants," has been evaluated  
> by outside reviewers and by the editors. Although it is not acceptable  
> for publication in its present form, we would be pleased to consider a  
> revised version that responds to the enclosed comments of the outside  
> reviewers and to the editors' points noted below. Please understand  
> that we cannot commit to publication until we have evaluated a revised  
> version.

>

> Please address in particular the concerns raised by the statistical  
> reviewer regarding (b) (4)

[REDACTED]

>

> Please note that we are also inviting a revised version of the  
> companion manuscript. If/when both manuscripts are satisfactorily  
> revised, we would anticipate publishing them back to back. The  
> companion manuscript should be cited in your report, and overlap kept  
> to a minimum.

>

> When you send in your revised manuscript, please provide a  
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> covering letter and return two copies of the revision, one in which  
> the changes you have made are highlighted and the other a clean copy.  
> Please  
> include a word count for the text. Any changes in authorship must be  
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>

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>

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> Manuscripts. It is essential that you return the forms as soon as  
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> Please  
> be aware that in the event of publication, each author's submitted  
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>

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- > The information should be consistent with the authors' signed
- > financial disclosure forms. The statement should be inserted before
- > the Acknowledgment section of the text and labeled "Disclosure." If
- > you have nothing relevant to disclose, please indicate this.
- >
- > We also ask that you make clear in your cover letter who designed the
- > study, who gathered the data, who analyzed the data, who vouches for
- > the data and the analysis, who wrote the paper, and who decided to
- > publish the paper. If there was an industry sponsor, please include in
- > the Methods section of the manuscript a statement on the role of the
- > industry sponsor in each of these activities; an investigator should
- > be named who takes responsibility for the data and analyses. Please
- > state as well if there were any agreements concerning confidentiality
- > of the data between the sponsor and the authors or the institutions
- > named in the credit lines. (see the editorial in the September 13,
- > 2001, issue of the Journal).
- >
- > In addition, please indicate who wrote the first draft of your
- > manuscript. If it was not one of the authors, please name the person
- > or persons and indicate who paid them. If any writing assistance other
- > than copy editing was provided, please name the person or persons and
- > indicate who paid them.
- >
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- > up-to-date reporting of adverse events. In general, this should be in
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- > events and all other common or important adverse events. The abstract
- > should contain a statement regarding adverse events.
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- > Please recall that the Journal requires that neither an article under
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- > figures has been or will be published or submitted elsewhere before
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- > If you have any questions about compliance with these policies, please
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- > Although we cannot commit to publication of your revised manuscript
- > until we have had the opportunity to evaluate it, we look forward to
- > receiving it and assure you of a prompt evaluation when it arrives.
- > Please submit your revised manuscript no later than February 16th,

> 2010.

>

> Thank you for sending us your work.

>

> Sincerely,

>

>

> Caren G. Solomon, MD Michael F. Greene, MD Deputy Editor Associate

> Editor

>

> New England Journal of Medicine

> 10 Shattuck Street

> Boston, MA 02115

> (617) 734-9800

> Fax: (617) 739-9864

> <http://www.nejm.org>

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> Reviewer: 1

> Comments for the Author

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> ADDITIONAL COMMENTS OF THE EDITORS

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- > <Attached file: NEJM-instructions-for-ICMJE-form.pdf>
- > <Attached file: ICMJE-Disclosure-form.pdf>

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Finer, Neil"; "Wally Carlo, M.D."; "Michele Walsh"; "Bradley Yoder"; "Roger Faix"; "Kurt Schibler"; "Nancy Newman"; "Rich, Wade"; "Gantz, Marie"; "Das, Abhik"; "Abbot Laptook"  
**Cc:** "Cunningham, Meg"; Archer, Stephanie (NIH/NICHD) [E]; "Zaterka-Baxter, Kristin"  
**Subject:** CONFIDENTIAL FW: New England Journal of Medicine 09-11783  
**Date:** Tuesday, January 26, 2010 4:47:00 PM  
**Attachments:** Subgroups.pdf  
NEJM-CTA-2009.pdf  
NEJM-inst-for-ICMJE-form.pdf  
ICMJE-Disclosure-Form-102309.pdf  
FW New England Journal of Medicine 09-11781.txt  
**Importance:** High

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To the SUPPORT Subcommittee:

First, thanks to all of you for the incredible work - we are getting close.

The reviews are below and attached. Neil and Wally are revising the manuscripts and we should have updated versions in the very near future.

Again, thanks for all the hard work!!!

Rose

-----Original Message-----

**From:** Finer, Neil [mailto:nfiner@ucsd.edu]  
**Sent:** Tuesday, January 26, 2010 10:47 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; wcarlo@peds.uab.edu  
**Cc:** Rich, Wade; 'mgantz@rti.org'; 'adas@rti.org'  
**Subject:** FW: New England Journal of Medicine 09-11783

Good Morning

Here is the NEJM response. There are a number of statistical issues that we will need to address - I will need Abhik and Marie to help (b) (4) - do we do this? (b) (4)

Please have a look and I will begin the basic process.

Rose I don't know if you want this more widely circulated - I think we should deal with the queries and then perhaps send out a final version

I will await your reply

Be well

Neil

-----Original Message-----

**From:** onbehalfof+editorial+nejm.org@manuscriptcentral.com  
[mailto:onbehalfof+editorial+nejm.org@manuscriptcentral.com] On Behalf Of editorial@nejm.org  
**Sent:** Tuesday, January 26, 2010 5:58 AM  
**To:** Finer, Neil  
**Subject:** New England Journal of Medicine 09-11783

Dear Dr. Finer:

Your manuscript, "Early CPAP versus Surfactant in Very Preterm Infants: The SUPPORT Trial," has been evaluated by outside reviewers and by the editors. Although it is not acceptable for publication in its present form, we would be pleased to consider a revised version that responds to the enclosed comments of the outside reviewers and to the editors' points noted below. Please understand that we cannot commit to publication until we have evaluated a revised version.

We ask that you attend in particular to the comments of the statistical reviewer regarding (b) (4)

[REDACTED]

Please note that we are also inviting a revised version of the companion manuscript. If/when both manuscripts are satisfactorily revised, we would anticipate publishing them back to back. The companion manuscript should be cited in your report, and overlap kept to a minimum.

When you send in your revised manuscript, please provide a point-by-point response to the editors' and reviewers' comments in a covering letter and return two copies of the revision, one in which the changes you have made are highlighted and the other a clean copy. Please include a word count for the text. Any changes in authorship must be made in writing, signed by all authors.

To revise your manuscript, log into <http://mc.manuscriptcentral.com/nejm> and enter For Authors, where you will find a button to "Submit a Revision."

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The Universal Disclosure form is also attached. Each author must complete it. After you have filled in the appropriate information in the spaces provided, you may either e-mail your completed form to [editorial@nejm.org](mailto:editorial@nejm.org) or upload it to your Author Dashboard of ScholarOne Manuscripts. It is essential that you return the forms as soon as possible, because we cannot process your manuscript without them. Please be aware that in the event of publication, each author's submitted disclosure form will be posted on the web (with any dollar amounts redacted).

We ask that you, as the corresponding author, prepare a financial disclosure statement for publication with the manuscript. The statement should describe the relationships of all authors with companies that make products relevant to the manuscript. The statement should specify the type of relationship (e.g., consulting, paid speaking, grant support, equity, patents, royalties) each author has with each company. The information should be consistent with the authors' signed financial disclosure forms. The statement should be inserted before the Acknowledgment section of the text and labeled "Disclosure." If you have nothing relevant to disclose, please indicate this.

We also ask that you make clear in your cover letter who designed the study, who gathered the data, who analyzed the data, who vouches for the data and the analysis, who wrote the paper, and who decided to publish the paper. If there was an industry sponsor, please include in the Methods section of the manuscript a statement on the role of the industry sponsor in each of these activities; an investigator should be named who takes responsibility for the data and analyses. Please state as well if there were any agreements concerning confidentiality of the data between the sponsor and the authors or the institutions named in the credit lines. (see the editorial in the September 13, 2001, issue of the Journal).

In addition, please indicate who wrote the first draft of your manuscript. If it was not one of the authors, please name the person or persons and indicate who paid them. If any writing assistance other than copy editing was provided, please name the person or persons and indicate who paid them.

We expect your revised manuscript to include full, accurate, and up-to-date reporting of adverse events. In general, this should be in the form of a table containing descriptions of all serious adverse events and all other common or important adverse events. The abstract should contain a statement regarding adverse events.

Please recall that the Journal requires that neither an article under consideration nor any part of its essential substance, tables, or figures has been or will be published or submitted elsewhere before appearing in the Journal.

If you have not done so already, 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.

If you have any questions about compliance with these policies, please contact the editorial office for clarification.

Although we cannot commit to publication of your revised manuscript until we have had the opportunity to evaluate it, we look forward to receiving it and assure you of a prompt evaluation when it arrives. Please submit your

revised manuscript no later than February 16th, 2010.

Thank you for sending us your work.

Sincerely,

Caren G. Solomon, MD  
Deputy Editor

Michael F. Greene, MD  
Associate Editor

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Boston, MA 02115  
(617) 734-9800  
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Reviewer: 1

<b>Comments for the Author</b>

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Introduction:

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Methods:

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Results:

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Reviewer: 2

<b>Comments for the Author</b>

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Conclusion

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Statistical Reviewer: 1

Comments for the Author:

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Editorial Comments:

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ADDITIONAL COMMENTS OF THE EDITORS

Title: should be no more than 75 characters.

Abstract:

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SPECIAL REPORT

## Statistics in Medicine — Reporting of Subgroup Analyses in Clinical Trials

Rui Wang, M.S., Stephen W. Lagakos, Ph.D., James H. Ware, Ph.D., David J. Hunter, M.B., B.S., and Jeffrey M. Drazen, M.D.

Medical research relies on clinical trials to assess therapeutic benefits. Because of the effort and cost involved in these studies, investigators frequently use analyses of subgroups of study participants to extract as much information as possible. Such analyses, which assess the heterogeneity of treatment effects in subgroups of patients, may provide useful information for the care of patients and for future research. However, subgroup analyses also introduce analytic challenges and can lead to overstated and misleading results.<sup>1-7</sup> This report outlines the challenges associated with conducting and reporting subgroup analyses, and it sets forth guidelines for their use in the *Journal*. Although this report focuses on the reporting of clinical trials, many of the issues discussed also apply to observational studies.

### SUBGROUP ANALYSES AND RELATED CONCEPTS

#### SUBGROUP ANALYSIS

By “subgroup analysis,” we mean any evaluation of treatment effects for a specific end point in subgroups of patients defined by baseline characteristics. The end point may be a measure of treatment efficacy or safety. For a given end point, the treatment effect — a comparison between the treatment groups — is typically measured by a relative risk, odds ratio, or arithmetic difference. The research question usually posed is this: Do the treatment effects vary among the levels of a baseline factor?

A subgroup analysis is sometimes undertaken to assess treatment effects for a specific patient characteristic; this assessment is often listed as a primary or secondary study objective. For example, Sacks et al.<sup>8</sup> conducted a placebo-controlled trial in which the reduction in the incidence of

coronary events with the use of pravastatin was examined in a diverse population of persons who had survived a myocardial infarction. In subgroup analyses, the investigators further examined whether the efficacy of pravastatin relative to placebo in preventing coronary events varied according to the patients’ baseline low-density lipoprotein (LDL) levels.

Subgroup analyses are also undertaken to investigate the consistency of the trial conclusions among different subpopulations defined by each of multiple baseline characteristics of the patients. For example, Jackson et al.<sup>9</sup> reported the outcomes of a study in which 36,282 postmenopausal women 50 to 79 years of age were randomly assigned to receive 1000 mg of elemental calcium with 400 IU of vitamin D<sub>3</sub> daily or placebo. Fractures, the primary outcome, were ascertained over an average follow-up period of 7.0 years; bone density was a secondary outcome. Overall, no treatment effect was found for the primary outcome; that is, the active treatment was not shown to prevent fractures. The effect of calcium plus vitamin D supplementation relative to placebo on the risk of each of four fracture outcomes was further analyzed for consistency in subgroups defined by 15 characteristics of the participants.

#### HETEROGENEITY AND STATISTICAL INTERACTIONS

The heterogeneity of treatment effects across the levels of a baseline variable refers to the circumstance in which the treatment effects vary across the levels of the baseline characteristic. Heterogeneity is sometimes further classified as being either quantitative or qualitative. In the first case, one treatment is always better than the other, but by various degrees, whereas in the second case, one treatment is better than the other for one subgroup of patients and worse than the other for

another subgroup of patients. Such variation, also called "effect modification," is typically expressed in a statistical model as an interaction term or terms between the treatment group and the baseline variable. The presence or absence of interaction is specific to the measure of the treatment effect.

The appropriate statistical method for assessing the heterogeneity of treatment effects among the levels of a baseline variable begins with a statistical test for interaction.<sup>10-13</sup> For example, Sacks et al.<sup>8</sup> showed the heterogeneity in pravastatin efficacy by reporting a statistically significant ( $P=0.03$ ) result of testing for the interaction between the treatment and baseline LDL level when the measure of the treatment effect was the relative risk. Many trials lack the power to detect heterogeneity in treatment effect; thus, the inability to find significant interactions does not show that the treatment effect seen overall necessarily applies to all subjects. A common mistake is to claim heterogeneity on the basis of separate tests of treatment effects within each of the levels of the baseline variable.<sup>6,7,14</sup> For example, testing the hypothesis that there is no treatment effect in women and then testing it separately in men does not address the question of whether treatment differences vary according to sex. Another common error is to claim heterogeneity on the basis of the observed treatment-effect sizes within each subgroup, ignoring the uncertainty of these estimates.

#### MULTIPLICITY

It is common practice to conduct a subgroup analysis for each of several — and often many — baseline characteristics, for each of several end points, or for both. For example, the analysis by Jackson and colleagues<sup>9</sup> of the effect of calcium plus vitamin D supplementation relative to placebo on the risk of each of four fracture outcomes for 15 participant characteristics resulted in a total of 60 subgroup analyses.

When multiple subgroup analyses are performed, the probability of a false positive finding can be substantial.<sup>7</sup> For example, if the null hypothesis is true for each of 10 independent tests for interaction at the 0.05 significance level, the chance of at least one false positive result exceeds 40%. Thus, one must be cautious in the interpretation of such results.

There are several methods for addressing multiplicity that are based on the use of more stringent criteria for statistical significance than the customary  $P<0.05$ .<sup>7,15</sup> A less formal approach for addressing multiplicity is to note the number of nominally significant interaction tests that would be expected to occur by chance alone. For example, after noting that 60 subgroup analyses were planned, Jackson et al.<sup>9</sup> pointed out that "Up to three statistically significant interaction tests ( $P<0.05$ ) would be expected on the basis of chance alone," and then they incorporated this consideration in their interpretation of the results.

#### PRESPECIFIED ANALYSIS VERSUS POST HOC ANALYSIS

A prespecified subgroup analysis is one that is planned and documented before any examination of the data, preferably in the study protocol. This analysis includes specification of the end point, the baseline characteristic, and the statistical method used to test for an interaction. For example, the Heart Outcomes Prevention Evaluation 2 investigators<sup>16</sup> conducted a study involving 5522 patients with vascular disease or diabetes to assess the effect of homocysteine lowering with folic acid and B vitamins on the risk of a major cardiovascular event. The primary outcome was a composite of death from cardiovascular causes, myocardial infarction, and stroke. In the Methods section of their article, the authors noted that "Prespecified subgroup analyses involving Cox models were used to evaluate outcomes in patients from regions with folate fortification of food and regions without folate fortification, according to the baseline plasma homocysteine level and the baseline serum creatinine level." Post hoc analyses refer to those in which the hypotheses being tested are not specified before any examination of the data. Such analyses are of particular concern because it is often unclear how many were undertaken and whether some were motivated by inspection of the data. However, both prespecified and post hoc subgroup analyses are subject to inflated false positive rates arising from multiple testing. Investigators should avoid the tendency to prespecify many subgroup analyses in the mistaken belief that these analyses are free of the multiplicity problem.

SPECIAL REPORT

**SUBGROUP ANALYSES IN THE JOURNAL — ASSESSMENT OF REPORTING PRACTICES**

As part of internal quality-control activities at the *Journal*, we assessed the completeness and quality of subgroup analyses reported in the *Journal* during the period from July 1, 2005, through June 30, 2006. A detailed description of the study methods can be found in the Supplementary Appendix, available with the full text of this article at [www.nejm.org](http://www.nejm.org). In this report, we describe the clarity and completeness of subgroup-analysis reporting, evaluate the authors' interpretation and justification of the results of subgroup analyses, and recommend guidelines for reporting subgroup analyses.

Among the original articles published in the *Journal* during the period from July 1, 2005, through June 30, 2006, a total of 95 articles reported primary outcome results from randomized clinical trials. Among these 95 articles, 93 reported results from one clinical trial; the remaining 2 articles reported results from two trials. Thus, results from 97 trials were reported, from which subgroup analyses were reported for 59 trials (61%). Table 1 summarizes the characteristics of the trials. We found that larger trials and multicenter trials were significantly more likely to report subgroup analyses than smaller trials and single-center trials, respectively. With the use of multivariate logistic-regression models, when ranked according to the number of participants enrolled in a trial and compared with trials with the fewest participants, the odds ratio for reporting subgroup analyses for the second quartile was 1.38 (95% confidence interval [CI], 0.45 to 4.20), for the third quartile was 1.98 (95% CI, 0.62 to 6.24), and for the fourth quartile was 8.90 (95% CI, 2.10 to 37.78) ( $P=0.02$ , trend test). The odds ratio for reporting subgroup analyses in multicenter trials as compared with single-center trials was 4.33 (95% CI, 1.56 to 12.16).

Among the 59 trials that reported subgroup analyses, these analyses were mentioned in the Methods section for 21 trials (36%), in the Results section for 57 trials (97%), and in the Discussion section for 37 trials (63%); subgroup analyses were reported in both the text and a figure or table for 39 trials (66%). Other characteristics of the reports

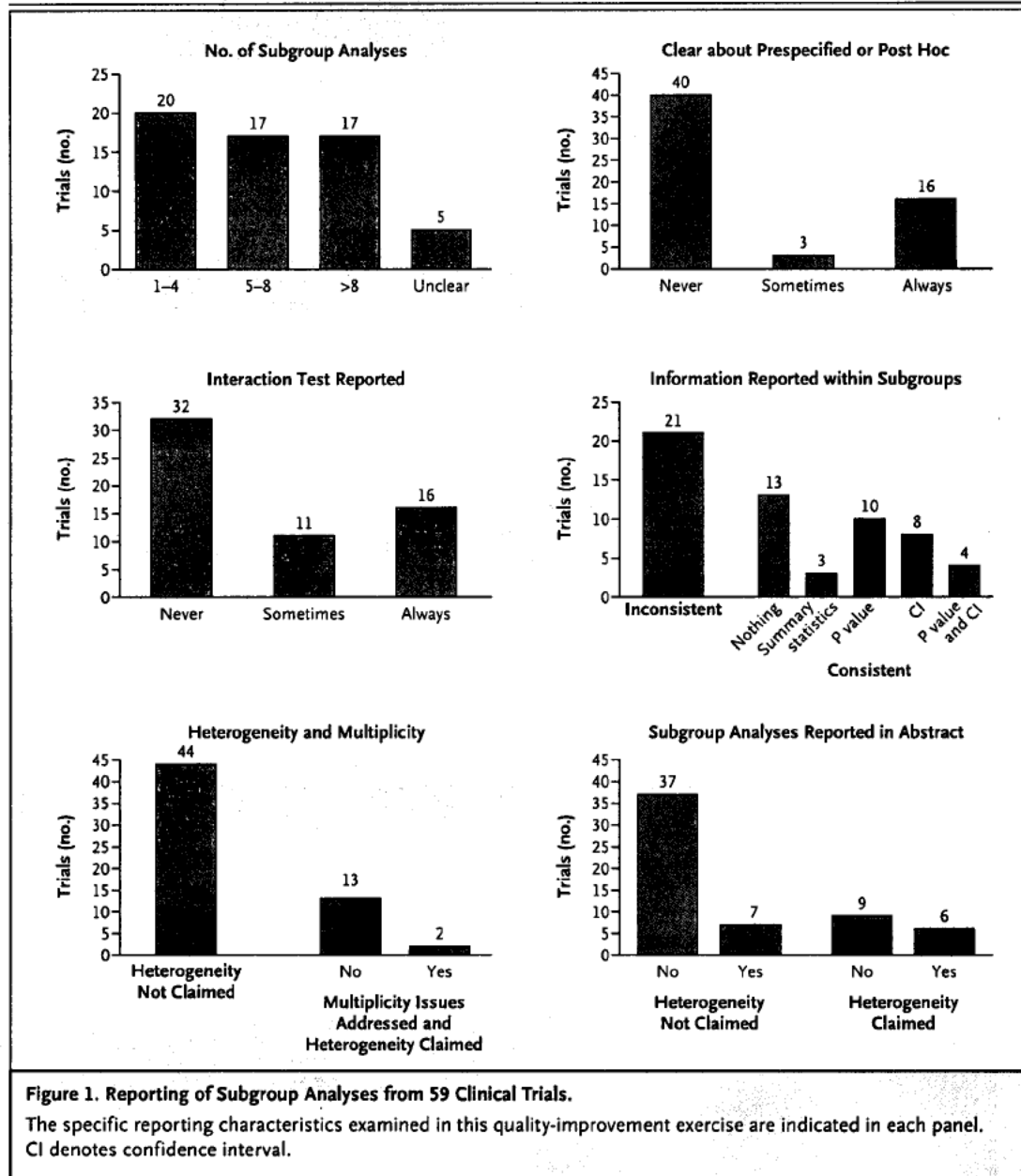
are shown in Figure 1. In general, we are unable to determine the number of subgroup analyses conducted; we attempted to count the number of subgroup analyses reported in the article and found that this number was unclear in nine articles (15%). For example, Lees et al.<sup>17</sup> reported that "We explored analyses of numerous other subgroups to assess the effect of baseline prognostic factors or coexisting conditions on the

**Table 1. Characteristics and Predictors of Reporting Subgroup Analyses in 97 Clinical Trials.\***

Variable	Trials Reporting Subgroup Analyses No. of Trials/ Total No. (%)	P Value†	
		Univariate Odds Ratio	Multivariate Odds Ratio
No. of subjects		0.002†	0.02†
≤218	11/25 (44)		
219–429	13/25 (52)		
430–1012	14/23 (61)		
>1012	21/24 (88)		
Superiority trial		0.25	0.89
Yes	53/84 (63)		
No	6/13 (46)		
Trial sites		0.005	0.05
Single-center	7/21 (33)		
Multicenter	52/76 (68)		
Type of disease studied		0.18	0.37
Cardiovascular	16/20 (80)		
Infectious	2/7 (29)		
Oncologic	9/11 (82)		
Respiratory	7/10 (70)		
Pediatric	5/10 (50)		
Psychiatric or neurologic	6/10 (60)		
Metabolic, endocrine, or gastrointestinal	5/10 (50)		
Gynecologic	3/6 (50)		
Other	6/13 (46)		
Statistically significant primary end point		0.24	0.38
Yes	35/62 (56)		
No	24/35 (69)		

\* A total of 59 trials reported subgroup analyses.

† P values were determined with the use of trend tests.



treatment effect but found no evidence of nominal significance for any biologically likely factor.” For four of these nine articles, we were able to determine that at least eight subgroup analyses were reported. In 40 trials (68%), it was unclear whether any of the subgroup analyses were prespecified or post hoc, and in 3 others (5%) it was unclear whether some were prespecified or post hoc. Interaction tests were reported to have been used to assess the heterogeneity of treatment effects for all subgroup analyses in only 16 trials (27%), and

they were reported to be used for some, but not all, subgroup analyses in 11 trials (19%).

We assessed whether information was provided about treatment effects within the levels of each subgroup variable (Fig. 1). In 25 trials (42%), information about treatment effects was reported consistently for all of the reported subgroup analyses, and in 13 trials (22%), nothing was reported. Investigators in 15 trials (25%), all using superiority designs,<sup>10</sup> claimed heterogeneity of treatment effects between at least one subject sub-



SPECIAL REPORT

group and the overall study population (see Table 1 of the Supplementary Appendix). For 4 of these 15 trials, this claim was based on a nominally significant interaction test, and for 4 others it was based on within-subgroup comparisons only. In the remaining seven trials, significant results of interaction tests were reported for some but not all subgroup analyses. When heterogeneity in the treatment effect was reported, for two trials (13%), investigators offered caution about multiplicity, and for four trials (27%), investigators noted the heterogeneity in the Abstract section.

ANALYSIS OF OUR FINDINGS  
AND GUIDELINES FOR REPORTING  
SUBGROUPS

In the 1-year period studied, the reporting of subgroup analyses was neither uniform nor complete. Because the design of future clinical trials can depend on the results of subgroup analyses, uniformity in reporting would strengthen the foundation on which such research is built. Furthermore, uniformity of reporting will be of value in the interval between recognition of a potential subgroup effect and the availability of adequate data on which to base clinical decisions.

Problems in the reporting of subgroup analyses are not new.<sup>1-6,18</sup> Assmann et al.<sup>2</sup> reported shortcomings of subgroup analyses in a review of the results of 50 trials published in 1997 in four leading medical journals. More recently, Hernández et al.<sup>4</sup> reviewed the results of 63 cardiovascular trials published in 2002 and 2004 and noted the same problems. To improve the quality of reports of parallel-group randomized trials, the Consolidated Standards of Reporting Trials statement was proposed in the mid-1990s and revised in 2001.<sup>19</sup> Although there has been considerable discussion of the potential problems associated with subgroup analysis and recommendations on when and how subgroup analyses should be conducted and reported,<sup>19,20</sup> our analysis of recent articles shows that problems and ambiguities persist in articles published in the *Journal*. For example, we found that in about two thirds of the published trials, it was unclear whether any of the reported subgroup analyses were prespecified or post hoc. In more than half of the trials, it was unclear whether interaction tests were used, and in about one third of the trials, within-level results were not presented in a consistent way.

Guidelines for Reporting Subgroup Analysis.

**In the Abstract:**

Present subgroup results in the Abstract only if the subgroup analyses were based on a primary study outcome, if they were prespecified, and if they were interpreted in light of the totality of prespecified subgroup analyses undertaken.

**In the Methods section:**

Indicate the number of prespecified subgroup analyses that were performed and the number of prespecified subgroup analyses that are reported.

Distinguish a specific subgroup analysis of special interest, such as that in the article by Sacks et al.,<sup>8</sup> from the multiple subgroup analyses typically done to assess the consistency of a treatment effect among various patient characteristics, such as those in the article by Jackson et al.<sup>9</sup> For each reported analysis, indicate the end point that was assessed and the statistical method that was used to assess the heterogeneity of treatment differences:

Indicate the number of post hoc subgroup analyses that were performed and the number of post hoc subgroup analyses that are reported. For each reported analysis, indicate the end point that was assessed and the statistical method used to assess the heterogeneity of treatment differences. Detailed descriptions may require a supplementary appendix.

Indicate the potential effect on type I errors (false positives) due to multiple subgroup analyses and how this effect is addressed. If formal adjustments for multiplicity were used, describe them; if no formal adjustment was made, indicate the magnitude of the problem informally, as done by Jackson et al.<sup>9</sup>

**In the Results section:**

When possible, base analyses of the heterogeneity of treatment effects on tests for interaction, and present them along with effect estimates (including confidence intervals) within each level of each baseline covariate analyzed. A forest plot<sup>21,22</sup> is an effective method for presenting this information.

**In the Discussion section:**

Avoid overinterpretation of subgroup differences. Be properly cautious in appraising their credibility, acknowledge the limitations, and provide supporting or contradictory data from other studies, if any.

When properly planned, reported, and interpreted, subgroup analyses can provide valuable information. With the availability of Web supplements, the opportunity exists to present more detailed information about the results of a trial. The purpose of the guidelines (see box) is to encourage more clear and complete reporting of subgroup analyses. In some settings, a trial is conducted with a subgroup analysis as one of the primary objectives. These guidelines are directly applicable to the reporting of subgroup analyses in the primary publication of a clinical trial when the subgroup analyses are not among the primary objectives. In other settings, including observational studies, we encourage complete and thorough reporting of the subgroup analyses in the spirit of the guidelines listed.

The editors and statistical consultants of the *Journal* consider these guidelines to be important in the reporting of subgroup analyses. The goal is to provide transparency in the statistical meth-

SPECIAL REPORT

ods used in order to increase the clarity and completeness of the information reported. As always, these are guidelines and not rules; additions and exemptions can be made as long as there is a clear case for such action.

No potential conflict of interest relevant to this article was reported.

We thank Doug Altman, John Bailar, Colin Begg, Mohan Beltangady, Marc Buyse, David DeMets, Stephen Evans, Thomas Fleming, David Harrington, Joe Heyse, David Hoaglin, Michael Hughes, John Ioannidis, Curtis Meinert, James Neaton, Robert O'Neill, Ross Prentice, Stuart Pocock, Robert Temple, Janet Wittes, and Marvin Zelen for their helpful comments.

1. Yusuf S, Wittes J, Probstfield J, Tyroler HA. Analysis and interpretation of treatment effects in subgroups of patients in randomized clinical trials. *JAMA* 1991;266:93-8.
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# The NEW ENGLAND JOURNAL of MEDICINE

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### **Section 4. Information about financial relationships involving your spouse or partner or your children (under 18 years of age).**

Do your children or your spouse or partner have financial relationships with entities that have an interest in the content of the submitted work?

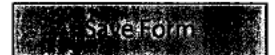
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FW New England Journal of Medicine 09-11781

From: Wally Carlo, M.D. [WCarlo@peds.uab.edu]  
Sent: Tuesday, January 26, 2010 1:47 PM  
To: Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil; Das, Abhik; Gantz, Marie  
Subject: FW: New England Journal of Medicine 09-11781

Attachments: Attached file: Subgroups.pdf; Attached file: NEJM-CTA-form.pdf; Attached file: NEJM-instructions-for-ICMJE-form.pdf; Attached file: ICMJE-Disclosure-form.pdf

Wally Carlo, M.D.  
Edwin M. Dixon Professor of Pediatrics  
University of Alabama at Birmingham  
Director, Division of Neonatology  
Director, Newborn Nurseries  
619 South 20th Street  
525 New Hillman Building  
Birmingham, AL 35233-7335  
Phone: 205 934 4680  
FAX: 205 934 3100  
Cell: 205 266 (b)

-----Original Message-----

From: Wally Carlo, M.D.  
Sent: Tuesday, January 26, 2010 12:47 PM  
To: Marsha Sumner  
Cc: Wally Carlo, M.D.  
Subject: FW: New England Journal of Medicine 09-11781

Wally Carlo, M.D.  
Edwin M. Dixon Professor of Pediatrics  
University of Alabama at Birmingham  
Director, Division of Neonatology  
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619 South 20th Street  
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Cell: 205 266 (b)

-----Original Message-----

From: Wally Carlo, M.D.  
Sent: Tuesday, January 26, 2010 8:29 AM  
To: 'Higgins, Rosemary (NIH/NICHD) [E]'; 'Finer, Neil'; Das, Abhik; Gantz, Marie  
Subject: FW: New England Journal of Medicine 09-11781

Dear Rose, Neil, Abhik, Marie and Abhik:

This is outstanding. BOTH ACCEPTED!!! I think we should try to respond to each of the comment and compromise with their requests as much as possible as long as the revisions do not compromise the integrity of the message.

How do we proceed to include the rest of the authors in the review process?

wally

FW New England Journal of Medicine 09-11781

Wally Carlo, M.D.  
Edwin M. Dixon Professor of Pediatrics  
University of Alabama at Birmingham  
Director, Division of Neonatology  
Director, Newborn Nurseries  
619 South 20th Street  
525 New Hillman Building  
Birmingham, AL 35233-7335  
Phone: 205 934 4680  
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From: onbehalfof+editorial+nejm.org@manuscriptcentral.com  
[mailto:onbehalfof+editorial+nejm.org@manuscriptcentral.com] On Behalf of  
editorial@nejm.org  
Sent: Tuesday, January 26, 2010 8:07 AM  
To: Wally Carlo, M.D.  
Subject: New England Journal of Medicine 09-11781

Re: 09-11781 - The SUPPORT Trial: Randomized Trial of Oxygen Saturation Targets in Extremely Premature Infants

Dear Dr. Carlo:

Your manuscript, "The SUPPORT Trial: Randomized Trial of Oxygen Saturation Targets in Extremely Premature Infants," has been evaluated by outside reviewers and by the editors. Although it is not acceptable for publication in its present form, we would be pleased to consider a revised version that responds to the enclosed comments of the outside reviewers and to the editors' points noted below. Please understand that we cannot commit to publication until we have evaluated a revised version.

Please address in particular the concerns raised by the statistical reviewer regarding (b) (4)

Please note that we are also inviting a revised version of the companion manuscript. If/when both manuscripts are satisfactorily revised, we would anticipate publishing them back to back. The companion manuscript should be cited in your report, and overlap kept to a minimum.

When you send in your revised manuscript, please provide a point-by-point response to the editors' and reviewers' comments in a covering letter and return two copies of the revision, one in which the changes you have made are highlighted and the other a clean copy. Please include a word count for the text. Any changes in authorship must be made in writing, signed by all authors.

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FW New England Journal of Medicine 09-11781

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If you have not done so already, 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.

If you have any questions about compliance with these policies, please contact the editorial office for clarification.

Although we cannot commit to publication of your revised manuscript until we have had the opportunity to evaluate it, we look forward to receiving it and assure you of a prompt evaluation when it arrives.

Please submit your revised manuscript no later than February 16th, 2010.

Thank you for sending us your work.

Sincerely,

Caren G. Solomon, MD Michael F. Greene, MD Deputy Editor Associate Editor

FW New England Journal of Medicine 09-11781

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Reviewer: 1  
Comments for the Author

(b) (4)

(b) (4)

[Redacted]

Reviewer: 2  
Comments for the Author

(b) (4)

EW New England Journal of Medicine 09-11781

(b) (4)

[Redacted text block]

[Redacted text block]

2. Specific Comments:

(b) (4)

[Redacted text block]

[Redacted text block]

[Redacted text block]

[Redacted text block]

EW New England Journal of Medicine 09-11781

(b) (4) [Redacted text block]

Discussion:

First paragraph, page 22: It is noted that longer follow up is needed to determine

(b) (4) [Redacted text block]

Statistical Reviewer: 1

(b) (4) [Redacted text block]

ADDITIONAL COMMENTS OF THE EDITORS

Title should be shortened to no more than 75 characters.

Introduction: (b) (4) [Redacted text block]

FW New England Journal of Medicine 09-11781

(b) (4)

[Redacted text block]

[Redacted text block]

[Redacted text block]

[Redacted text block]

[Redacted text block] then  
need

[Redacted text block]

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Finer, Neil"; "Das, Abhik"  
**Cc:** "Gantz, Marie"; "wcarlo@peds.uab.edu"; "Rich, Wade"  
**Subject:** RE: New England Journal of Medicine 09-11783  
**Date:** Tuesday, January 26, 2010 2:00:00 PM

---

Hi

Wally got a letter and has tried to forward it twice but there seems to be an email problem.

The Steering Committee has their standing call this afternoon and I will update folks with the following information taken directly from Neil's letter:

We have heard back from NEJM . Although it is not acceptable for publication in its present form, we would be pleased to consider a revised version that responds to the enclosed comments.

Please note that we are also inviting a revised version of the companion manuscript. If/when both manuscripts are satisfactorily revised, we would anticipate publishing them back to back. The companion manuscript should be cited in your report, and overlap kept to a minimum.

This large RCT in such a difficult area is a fantastic achievement and you need to be congratulated.

I will inform folks that the Drs. Finer and Carlo along with the subcommittee will revise and send an updated version.

Thanks

Rose

-----Original Message-----

From: Finer, Neil [mailto:nfiner@ucsd.edu]

Sent: Tuesday, January 26, 2010 1:28 PM

To: Das, Abhik

Cc: Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; wcarlo@peds.uab.edu; Rich, Wade

Subject: Re: New England Journal of Medicine 09-11783

I agree

I think we could plea bargain and use 98 for the primary and the rest the conventional 95

I would like to prepare a response with you for this issue

Be well

Neil

Sent from my iPhone

On Jan 26, 2010, at 10:22 AM, "Das, Abhik" <adas@rti.org> wrote:

> Perhaps we should think about that a little more. While I don't  
> think this is an issue that we put up a fight with the NEJM on, the  
> ordinary reader may get confused by (b) (4) it will also make the  
> results non-comparable across other studies. I am not talking about  
> formal meta-analyses here, but just readers trying to synthesize  
> information across different papers. We do report that the study was  
> powered at 0.02 and we do present all p values so that readers can  
> easily apply that cut-off to ascribe statistical significance to the  
> reported results.

>

> Thanks

>

> Abhik

>

> -----Original Message-----



> From: Finer, Neil [mailto:nfiner@ucsd.edu]  
> Sent: Tuesday, January 26, 2010 11:48 AM  
> To: Gantz, Marie; Higgins, Rosemary (NIH/NICHD) [E]; wcarlo@peds.uab.edu  
> Cc: Rich, Wade; Das, Abhik  
> Subject: RE: New England Journal of Medicine 09-11783

>  
> Thanks Marie  
> You might as well do that now and we can redo the Tables  
> Neil

> -----Original Message-----

> From: Gantz, Marie [mailto:mgantz@rti.org]  
> Sent: Tuesday, January 26, 2010 8:20 AM  
> To: Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil;  
> wcarlo@peds.uab.edu  
> Cc: Rich, Wade; Das, Abhik  
> Subject: RE: New England Journal of Medicine 09-11783

>  
> Congratulations to all! Did we hear back about the other paper as  
> well?

> Neil, I think that it is reasonable to (b) (4) [REDACTED]  
[REDACTED] was our predefined level  
> of significance.

> 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, January 26, 2010 11:04 AM  
> To: 'nfiner@ucsd.edu'; 'wcarlo@peds.uab.edu'  
> Cc: 'wrich@ucsd.edu'; Gantz, Marie; Das, Abhik  
> Subject: Re: New England Journal of Medicine 09-11783

> I am at a meeting and will be back in the office this afternoon.

> I propose this plan -  
> Revision of both papers and Subcommittee approval. We can then  
> distribute to the wider group.

> I can let the steering committee know we have a favorable review and  
> that the subcommittee is working on the revision. I will let them  
> know that we will circulate the revised papers once ready for  
> resubmission.

> This is extremely impressive - they will published both together!!!!

> Thank you for all the hard work and continued effort!!!

> ----- Original Message -----

> From: Finer, Neil <nfiner@ucsd.edu>

> To: Higgins, Rosemary (NIH/NICHD) [E]; wcarlo@peds.uab.edu <wcarlo@peds.uab.edu  
>>  
> Cc: Rich, Wade <wrich@ucsd.edu>; 'mgantz@rti.org' <mgantz@rti.org>; 'adas@rti.org  
>' <adas@rti.org>  
> Sent: Tue Jan 26 10:47:25 2010  
> Subject: FW: New England Journal of Medicine 09-11783  
>  
> Good Morning  
> Here is the NEJM response. There are a number of statistical issues  
> that we will need to address - I will need Abhik and Marie to help -  
> (b) (4)  
> Please have a look and I will begin the basic process.  
> Rose I don't know if you want this more widely circulated - I think  
> we should deal with the queries and then perhaps send out a final  
> version  
> I will await your reply  
> Be well  
> Neil  
>  
> -----Original Message-----  
> From: onbehalfof+editorial+nejm.org@manuscriptcentral.com  
> [mailto:onbehalfof+editorial+nejm.org@manuscriptcentral.com] On  
> Behalf Of editorial@nejm.org  
> Sent: Tuesday, January 26, 2010 5:58 AM  
> To: Finer, Neil  
> Subject: New England Journal of Medicine 09-11783  
>  
> Dear Dr. Finer:  
>  
> Your manuscript, "Early CPAP versus Surfactant in Very Preterm  
> Infants: The SUPPORT Trial," has been evaluated by outside reviewers  
> and by the editors. Although it is not acceptable for publication  
> in its present form, we would be pleased to consider a revised  
> version that responds to the enclosed comments of the outside  
> reviewers and to the editors' points noted below. Please understand  
> that we cannot commit to publication until we have evaluated a  
> revised version.  
>  
> We ask that you attend in particular to the comments of the  
> statistical reviewer (b) (4)  
> [REDACTED]  
> [REDACTED]  
> [REDACTED]t.  
>  
> Please note that we are also inviting a revised version of the  
> companion manuscript. If/when both manuscripts are satisfactorily  
> revised, we would anticipate publishing them back to back. The  
> companion manuscript should be cited in your report, and overlap  
> kept to a minimum.  
>  
>  
> When you send in your revised manuscript, please provide a point-by-  
> point response to the editors' and reviewers' comments in a covering  
> letter and return two copies of the revision, one in which the  
> changes you have made are highlighted and the other a clean copy.  
> Please include a word count for the text. Any changes in authorship  
> must be made in writing, signed by all authors.

- >
- > To revise your manuscript, log into <http://mc.manuscriptcentral.com/nejm>
- > and enter For Authors, where you will find a button to "Submit a
- > Revision."
- >
- > Journal policy dictates that we must have on file a signed Copyright
- > Transfer Agreement from each author before a manuscript can be
- > accepted. Please ask all authors to sign and fax back the enclosed
- > form as soon as possible to (781) 207-6529. This will eliminate
- > unnecessary delays in the event that your manuscript is accepted.
- >
- > The Universal Disclosure form is also attached. Each author must
- > complete it. After you have filled in the appropriate information
- > in the spaces provided, you may either e-mail your completed form to [editorial@nejm.org](mailto:editorial@nejm.org)
- > or upload it to your Author Dashboard of ScholarOne Manuscripts. It
- > is essential that you return the forms as soon as possible, because
- > we cannot process your manuscript without them. Please be aware
- > that in the event of publication, each author's submitted disclosure
- > form will be posted on the web (with any dollar amounts redacted).
- >
- > We ask that you, as the corresponding author, prepare a financial
- > disclosure statement for publication with the manuscript. The
- > statement should describe the relationships of all authors with
- > companies that make products relevant to the manuscript. The
- > statement should specify the type of relationship (e.g., consulting,
- > paid speaking, grant support, equity, patents, royalties) each
- > author has with each company. The information should be consistent
- > with the authors' signed financial disclosure forms. The statement
- > should be inserted before the Acknowledgment section of the text and
- > labeled "Disclosure." If you have nothing relevant to disclose,
- > please indicate this.
- >
- > We also ask that you make clear in your cover letter who designed
- > the study, who gathered the data, who analyzed the data, who vouches
- > for the data and the analysis, who wrote the paper, and who decided
- > to publish the paper. If there was an industry sponsor, please
- > include in the Methods section of the manuscript a statement on the
- > role of the industry sponsor in each of these activities; an
- > investigator should be named who takes responsibility for the data
- > and analyses. Please state as well if there were any agreements
- > concerning confidentiality of the data between the sponsor and the
- > authors or the institutions named in the credit lines. (see the
- > editorial in the September 13, 2001, issue of the Journal).
- >
- > In addition, please indicate who wrote the first draft of your
- > manuscript. If it was not one of the authors, please name the person
- > or persons and indicate who paid them. If any writing assistance
- > other than copy editing was provided, please name the person or
- > persons and indicate who paid them.
- >
- > We expect your revised manuscript to include full, accurate, and up-
- > to-date reporting of adverse events. In general, this should be in
- > the form of a table containing descriptions of all serious adverse
- > events and all other common or important adverse events. The
- > abstract should contain a statement regarding adverse events.
- >
- > Please recall that the Journal requires that neither an article

- > under consideration nor any part of its essential substance, tables,
- > or figures has been or will be published or submitted elsewhere
- > before appearing in the Journal.
- >
- > If you have not done so already, 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.
- >
- > If you have any questions about compliance with these policies,
- > please contact the editorial office for clarification.
- >
- > Although we cannot commit to publication of your revised manuscript
- > until we have had the opportunity to evaluate it, we look forward to
- > receiving it and assure you of a prompt evaluation when it arrives.
- > Please submit your revised manuscript no later than February 16th,
- > 2010.

> Thank you for sending us your work.

> Sincerely,

> Caren G. Solomon, MD                      Michael F. Greene, MD  
> Deputy Editor                              Associate Editor

> New England Journal of Medicine  
> 10 Shattuck Street  
> Boston, MA 02115  
> (617) 734-9800  
> Fax: (617) 739-9864  
> <http://www.nejm.org>

> Reviewer: 1  
> <b>Comments for the Author</b>

(b) (4)  
[Redacted]

> Introduction:

> 1. Th (b) (4)  
[Redacted]

> Methods:

> 3. (b) (4)  
[Redacted]



> Comments

> 1. (b) (4)

[Redacted text block]

>

>

> Methods

> Comments

> 1. (b) (4)

[Redacted text block]

(b) (4)

> (b) (4) [Redacted text block]

> Results

> (b) (4) [Redacted text block]

> Discussion

> (b) (4) [Redacted text block]

> (b) (4)  
[Redacted text block]

>  
> Conclusion

> (b) (4)  
[Redacted text block]

>  
> References

> 1. (b) (4)  
[Redacted text block]

>  
> Statistical Reviewer: 1

> (b) (4)  
[Redacted text block]

>  
>  
> (b) (4)  
[Large redacted text block]



(b) (4) [Redacted]

>  
> Editorial Comments:

>  
> (b) (4) [Redacted]

>  
>  
> ADDITIONAL COMMENTS OF THE EDITORS

> Title: should be no more than 75 characters.

> Abstract:

> (b) (4) [Redacted]

>  
> Introduction:

> (b) (4) [Redacted]

> Methods:

> (b) (4) [Redacted]

> Results:

> (b) (4) [Redacted]

>

(b) (4)  
[Redacted text block]

>  
> Discussion:

> (b) (4)  
[Redacted text block]

>  
>  
>  
>  
>

## Higgins, Rosemary (NIH/NICHD) [E]

---

**From:** Finer, Neil <nfiner@ucsd.edu>  
**Sent:** Tuesday, January 26, 2010 10:47 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; wcarlo@peds.uab.edu  
**Cc:** Rich, Wade; 'mgantz@rti.org'; 'adas@rti.org'  
**Subject:** FW: New England Journal of Medicine 09-11783  
**Attachments:** Attached standard file: \* Subgroups.pdf; Attached standard file: \* NEJM-CTA-2009.pdf; Attached standard file: \* NEJM-inst-for-ICMJE-form.pdf; Attached standard file: \* ICMJE-Disclosure-Form-102309.pdf

Good Morning

Here is the NEJM response. There are a number of statistical issues that we will need to address - I will need Abhik and Marie to help - ie (b) (4) do we do this? (b) (4) Please have a look and I will begin the basic process. Rose I don't know if you want this more widely circulated - I think we should deal with the queries and then perhaps send out a final version I will await your reply Be well Neil

-----Original Message-----

**From:** onbehalfof+editorial+nejm.org@manuscriptcentral.com  
[mailto:onbehalfof+editorial+nejm.org@manuscriptcentral.com] On Behalf Of editorial@nejm.org  
**Sent:** Tuesday, January 26, 2010 5:58 AM  
**To:** Finer, Neil  
**Subject:** New England Journal of Medicine 09-11783

Dear Dr. Finer:

Your manuscript, "Early CPAP versus Surfactant in Very Preterm Infants: The SUPPORT Trial," has been evaluated by outside reviewers and by the editors. Although it is not acceptable for publication in its present form, we would be pleased to consider a revised version that responds to the enclosed comments of the outside reviewers and to the editors' points noted below. Please understand that we cannot commit to publication until we have evaluated a revised version.

We ask that you attend in particular to the comments of the statistical reviewer regarding (b) (4)

Please note that we are also inviting a revised version of the companion manuscript. If/when both manuscripts are satisfactorily revised, we would anticipate publishing them back to back. The companion manuscript should be cited in your report, and overlap kept to a minimum.

When you send in your revised manuscript, please provide a point-by-point response to the editors' and reviewers' comments in a covering letter and return two copies of the revision, one in which the changes you have made are highlighted and the other a clean copy. Please include a word count for the text. Any changes in authorship must be made in writing, signed by all authors.

To revise your manuscript, log into <http://mc.manuscriptcentral.com/nejm> and enter For Authors, where you will find a button to "Submit a Revision."

Journal policy dictates that we must have on file a signed Copyright Transfer Agreement from each author before a manuscript can be accepted. Please ask all authors to sign and fax back the enclosed form as soon as possible to (781) 207-6529. This will eliminate unnecessary delays in the event that your manuscript is accepted.

The Universal Disclosure form is also attached. Each author must complete it. After you have filled in the appropriate information in the spaces provided, you may either e-mail your completed form to editorial@nejm.org or upload it to your Author Dashboard of ScholarOne Manuscripts. It is essential that you return the forms as soon as possible, because we cannot process your manuscript without them. Please be aware that in the event of publication, each author's submitted disclosure form will be posted on the web (with any dollar amounts redacted).

We ask that you, as the corresponding author, prepare a financial disclosure statement for publication with the manuscript. The statement should describe the relationships of all authors with companies that make products relevant to the manuscript. The statement should specify the type of relationship (e.g., consulting, paid speaking, grant support, equity, patents, royalties) each author has with each company. The information should be consistent with the authors' signed financial disclosure forms. The statement should be inserted before the Acknowledgment section of the text and labeled "Disclosure." If you have nothing relevant to disclose, please indicate this.

We also ask that you make clear in your cover letter who designed the study, who gathered the data, who analyzed the data, who vouches for the data and the analysis, who wrote the paper, and who decided to publish the paper. If there was an industry sponsor, please include in the Methods section of the manuscript a statement on the role of the industry sponsor in each of these activities; an investigator should be named who takes responsibility for the data and analyses. Please state as well if there were any agreements concerning confidentiality of the data between the sponsor and the authors or the institutions named in the credit lines. (see the editorial in the September 13, 2001, issue of the Journal).

In addition, please indicate who wrote the first draft of your manuscript. If it was not one of the authors, please name the person or persons and indicate who paid them. If any writing assistance other than copy editing was provided, please name the person or persons and indicate who paid them.

We expect your revised manuscript to include full, accurate, and up-to-date reporting of adverse events. In general, this should be in the form of a table containing descriptions of all serious adverse events and all other common or important adverse events. The abstract should contain a statement regarding adverse events.

Please recall that the Journal requires that neither an article under consideration nor any part of its essential substance, tables, or figures has been or will be published or submitted elsewhere before appearing in the Journal.

If you have not done so already, 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.

If you have any questions about compliance with these policies, please contact the editorial office for clarification.

Although we cannot commit to publication of your revised manuscript until we have had the opportunity to evaluate it, we look forward to receiving it and assure you of a prompt evaluation when it arrives. Please submit your revised manuscript no later than February 16th, 2010.

Thank you for sending us your work.

Sincerely,

Caren G. Solomon, MD  
Deputy Editor

Michael F. Greene, MD  
Associate Editor

New England Journal of Medicine  
10 Shattuck Street  
Boston, MA 02115  
(617) 734-9800  
Fax: (617) 739-9864  
<http://www.nejm.org>

Reviewer: 1

<b>Comments for the Author</b>

(b) (4)  
[Redacted text block]

Introduction:

1. (b) (4)  
[Redacted text block]

Methods:

3. (b) (4)  
[Redacted text block]

Results:

9. (b) (4)  
[Redacted text block]

Reviewer: 2

<b>Comments for the Author</b>

(b) (4) [Redacted]

Abstract  
Comments

1. (b) (4) [Redacted]

Introduction  
Comments

1. (b) (4) [Redacted]

Methods  
Comments

1. (b) (4) [Redacted]

11. (b) (4) [Redacted text block]

Results

(b) (4) [Redacted text block]

Discussion

Comments

1. (b) (4) [Redacted text block]

Conclusion

Comments

1. (b) (4) [Redacted text block]

References

1. (b) (4) [Redacted text block]

Statistical Reviewer: 1

Comments for the Author:

(b) (4)  
[Redacted]

[Redacted]

[Redacted]

[Redacted]

Editorial Comments:

(b) (4)  
[Redacted]

ADDITIONAL COMMENTS OF THE EDITORS

Title: should be no more than 75 characters.

Abstract:

(b) (4)  
[Redacted]

Introduction:

(b) (4)  
[Redacted]



(b) (4) [Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

Discussion:

(b) (4) [Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "wrich@ucsd.edu"; "auten002@mc.duke.edu"; "mgantz@rti.org"; "Ellen.Hale@oz.ped.emory.edu"; "ahensman@wihri.org"; "nxs5@case.edu"  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** Re: PEDIATRICS: Decision Letter for MS ID 2009-3353  
**Date:** Tuesday, January 26, 2010 8:55:57 AM

---

This is nice!!  
We may know more on the main trial papers soon.  
Thanks for all the effort!  
Rose

----- Original Message -----

From: Rich, Wade <wrich@ucsd.edu>  
To: Higgins, Rosemary (NIH/NICHD) [E]; Kathy J Auten <auten002@mc.duke.edu>; 'mgantz@rti.org' <mgantz@rti.org>; Ellen Hale <Ellen.Hale@oz.ped.emory.edu>; Hensman, Angelita <AHensman@WIHRI.org>; nancy newman <nxs5@case.edu>  
Sent: Mon Jan 25 15:24:57 2010  
Subject: FW: PEDIATRICS: Decision Letter for MS ID 2009-3353

We got our decision letter on the Antenatal paper. I will be working on the revisions and will forward to the group for review.

Wade

-----Original Message-----

From: onbehalfof+PediatricsEditorial+aap.org@manuscriptcentral.com  
[mailto:onbehalfof+PediatricsEditorial+aap.org@manuscriptcentral.com] On Behalf Of  
PediatricsEditorial@aap.org  
Sent: Monday, January 25, 2010 11:50 AM  
To: Rich, Wade  
Subject: PEDIATRICS: Decision Letter for MS ID 2009-3353

25-Jan-2010

Manuscript #: 2009-3353

Title: Antenatal Consent in a Large Multicenter Trial - At What Cost?

Dear Mr. Rich:

The editors of Pediatrics are pleased to report that your manuscript is being considered for publication. However, we will require additional revisions before a final decision is made. You will have 6 months to submit a revised paper.

Please respond in detail to the reviewers' comments included at the bottom of this e-mail. In addition, please address or include these items from the editors:

--Please list any abbreviations used on the title page.

When submitting your revised manuscript, you will be able to respond to the comments made by the reviewers and the editors in the space provided under "Author's Response." You can use this space to document any additional changes you make to the original manuscript. In addressing any substantive suggestions or criticisms made by our reviewers, please make a numerical listing of what you have done, or not done, in regard to each suggestion of the reviewers. If the reviewer's request is for clarification, please make the clarification in the text of the paper. Remember that explaining what you mean to the editors and reviewers does not help the reader.

Your revision should be submitted via <http://mc.manuscriptcentral.com/pediatrics>. In your "Author Center," click on "Manuscripts with Decisions." In the "Actions" box, click on "Create a Revision." Please upload the revised version of your manuscript and delete the older version from the system before completing the submission. The revised manuscript should have no editing tags; it should be an unmarked version without margin notes or boldface notes. Once submitted, your revised manuscript's number will be appended to denote a particular revision (R1, R2, etc).

Your 6-month period for submitting a revised paper begins today. You can monitor the time remaining through your Author Center. If you are unable to resubmit in the time allotted, please contact my office.

For additional requirements, see the attached document.

We look forward to receiving your revised manuscript.

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  
Email: PediatricsEditorial@aap.org

Reviewer: 1

(b) (4)  
[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

(b) (4) [Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

Reviewer: 2

(b) (4) [Redacted]

[Redacted]

[Redacted]

[Redacted]

Methods:

(b) (4)

Results:

1. (b) (4)

Discussion:

1. (b) (4)

Reviewer: 3

(b) (4)

(b) (4)

Major points:

(b) (4)

(b) (4)  
[Redacted text block]

[Redacted text block]

Minor points:

- 1) (b) (4)  
[Redacted list item]
- [Redacted text block]
- [Redacted text block]
- [Redacted text block]

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "diane-eastman@uiowa.edu"  
**Cc:** "edward-bell@uiowa.edu"; "karen-johnson@uiowa.edu"  
**Subject:** Re: Support trial f/u & bad Iowa weather  
**Date:** Monday, January 25, 2010 11:38:05 AM

---

Thanks for the update - good luck with the weather! Thanks for going the extra mile!!  
Rose

---

**From:** Eastman, Diane <diane-eastman@uiowa.edu>  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Bell, Edward <edward-bell@uiowa.edu>; Johnson, Karen <karen-johnson@uiowa.edu>  
**Sent:** Mon Jan 25 11:33:39 2010  
**Subject:** Support trial f/u & bad Iowa weather

Rose,

Our twins from the support trial that you emailed about last week were not able to come today again. We are having snow and 30-40 mph winds in their area. Mom started out to come this AM, but had to go back home due to icy roads and poor visibility. We have reservations for next week. If they can't get here next week, Mike says we'll pack up and go to them. Just wanted to let you know that their data will not be coming this week. Diane

*Diane Eastman, ARNP*

*High Risk Infant Followup Program*

*Children's Hospital of Iowa*

*319-353-6880*

## Higgins, Rosemary (NIH/NICHD) [E]

---

**From:** Finer, Neil <nfiner@ucsd.edu>  
**Sent:** Thursday, January 21, 2010 12:25 PM  
**To:** Juliann DiFiore; Walsh, Michele; Rich, Wade  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]; Julie DiFiore; Martin, Richard  
**Subject:** RE: SUPPORT Updates

Hi Julie

Can you send me whatever you have. We need to decide how to look at the larger data set for intermittent events – with a 10 sampling

Do you think this will prove useful I am concerned that we will not be able to reconstruct most events at this resolution

Your thoughts

Neil

---

**From:** Juliann DiFiore [mailto:juliann.difiore@case.edu]  
**Sent:** Tuesday, January 19, 2010 10:17 AM  
**To:** Walsh, Michele  
**Cc:** Finer, Neil; rose higgins; Julie DiFiore; Martin, Richard  
**Subject:** Re: SUPPORT Updates

I sent out the latest draft of the proposal on Friday. I am hoping we can have it finalized by later this week.

Regards,

Julie

On 1/19/2010 12:19 PM, Walsh, Michele wrote:  
Hi Julie and Richard:  
On the conference call today, there was a request for  
The formal proposal to analyze the entire trial saturation profiles.  
I know that your protocol was near final. Could you update the group  
On the status? Thanks

Michele Walsh  
beeper (b) (6)  
Ph 216 844 3759

---

**From:** Finer, Neil [mailto:nfiner@ucsd.edu]  
**Sent:** Monday, January 18, 2010 7:07 PM  
**To:** Finer, Neil; 'Higgins, Rosemary (NIH/NICHD) [E]'; 'Wally Carlo, M.D.'; 'Michele Walsh'; 'Bradley Yoder'; 'Roger Faix'; 'Abbot Laptook'; 'kurt.schibler@cchmc.org'; 'Das, Abhik'; 'Nancy Newman'; 'Gantz, Marie'; 'Poole, W. Kenneth'  
**Cc:** 'Petrie, Carolyn'; 'Zaterka-Baxter, Kristin'; Rich, Wade  
**Subject:** RE: SUPPORT Updates

Hi Everyone

We will have a brief meeting tomorrow morning at 11:30 ETime

We have no news from the NEJM about the manuscripts

Agenda

Review current follow-up progress



Review the ROP adjudication data  
Review the FiO2 and SpO2 analyses  
Discuss Secondaries – MRI, Growth and Pulmonary  
Discuss other papers from secondary hypotheses  
New Items

Talk to you in the morning

Neil

Visit us at [www.UHhospitals.org](http://www.UHhospitals.org).

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**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "mgfuller@ucsd.edu"; "nfiner@ucsd.edu"; "yvaucher@ucsd.edu"; "wrich@ucsd.edu"  
**Cc:** "mgantz@rti.org"  
**Subject:** Re: SUPPORT FU  
**Date:** Wednesday, January 20, 2010 6:28:43 PM

---

Great!  
Thanks  
Rose

---

**From:** Fuller, Martha <mgfuller@ucsd.edu>  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil <nfiner@ucsd.edu>; Vaucher, Yvonne <yvaucher@ucsd.edu>; Rich, Wade <wrich@ucsd.edu>  
**Cc:** 'Gantz, Marie' <mgantz@rti.org>  
**Sent:** Wed Jan 20 18:22:34 2010  
**Subject:** RE: SUPPORT FU

(b) seen on 1/15/2010 (outside window by few weeks). Data entry pending update of system to allow new SFO9A to be entered (BSID III with motor components).

Will pull other folders to check on status.

Martha

Martha G. Fuller, RN, MSN  
Pediatric Nurse Practitioner  
UCSD Infant Special Care Follow-up Program  
(619) 543-3771 (office)  
(619) 543-3822 (direct line/voice mail)

Confidentiality Notice: The information transmitted is intended only for the person or entity to which it is addressed and may contain confidential and/or privileged material. Any review, retransmission, dissemination or other use of, or taking any action in reliance upon this information by persons or entities other than the intended recipient is prohibited. If you have received this in error, please contact the sender and delete the material from any computer.

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Wednesday, January 20, 2010 12:30 PM  
**To:** Finer, Neil; Vaucher, Yvonne; Fuller, Martha; Rich, Wade  
**Cc:** 'Gantz, Marie'  
**Subject:** SUPPORT FU  
**Importance:** High

CENTER	NETWORK	FU_message
22	(b)	Infant is lost to FU per NF10/SF10 but NF12/SF12 has not been completed.
22	(b)	Infant is lost to FU per NF10/SF10 but NF12/SF12 has not been completed.
22	(b)	Infant is lost to FU per NF10/SF10 but NF12/SF12 has not been completed.
22	(b)	Infant is lost to FU per NF10/SF10 but NF12/SF12 has not been completed.
22	(b)	FU window has closed but NF05 and NF09a have not been completed.

Hi,

We are missing a few outcomes for the SUPPORT FU. Let us know how you are doing.

Thanks for all the effort!!  
Rose

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network  
Pregnancy and Perinatology Branch  
Center for Developmental Biology and Perinatal Medicine  
Eunice Kennedy Shriver National Institute of Child Health and Human Development  
National Institutes of Health  
6100 Executive Blvd., Room 4B03  
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Bethesda, MD 20892  
For overnight delivery use Rockville, MD 20852  
301-496-5575  
301-496-3790 (FAX)  
higginsr@mail.nih.gov

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Eastman, Diane"; "Acarregui, Michael"; "Bell, Edward"; "Johnson, Karen"  
**Cc:** "Gantz, Marie"  
**Subject:** RE: SUPPORT FU  
**Date:** Wednesday, January 20, 2010 4:58:00 PM

---

Your weather currently isn't too good (ICE STORMS in Iowa made the National news). We will hope for better weather.

Thanks for all the effort!  
Rose

---

**From:** Eastman, Diane [mailto:diane-eastman@uiowa.edu]  
**Sent:** Wednesday, January 20, 2010 4:47 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Acarregui, Michael; Bell, Edward; Johnson, Karen  
**Cc:** Gantz, Marie  
**Subject:** RE: SUPPORT FU

Rose,

This is a set of twins that have been scheduled several times and appts were cancelled d/t illness and bad weather. They are re-scheduled for next week. Hopefully they will be healthy and we will not have weather like today to keep them from having to r/s again. If all goes well, we'll have them done soon.  
Diane

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Wed 1/20/2010 2:31 PM  
**To:** Acarregui, Michael; Bell, Edward; Johnson, Karen; Eastman, Diane  
**Cc:** 'Gantz, Marie'  
**Subject:** SUPPORT FU

Hi,

We are missing a few outcomes for the SUPPORT FU. Let us know how you are doing.

CENTER	NETWORK	FU_message
24	(b)	FU window has closed but NF05 and NF09a have not been completed.
24	(b)	FU window has closed but NF05 and NF09a have not been completed.

Thanks for all the effort!!  
Rose

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

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Bethany Ball"  
**Cc:** "Susan Hintz"; "Krisa Van Meurs"; "Gantz, Marie"  
**Subject:** RE: SUPPORT FU  
**Date:** Wednesday, January 20, 2010 4:37:00 PM

---

Great!  
Thanks  
Rose

---

**From:** Bethany Ball [mailto:mbball@stanford.edu]  
**Sent:** Wednesday, January 20, 2010 4:37 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** 'Susan Hintz'; Krisa Van Meurs; 'Gantz, Marie'  
**Subject:** Re: SUPPORT FU

This child has been seen. I need to review the data but they will be keyed before the end of the month.  
MBB

On Jan 20, 2010, at 12:24 PM, Higgins, Rosemary (NIH/NICHD) [E] wrote:

Hi,  
We are missing a few outcomes for the SUPPORT FU. Let us know how you are doing.  
CENTER NETWORK FU\_message  
15 (b) FU window has closed but NF05 and NF09a have not been completed.

Thanks for all the effort!!  
Rose

Rosemary D. Higgins, MD  
Program Scientist for the 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:** "Irene, Amanda"  
**Subject:** SUPPORT19Jan2010 2  
**Date:** Wednesday, January 20, 2010 4:35:00 PM  
**Attachments:** SUPPORT19Jan2010 2.doc

---

MINOR

## SUPPORT Subcommittee Call January 19, 2010

**Participants:** Neil Finer, Rose Higgins, Kris Zaterka-Baxter, Abbott Laptok, Marie Gantz, Nancy Newman, Abhik Das, Roger Faix, Kurt Schibler, Michelle Walsh, Brad Yoder, Meg Cunningham, Stephanie Archer, Amanda Irene

- Dr. Finer has not heard back from the NEJM after submitting the SUPPORT papers.
- The follow up status report has a total of 688 infants; which is about 83% (THIS PERCENT IS NOT CORRECT) of the total sample size.
  - There are about 37 that are lost to follow up.
  - There are 240 windows not open yet.
  - About 5 infants have complete follow up information and could not be assigned a NDI score.
  - Dr. Gantz will look into if an infant can be assigned NDI if they are lost to follow up.
  - A list of how many infants are lost to follow up is sent to Dr. Higgins on a monthly basis.
  - The last follow up window closes April 2011.
- Ophthalmologists were asked to adjudicate ROP outcome for 97 infant who survived to discharge but were missing final ROP data.
- Effect of ROP adjudication for Low vs. High SpO2 was not significant when compared to analysis of cases with final ROP outcome. These data are consistent with the manuscript. Adjudication was felt to be a necessary step to be able to clearly answer potential questions regarding ROP outcome.
- Analysis of FiO2, SPO2
  - The goal of the analysis was to achieve separation by distinguishing the two groups by exposure to oxygen.
  - It was important to make sure the goal was achieved in the design of the oximeter.
  - The end result from a statistical standpoint did show significantly different FiO2 between the groups.
  - Some of the information on SPO2 will be used to look at if there is a relationship between low SPO2 and outcome.
  - Exposure to low oxygen differed as potential mechanism; important secondary to look at SPO2 short and longer term outcome
- SPO2 analysis comments/thoughts:
  - Dr. Yoder questioned how to take into account the oximeters measuring abilities when saturation drops below 80%; being that most machines aren't designed to look at that range.
    - Dr. Finer responded that there is uncertainty with how to deal with the calibration curves and whether or not they are real, but the oximeter direction change is not wrong.
  - Dr Higgins raised the question about if the amount of cumulative hours of exposure to low saturation is clinically significant even though it is statistically significant.
- MRI secondary
  - The head ultrasound portion is complete and the MRIs are being read at the moment.
  - The head ultrasound analysis is in process.
  - The head ultrasound portion will hopefully be submitted for a late breaker for PAS.

- Addition Business
  - There is no new information on the growth secondary; a statistician has just been assigned.
  - The breathing outcomes portion of SUPPORT is a longer term outcome and kids still being seen and interviewed.
- Dr. Finer opened the floor up to anyone who is interested in secondary studies. A tracker will be created to track all SUPPORT secondary studies.
  - A paper looking at the actual distribution of real saturations was proposed.
    - This would be a descriptive paper about what was achieved at the bedside.
  - A question was raised about the possibility of looking at how long the periods of low saturation were?
    - This could address the question as to whether protracted low saturation is any worse than intermittent periods of low saturation.
  - Dr. Richard Martin is interested in looking at fluctuations.
    - There are 2 centers that are recording data that frequently.
  - This will have a very large data set and it is important to figure out if the programmer can look at valleys within the data.
  - Drs. Gantz and Das will speak to the programmers to see if they are comfortable developing software to identify intermittent events.
  - Drs. Kennedy and Phelps mentioned an update on the natural history or ROP; but it is unsure a proposal was written.
    - Dr. Finer commented that he would be interested to see how this related to the data from the small strata.
  - Dr. Laptok spoke about comparing oxygen challenge vs. oxygen use at 36 weeks, looking specifically at pulmonary outcomes at the time of discharge and pulmonary outcomes at follow up.
  - Dr. Bell had requested forms for a potential study on rate of growth and evolution of ROP.
  - The MRI data will be data at discharge; relevant outcome may be second paper.
    - An important question to look at would be diagnosis MRI vs. head ultrasound.
  - The issue of the BPD oximeter usage was brought discussed.
    - Some infants were evaluated on nonstudy oximeters while others were evaluated on the study oximeter.

Formatted: Bullets and Numbering



**From:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**To:** ["Kennedy, Kathleen A"](#); ["Phelps, Dale"](#)  
**Subject:** SUPPORT ROP Natural history  
**Date:** Wednesday, January 20, 2010 4:34:00 PM

---

Hi

The SUPPORT Subcommittee met yesterday and potential secondary analyses were discussed. I seem to recall the two of you discussing a natural history ROP cohort at a previous meeting – is this of interest to you? If so, we will need a proposal for secondary analysis. If not, let me know. I would be happy to be involved in this.

Thanks

Rose

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network  
Pregnancy and Perinatology Branch  
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[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Kimberley A Fisher"  
**Subject:** RE: SUPPORT FU  
**Date:** Wednesday, January 20, 2010 4:15:00 PM

---

NO problem. We occasionally have data that was transmitted that doesn't make it to RTI.

Thanks  
Rose

---

**From:** Kimberley A Fisher [mailto:kimberley.fisher@duke.edu]  
**Sent:** Wednesday, January 20, 2010 4:15 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** Re: SUPPORT FU

No I just now did it-sorry for the lack of clarity on my part.

Thanks  
Kim  
Kim Fisher, Ph.D.  
Neonatology  
681-4913

---

**From:** "Higgins, Rosemary (NIH/NICHD) [E]" [higginsr@mail.nih.gov]  
**Sent:** 01/20/2010 04:09 PM EST  
**To:** Kimberley Fisher  
**Cc:** Michael Cotten; Gloria Siaw; Ronald Goldberg; Ricki Goldstein; Kim Lutz; "Gantz, Marie" <mgantz@rti.org>  
**Subject:** RE: SUPPORT FU

Was this done prior to the DMS data transmission last week??

---

**From:** Kimberley A Fisher [mailto:kimberley.fisher@duke.edu]  
**Sent:** Wednesday, January 20, 2010 4:05 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** 'Michael Cotten'; gloria.siaw@duke.edu; Ronald GOLdberg; golds005@mc.duke.edu; 'kim.lutz@duke.edu'; 'Gantz, Marie'  
**Subject:** Re: SUPPORT FU

Rose  
NF12 has been completed for this subject and the information has been entered into the DMS and transmitted to RTI.

Thanks  
Kim

Kim Fisher, Ph.D., FNP-BC, IBCLC  
Clinical Research Operations Director  
Dept of Pediatrics/Neonatology  
Clinical Associate Professor/SON  
DUMC 3179  
Durham, NC 27710  
Work: 919-681-4913  
Fax: 919-681-4868  
Pager: 919-970(b)  
Email: kimberley.fisher@duke.edu

"Higgins, Rosemary (NIH/NICHD) [E]"  
<higginsr@mail.nih.gov>

01/20/2010 03:28 PM

To Ronald Goldberg <goldb008@mc.duke.edu>, "golds005@mc.duke.edu" <golds005@mc.duke.edu>, "Kimberley A Fisher" <kimberley.fisher@duke.edu>, "gloria.siw@duke.edu" <gloria.siw@duke.edu>, "kim.lutz@duke.edu" <kim.lutz@duke.edu>, "Michael Cotten" <cotte010@mc.duke.edu>  
cc "Gantz, Marie" <mgantz@rti.org>  
Subject SUPPORT FU

Hi,  
We are missing a few outcomes for the SUPPORT FU. Let us know how you are doing.

CENTER NETWORK FU\_message

19 (b) Infant is lost to FU per NF10/SF10 but NF12/SF12 has not been completed.

Thanks for all the effort!!  
Rose

Rosemary D. Higgins, MD  
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higginsr@mail.nih.gov

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Joanne Williams"  
**Cc:** "richard.ehrenkranz@yale.edu"; "monica.konstantino@yale.edu"; "elaine.romano@yale.edu"; "Gantz, Marie"  
**Subject:** RE: SUPPORT FU  
**Date:** Wednesday, January 20, 2010 3:50:00 PM

---

Thanks for the quick response

Rose

---

**From:** Joanne Williams [mailto:joanne.williams@yale.edu]  
**Sent:** Wednesday, January 20, 2010 3:49 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** richard.ehrenkranz@yale.edu; 'monica.konstantino@yale.edu'; 'elaine.romano@yale.edu'; 'Gantz, Marie'  
**Subject:** Re: SUPPORT FU

Hi Rose,  
Thank you for the reminder. We will fill in the Bayley scores as soon as possible.  
Joanne

Higgins, Rosemary (NIH/NICHD) [E] wrote:

Hi,

We are missing a few outcomes for the SUPPORT FU. Let us know how you are doing.

CENTER	NETWORK	FU_message
13	(b)	FU marked as complete (per NF10/SF10) but NF09a has not been completed.
13	(b)	FU marked as complete (per NF10/SF10) but NF09a has not been completed.
13	(b)	FU marked as complete (per NF10/SF10) but NF09a has not been completed.

Thanks for all the effort!!

Rose

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--  
Joanne Williams  
Research Nurse  
Yale University Child Study Center  
230 South Frontage Road  
P.O. Box 207900  
New Haven, CT 06520-7900  
203.785-2710  
mailto:joanne.williams@yale.edu

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**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Furey, Anne M"; "McGowan, Elisabeth C"; "Frantz, Ivan"; "Mackinnon, Brenda"  
**Cc:** "Gantz, Marie"  
**Subject:** RE: SUPPORT FU  
**Date:** Wednesday, January 20, 2010 3:49:00 PM

---

OK  
Thanks

Rose

---

**From:** Furey, Anne M [mailto:afurey@tuftsmedicalcenter.org]  
**Sent:** Wednesday, January 20, 2010 3:48 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; McGowan, Elisabeth C; Frantz, Ivan; Mackinnon, Brenda  
**Cc:** Gantz, Marie  
**Subject:** RE: SUPPORT FU

The family of this baby is (b) (6)  
(b) (6) will fill out the NF12 indicating that there is not any information on this child from indirect sources and the date of our last contact.

Anne

Anne Furey, MPH  
Floating Hospital for Children at Tufts Medical Center  
800 Washington Street, Box 44  
Boston, MA 02111  
Phone: 617-636-7134  
Fax: 617-636-1456  
[afurey@tuftsmedicalcenter.org](mailto:afurey@tuftsmedicalcenter.org)

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "emcgowan@tuftsmedicalcenter.org"; "Frantz, Ivan"; "Mackinnon, Brenda"; "Furey, Anne M"  
**Cc:** "Gantz, Marie"  
**Subject:** SUPPORT FU  
**Date:** Wednesday, January 20, 2010 3:30:00 PM  
**Importance:** High

---

Hi,

We are missing a few outcomes for the SUPPORT FU. Let us know how you are doing.

CENTER NETWORK FU\_message

23

(b)

Infant is lost to FU per NF10/SF10 but NF12/SF12 has not been completed.

Thanks for all the effort!!

Rose

Rosemary D. Higgins, MD  
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higginsr@mail.nih.gov

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Finer, Neil"; "Yvonne Vaucher"; "mgfuller@ucsd.edu"; "Rich, Wade"  
**Cc:** "Gantz, Marie"  
**Subject:** SUPPORT FU  
**Date:** Wednesday, January 20, 2010 3:29:00 PM  
**Importance:** High

---

CENTER	NETWORK	FU_message
22	(b)	Infant is lost to FU per NF10/SF10 but NF12/SF12 has not been completed.
22	(6)	Infant is lost to FU per NF10/SF10 but NF12/SF12 has not been completed.
22		Infant is lost to FU per NF10/SF10 but NF12/SF12 has not been completed.
22		Infant is lost to FU per NF10/SF10 but NF12/SF12 has not been completed.
22		FU window has closed but NF05 and NF09a have not been completed.

Hi,

We are missing a few outcomes for the SUPPORT FU. Let us know how you are doing.

Thanks for all the effort!!  
Rose

Rosemary D. Higgins, MD  
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higginsr@mail.nih.gov



**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Evans, Patricia W"; "jon.e.tyson@uth.tmc.edu"; "Kennedy, Kathleen A"; "Mcdavid, Georgia E"  
**Cc:** "Gantz, Marie"  
**Subject:** SUPPORT FU  
**Date:** Wednesday, January 20, 2010 3:26:00 PM

---

Hi,

We are missing a few outcomes for the SUPPORT FU. Let us know how you are doing.

CENTER	NETWORK	FU_message
18	(b)	FU window has closed but NF05 and NF09a have not been completed.
18	(b)	FU window has closed but NF05 and NF09a have not been completed.

Thanks for all the effort!!

Rose

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301-496-3790 (FAX)  
higginsr@mail.nih.gov

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Wally Carlo, M.D."; "Vivien Phillips"; "Monica Collins"; "Shirley Cosby"; "Myriam Peralta, M.D."  
**Cc:** "Gantz, Marie"  
**Subject:** SUPPOR FU  
**Date:** Wednesday, January 20, 2010 3:26:00 PM  
**Importance:** High

---

Hi,

We are missing a few outcomes for the SUPPORT FU. Let us know how you are doing.

CENTER	NETWORK	FU_message
16	(b)	FU window has closed but NF05 and NF09a have not been completed.
16	(b)	FU window has closed but NF05 and NF09a have not been completed.
16	(b)	FU window has closed but NF05 and NF09a have not been completed.

Thanks for all the effort!!

Rose

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301-496-3790 (FAX)  
higginsr@mail.nih.gov

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Susan Hintz"; "Krisa Van Meurs"; "Bethany Ball"  
**Cc:** "Gantz, Marie"  
**Subject:** SUPPORT FU  
**Date:** Wednesday, January 20, 2010 3:24:00 PM

---

Hi,

We are missing a few outcomes for the SUPPORT FU. Let us know how you are doing.

CENTER NETWORK FU\_message

15 (b) FU window has closed but NF05 and NF09a have not been completed.

Thanks for all the effort!!

Rose

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

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Poindexter, Brenda B."; "Dusick, Anna M."; "fahamer@iupui.edu"; "Wilson, Leslie Dawn"  
**Cc:** "Gantz, Marie"  
**Subject:** SUPPORT FU  
**Date:** Wednesday, January 20, 2010 3:22:00 PM  
**Importance:** High

---

Hi,

We are missing a few outcomes for the SUPPORT FU. Let us know how you are doing.

CENTER	NETWORK	FU_message
12	(b)	FU window has closed but NF05 and NF09a have not been completed.
12	(b)	FU window has closed but NF09a has not been completed.

Thanks for all the effort!!

Rose

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

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Kimberly.Yolton@cchmc.org"; "steichtj@email.uc.edu"; "Teresa.Gratton@uc.edu"; "Grisby, Cathy (grisbyca)"  
**Cc:** "Gantz, Marie"  
**Subject:** SUPPORT FU  
**Date:** Wednesday, January 20, 2010 3:19:00 PM

---

Hi,

We are missing a few outcomes for the SUPPORT FU. Let us know how you are doing.

CENTER	NETWORK	FU_message
11	(b)	NF09a marked as complete but no data entered other than center and infant ID.
11	(b)	FU window has closed but NF05 and NF09a have not been completed.

Thanks for all the effort!!

Rose

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

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Ira Adams-Chapman"; "Barbara Stoll"; "ellen\_hale@oz.ped.emory.edu"  
**Cc:** "Gantz, Marie"  
**Subject:** SUPPORT FU  
**Date:** Wednesday, January 20, 2010 3:18:00 PM

---

Hi,

We are missing a few outcomes for the SUPPORT FU. Let us know how you are doing.

CENTER	NETWORK	FU_message
9	(b)	Infant is lost to FU per NF10/SF10 but NF12/SF12 has not been completed.
9	(b)	Infant is lost to FU per NF10/SF10 but NF12/SF12 has not been completed.

Thanks for all the effort!!

Rose

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

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Pappas, Athina"; "Shankaran, Seetha"; "Sood, Beena"; "Bara, Rebecca"  
**Cc:** "Gantz, Marie"  
**Subject:** SUPPORT FU  
**Date:** Wednesday, January 20, 2010 3:17:00 PM  
**Importance:** High

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Hi,

We are missing a few outcomes for the SUPPORT FU. Let us know how you are doing.

CENTER	NETWORK	FU_message
5	(b)	FU window has closed but NF05 and NF09a have not been completed.
5	(b)	FU window has closed but NF09a has not been completed.
5	(b)	FU window has closed but NF05 and NF09a have not been completed.

Thanks for all the effort!!

Rose

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network  
Pregnancy and Perinatology Branch  
Center for Developmental Biology and Perinatal Medicine  
Eunice Kennedy Shriver National Institute of Child Health and Human Development  
National Institutes of Health  
6100 Executive Blvd., Room 4B03  
MSC 7510  
Bethesda, MD 20892  
For overnight delivery use Rockville, MD 20852  
301-496-5575  
301-496-3790 (FAX)  
higginsr@mail.nih.gov

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Finer, Neil"; "Wally Carlo, M.D."; "Michele Walsh"; "Bradley Yoder"; "Roger Faix"; "Abbot Laptook"; "kurt.schibler@cchmc.org"; "Das, Abhik"; "Nancy Newman"; "Gantz, Marie"; "Poole, W. Kenneth"; "Das, Abhik"  
**Cc:** "Petrie, Carolyn"; "Zaterka-Baxter, Kristin"; "Rich, Wade"; Archer, Stephanie (NIH/NICHD) [E]; "Cunningham, Meg"  
**Subject:** RE: SUPPORT Updates  
**Date:** Tuesday, January 19, 2010 8:54:00 AM  
**Attachments:** Oximeter.xls

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Here is one more item for discussion – the issue of oximeters and 36 week BPD outcome – as you can see from the table there was some variability with which oximeters folks were using.

Rose

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**From:** Finer, Neil [mailto:nfiner@ucsd.edu]  
**Sent:** Monday, January 18, 2010 7:07 PM  
**To:** Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]; 'Wally Carlo, M.D.'; 'Michele Walsh'; 'Bradley Yoder'; 'Roger Faix'; 'Abbot Laptook'; 'kurt.schibler@cchmc.org'; 'Das, Abhik'; 'Nancy Newman'; 'Gantz, Marie'; 'Poole, W. Kenneth'  
**Cc:** 'Petrie, Carolyn'; 'Zaterka-Baxter, Kristin'; Rich, Wade  
**Subject:** RE: SUPPORT Updates

Hi Everyone

We will have a brief meeting tomorrow morning at 11:30 ETime

We have no news from the NEJM about the manuscripts

Agenda

1. Review current follow-up progress
2. Review the ROP adjudication data
3. Review the FiO2 and SpO2 analyses
4. Discuss Secondaries – MRI, Growth and Pulmonary
5. Discuss other papers from secondary hypotheses
6. New Items

Talk to you in the morning

Neil



	03 Case	04 Dallas	05 Wayne	09 Emory	11 Cincinnati	12 Indiana	13 Yale	14 Brown	15 Stanford	16 Alabama	18 Houston	19 Duke	23 Tufts	24 Iowa	25 Utah	26 New Mexico	RTI	NICHD	Chairman	Total	
<b>SUPPORT   Oximeters used for Physiologic Def. Challenge</b>																					
Voted	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V	V					15
For determination of eligibility for the challenge, did you determine eligibility using:																					
Study oximeter																					5
Clinical	1	1	1	1	1	1	1		1	1	1	1	1		1	1					10
Brown	Per FiO2 documentation in medical record at 36 weeks.																				
If a challenge occurred, did your site use:																					
Study Oximeter												1			1	1					3
Clinical	1	1	1	1	1	1	1	1	1	1	1	1	1		1	1					13
For BPD by oxygen definition, did you use:																					
Study oximeter															1	1					5
Clinical	1	1	1	1	1	1	1	1	1	1	1	1	1		1	1					11
Utah	Our answer is mixed. Some of the kids moved up to the extension unit, where we weren't allowed to use the study oximeters (they didn't speak to the central alarm system). So, some were on the study ox and																				
Indiana	We followed the manual guidelines for use of the study oximeters – so any baby on oxygen indeed was still on a study oximeter up until 36 weeks. We determined if babies were eligible for a challenge at 36 weeks –																				
Alabama	At UAB, determination of eligibility by study pulse oximeter used on 36 week PCA day. If infant had challenge done, it was done with a clinical pulse oximeter. Study PO left on baby on day 36 week because 4 data																				
Dallas	I looked at the completed PHY02BASE forms for our SUPPORT babies who had challenges. According to my records one of our infants was tested with a Masimo (not sure why or how it happened). All of the other																				
UNM	In New Mexico the Study oximeter was kept on the patient until 36 weeks, death, transfer, or room air. Therefore, the study oximeter was used to determine eligibility for RA challenge, and to record the use of oxygen																				
Emory	I went back through our SUPPORT folders and I think that only (b) and (b) were evaluated for BPD using the study monitors. Both coded as not eligible for reduction because sats too low. I think these are																				
Duke	The study oximeter was used to determine eligibility for the challenge (for those that were still on the study oximeter at 36 weeks) and was also used for the challenge.																				
IOWA	Our answer is mixed. Some of the kids moved up to the extension unit, where we weren't allowed to use the study oximeters (they didn't speak to the central alarm system). So, some were on the study ox and others on the clinical one. If you need me to se																				

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Das, Abhik"  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]  
**Subject:** FW: SUPPORT Updates  
**Date:** Tuesday, January 19, 2010 8:52:00 AM  
**Attachments:** [SUPPORT SpO2 Analysis for Time on Oxygen.doc](#)  
[SUPPORT FiO2 Analysis for First 14 Days of Life.doc](#)  
[Effect of ROP adjudication - 05JAN10.doc](#)

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**From:** Finer, Neil [mailto:nfiner@ucsd.edu]  
**Sent:** Monday, January 18, 2010 7:07 PM  
**To:** Finer, Neil; Higgins, Rosemary (NIH/NICHD) [E]; 'Wally Carlo, M.D.'; 'Michele Walsh'; 'Bradley Yoder'; 'Roger Faix'; 'Abbot Laptook'; 'kurt.schibler@cchmc.org'; 'Das, Abhik'; 'Nancy Newman'; 'Gantz, Marie'; 'Poole, W. Kenneth'  
**Cc:** 'Petrie, Carolyn'; 'Zaterka-Baxter, Kristin'; Rich, Wade  
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Neil

## SUPPORT SpO2 Analysis for Time on Oxygen

Differences in SpO2 values between oximetry groups were analyzed using pulse oximeter data for time on supplemental oxygen (approximated by matching oximeter data to FiO2 and oxygen use data collected on forms SUPP05 and SUPP11). In **Figures 1-4** histograms compare the percent of time infants in the high and low SpO2 groups spent with SpO2 values >96%, <80%, <75% and <70%.

Median tests were done to compare the percent of time infants in the two oximetry groups spent in certain SpO2 ranges while on supplemental oxygen. **Table 1** shows the median percent of time spent in the SpO2 ranges while on supplemental oxygen for infants assigned to the high and low SpO2 groups, with p-values from Rank Sums tests of the difference between the medians. The median percent of time spent at SpO2 values >96% was significantly higher for infants in the high SpO2 group, and the median percent of time spent at SpO2 values <80%, <75%, and <70% was significantly higher for infants in the low SpO2 group.

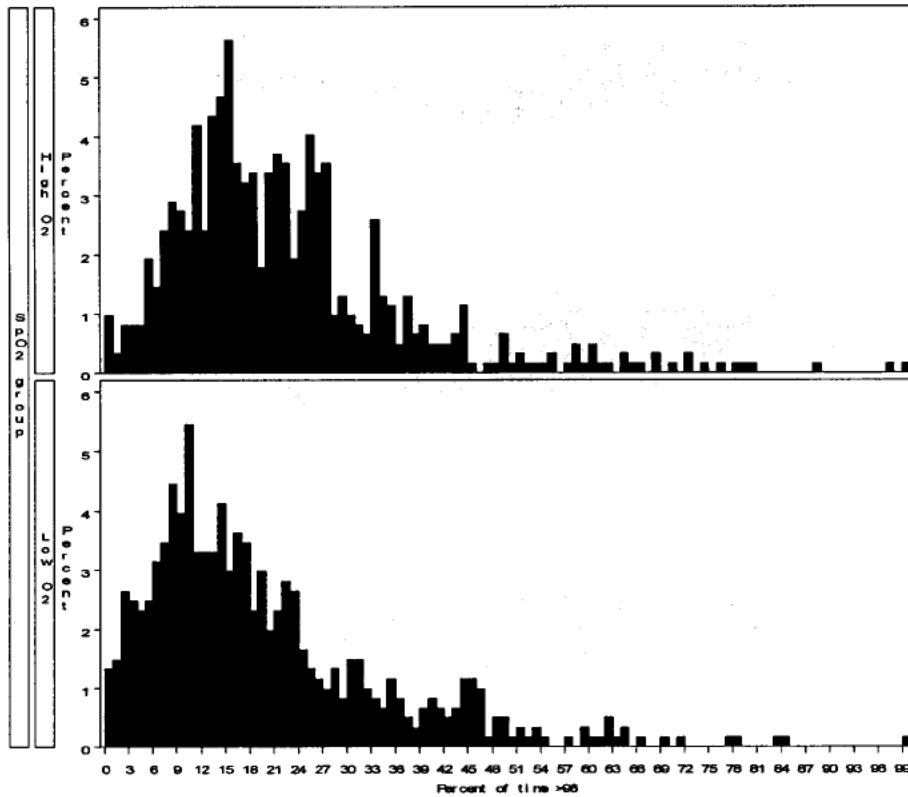
SpO2 range	High SpO2 group: Median % of time in range	Low SpO2 group: Median % of time in range	P-value
>96%	19.6	16.0	<0.0001
<80%	3.9	5.9	<0.0001
<75%	2.1	3.3	<0.0001
<70%	0.9	1.5	<0.0001

**Table 1. Median percent of time spent in SpO2 ranges while on supplemental oxygen for infants assigned to the high and low SpO2 groups, with p-values from Rank Sums tests of the difference between the medians**

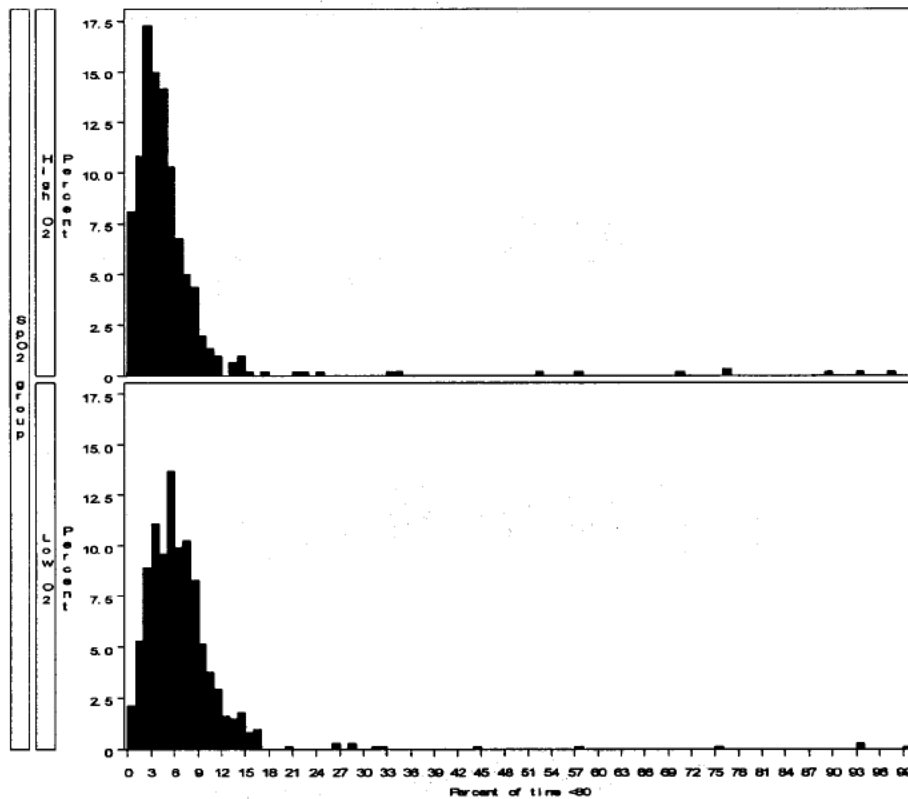
Although the distributions of the percent of time in the given SpO2 ranges was skewed, general linear mixed models were created to test differences in means between the oximetry groups. Predictive variables included oximetry group, center, and gestational age group (24-25 weeks vs. 26-27 weeks), and the models accounted for clustering by family. **Table 2** shows the mean percent of time spent in each SpO2 range by oximetry group, and p-values for differences between the means. The mean percent of time spent at SpO2 values >96% was significantly higher for infants in the high SpO2 group, and the mean percent of time spent at SpO2 values <80% and <75% was significantly higher for infants in the low SpO2 group. There was not a significant difference between groups for the mean percent of time spent at SpO2 values <70%.

SpO2 range	High SpO2 group: Mean % of time in range (95% CI)	Low SpO2 group: Mean % of time in range (95% CI)	P-value
>96%	23.2 (22.0, 24.5)	20.1 (18.8, 21.3)	0.0001
<80%	5.5 (4.8, 6.3)	7.3 (6.6, 8.1)	0.0002
<75%	3.6 (2.9, 4.3)	4.5 (3.8, 5.2)	0.0486
<70%	2.1 (1.5, 2.7)	2.5 (1.9, 3.1)	0.4090

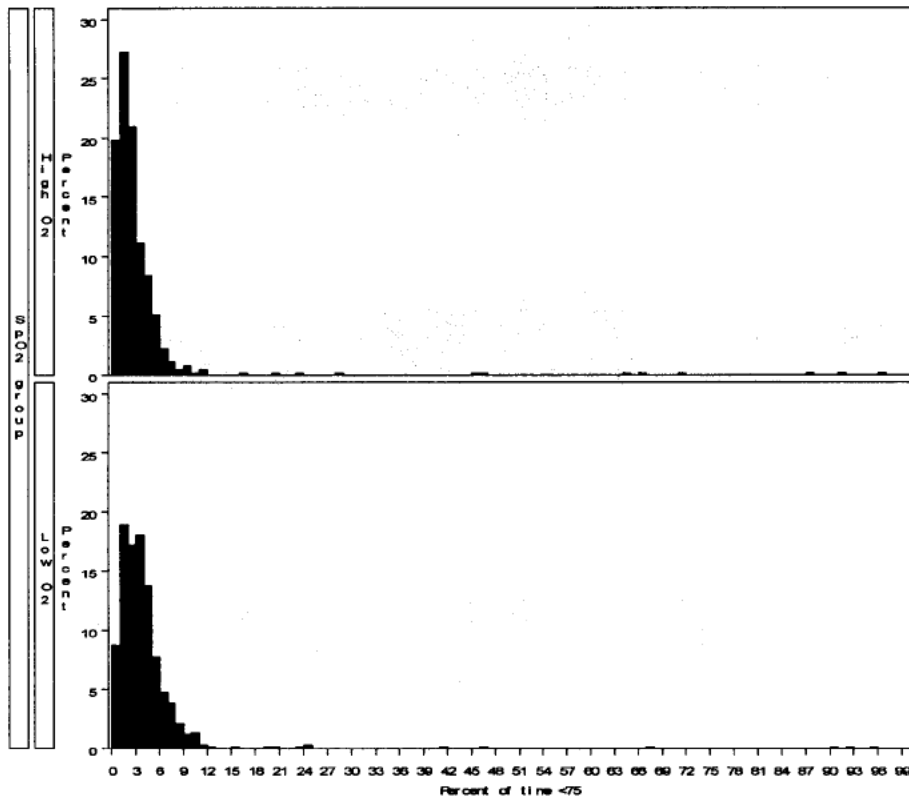
**Table 2. Mean percent of time spent in SpO2 ranges while on supplemental oxygen for infants assigned to the high and low SpO2 groups, with p-values from general linear mixed models to test for differences between the means**



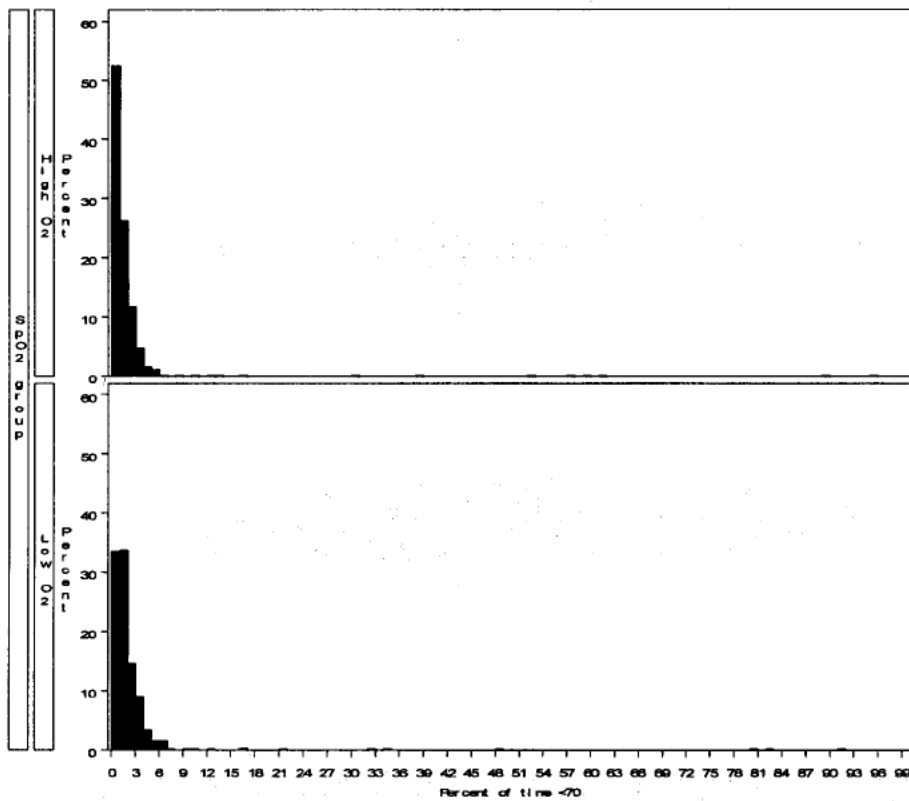
**Figure 1. Percent of time with SpO2 values >96% while on supplemental oxygen for infants assigned to the high (upper histogram) and low (lower histogram) SpO2 groups**



**Figure 2. Percent of time with SpO2 values <80% while on supplemental oxygen for infants assigned to the high (upper histogram) and low (lower histogram) SpO2 groups**



**Figure 3. Percent of time with SpO2 values <75% while on supplemental oxygen for infants assigned to the high (upper histogram) and low (lower histogram) SpO2 groups**



**Figure 4. Percent of time with SpO2 values <70% while on supplemental oxygen for infants assigned to the high (upper histogram) and low (lower histogram) SpO2 groups**

## SUPPORT FiO2 Analysis for First 14 Days of Life

Differences in FiO2 values between oximeter groups were analyzed using SUPP05 data for the first 14 days of life. In **Figures 1-14** histograms compare FiO2 values for infants assigned to the low and high SpO2 groups for days 1-14.

Although the histograms clearly show that the FiO2 values are skewed (with a large number of FiO2 values =0.21 and a long tail to the right) a general linear mixed model was created to predict average FiO2 for the two groups. After viewing the data graphically (see **Figures 15-17**), oximeter group, day of life, day of life squared, day of life cubed, and interactions between oximeter group and the linear, quadratic and cubic terms for day of life were included as predictors. The model controlled for gestational age group (24-25 vs. 26-27) and center, and it accounted for the repeated measurements for each subject. The interaction between oximeter group and day of life was significant, thus individual models were created for each day. Predictive variables were oximeter group, gestational age group, and center, and the models accounted for repeated measures (at up to 12 time points) for each infant. In all models, infants in the high SpO2 group had higher average FiO2 compared to those in the low SpO2 group. **Table 1** shows the average difference in FiO2 from the models for each day of life.

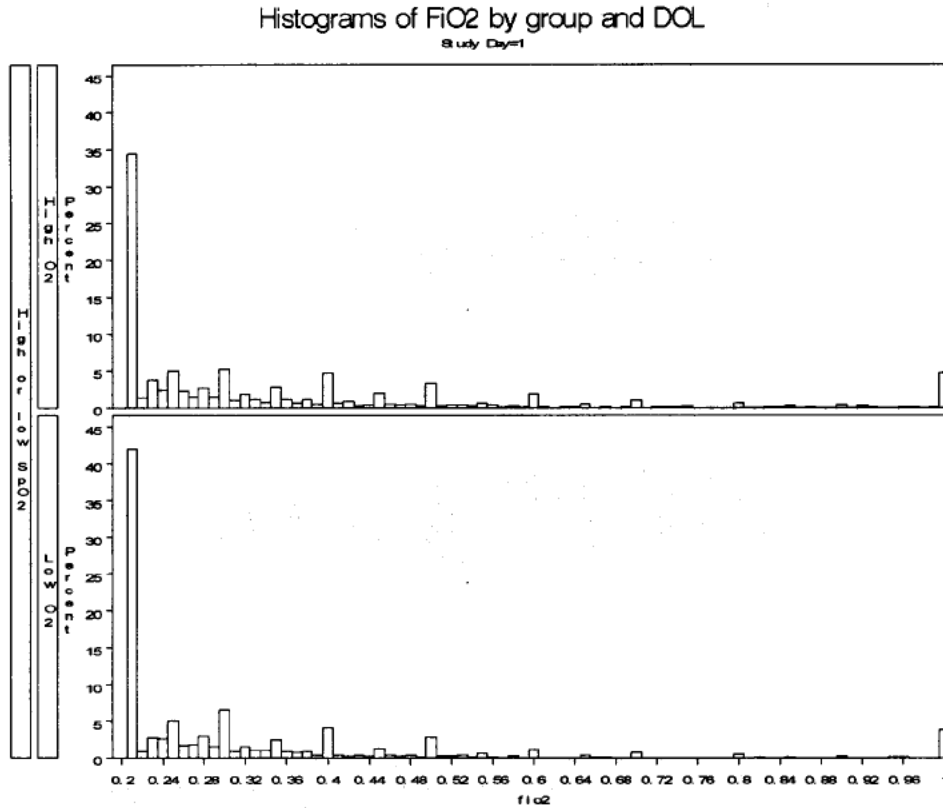
Because it appeared from the histograms that much of the difference between oximeter groups was in the percent of infants receiving supplemental oxygen, a GEE model (like those used for the primary analysis) was created to predict receipt of supplemental oxygen. After viewing the data graphically (see **Figures 18-20**), oximeter group, day of life, day of life squared, day of life cubed, and interactions between oximeter group and the linear, quadratic and cubic terms for day of life were included as predictors. The model also controlled for gestational age group and center, and accounted for the repeated measurements for each subject. The interaction between oximeter group and day of life was significant, thus individual GEE models were created for each day. Predictive variables were oximeter group, gestational age group, and center, and the models accounted for repeated measures (at up to 12 time points during the day) for each infant. In all models, infants in the high SpO2 group were more likely than those in the low SpO2 group to receive supplemental oxygen. **Table 2** shows the relative risks (RR) from the models for each day of life.

Day	Difference (95% CI)	P-value
1	0.029 (0.012, 0.047)	0.0010
2	0.015 (0.001, 0.029)	0.0321
3	0.022 (0.009, 0.035)	0.0009
4	0.019 (0.007, 0.031)	0.0014
5	0.017 (0.008, 0.026)	0.0002
6	0.016 (0.007, 0.025)	0.0007
7	0.020 (0.010, 0.031)	0.0002
8	0.018 (0.007, 0.029)	0.0014
9	0.023 (0.011, 0.035)	0.0002
10	0.032 (0.020, 0.045)	<.0001
11	0.033 (0.020, 0.046)	<.0001
12	0.031 (0.019, 0.044)	<.0001
13	0.028 (0.016, 0.041)	<.0001
14	0.032 (0.020, 0.045)	<.0001

**Table 1.** Difference in average FiO2 between the high and low SpO2 groups, from general linear mixed models to predict FiO2 on each day of life

Day	RR (95% CI)	P-value
1	1.14 (1.07, 1.21)	<.0001
2	1.16 (1.09, 1.25)	<.0001
3	1.20 (1.12, 1.29)	<.0001
4	1.24 (1.15, 1.34)	<.0001
5	1.25 (1.15, 1.37)	<.0001
6	1.26 (1.16, 1.38)	<.0001
7	1.24 (1.14, 1.35)	<.0001
8	1.18 (1.09, 1.28)	<.0001
9	1.18 (1.09, 1.27)	<.0001
10	1.18 (1.10, 1.27)	<.0001
11	1.17 (1.09, 1.25)	<.0001
12	1.13 (1.06, 1.21)	0.0003
13	1.14 (1.07, 1.21)	<.0001
14	1.12 (1.05, 1.19)	0.0003

**Table 2.** Relative risk of supplemental oxygen use for the high vs. low SpO2 groups, from GEE models to predict supplemental oxygen on each day of life



**Figure 1.** FiO2 on day of life 1 for infants assigned to the high and low SpO2 groups

### Histograms of FiO2 by group and DOL

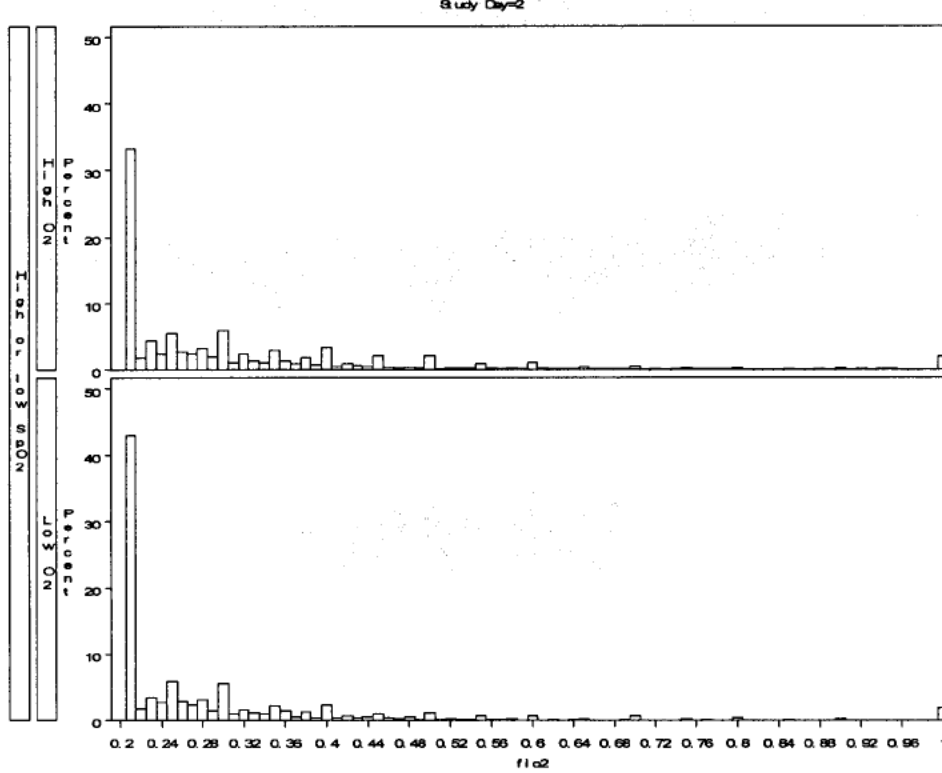


Figure 2. FiO2 on day of life 2 for infants assigned to the high and low SpO2 groups

### Histograms of FiO2 by group and DOL

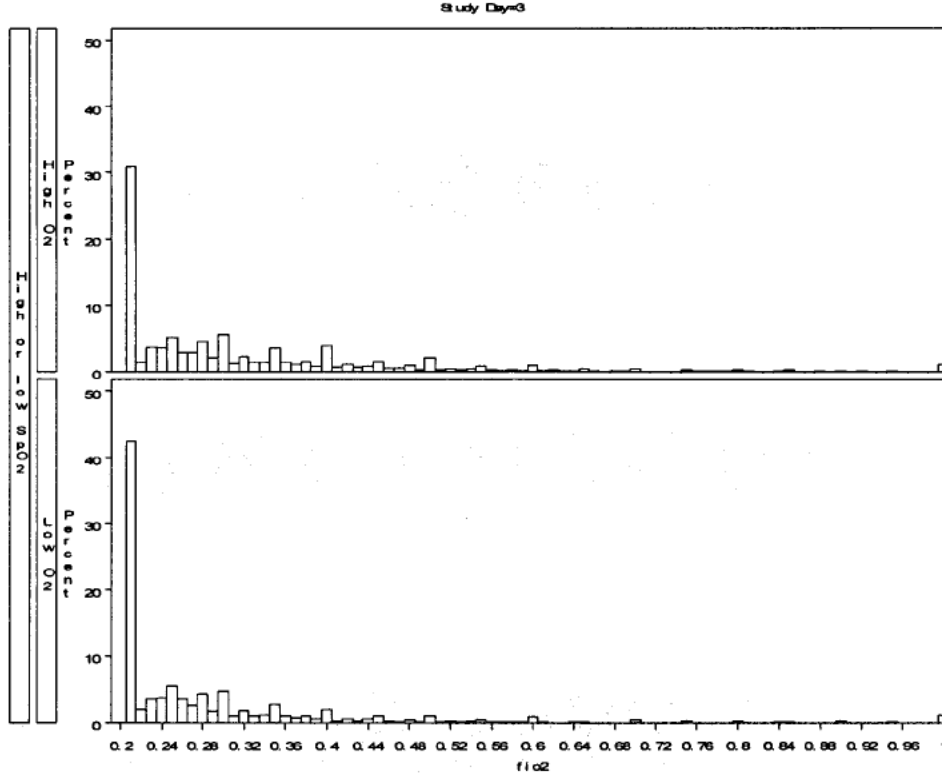


Figure 3. FiO2 on day of life 3 for infants assigned to the high and low SpO2 groups



### Histograms of FiO2 by group and DOL

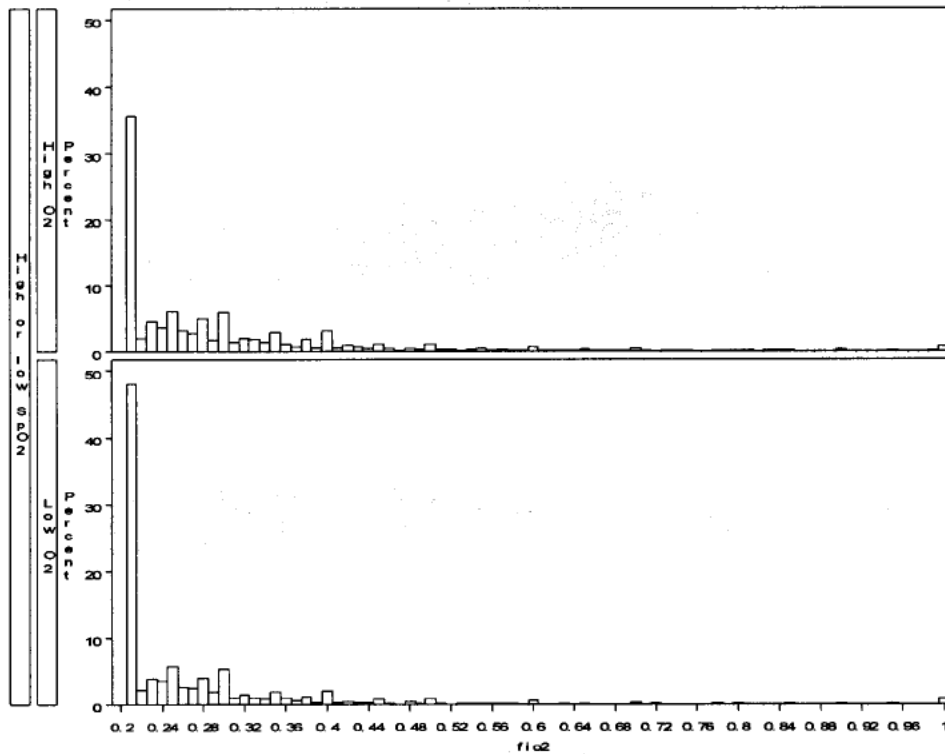


Figure 4. FiO2 on day of life 4 for infants assigned to the high and low SpO2 groups

### Histograms of FiO2 by group and DOL

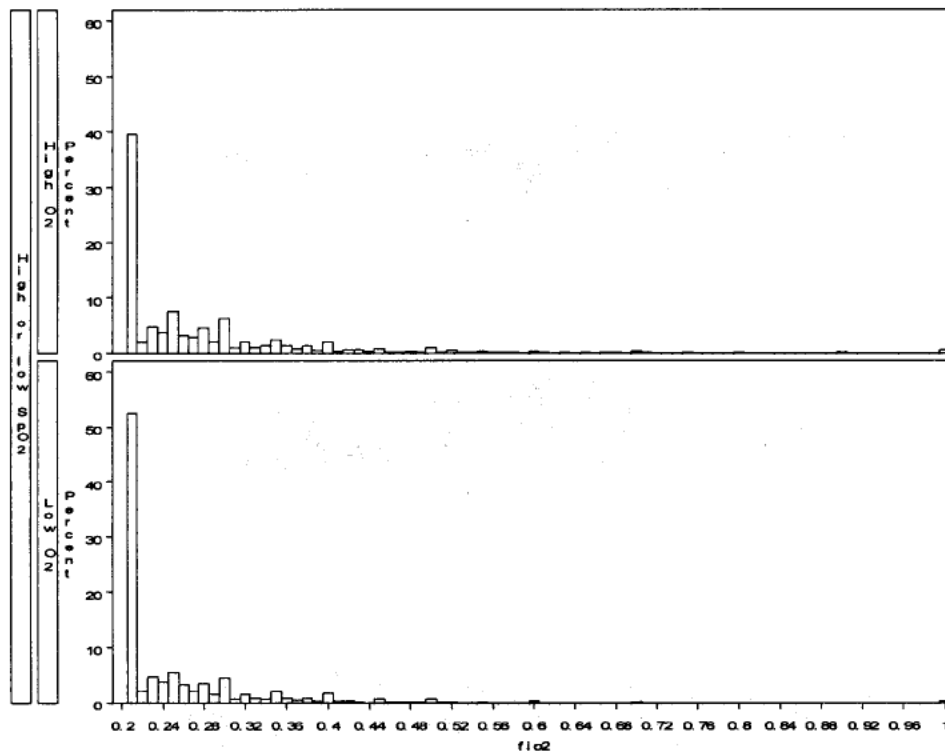


Figure 5. FiO2 on day of life 5 for infants assigned to the high and low SpO2 groups

### Histograms of FiO2 by group and DOL

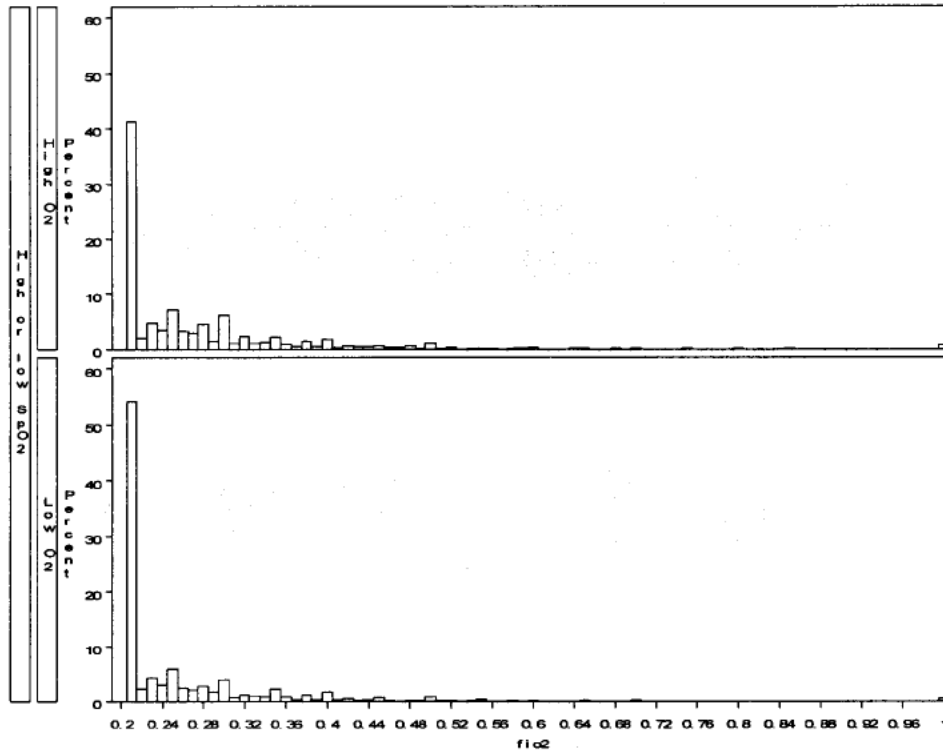


Figure 6. FiO2 on day of life 6 for infants assigned to the high and low SpO2 groups

### Histograms of FiO2 by group and DOL

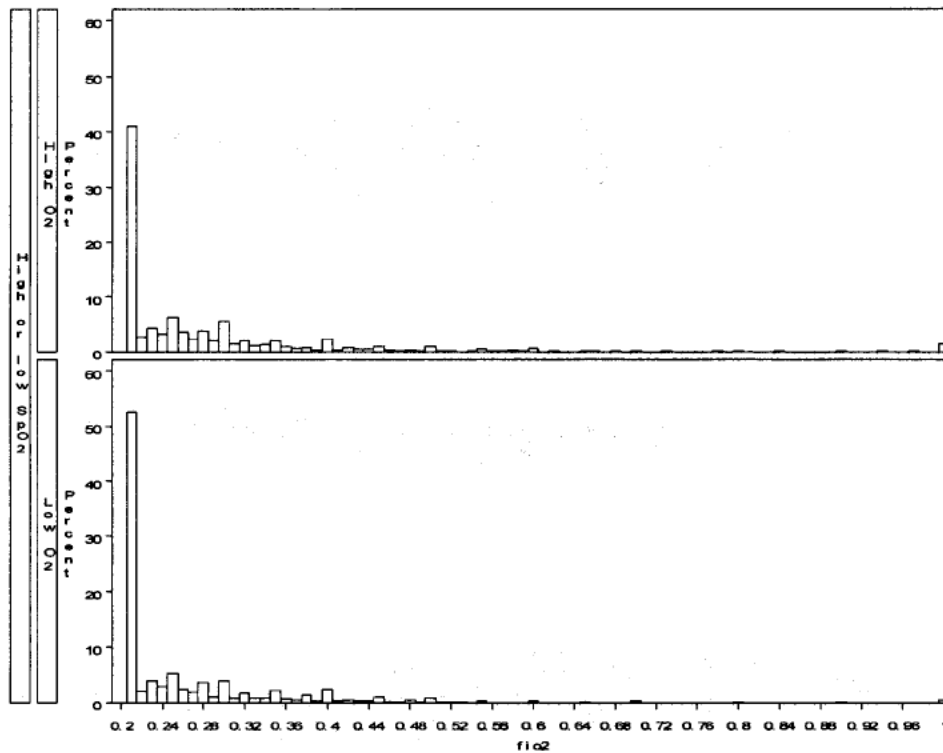


Figure 7. FiO2 on day of life 7 for infants assigned to the high and low SpO2 groups

### Histograms of FiO2 by group and DOL

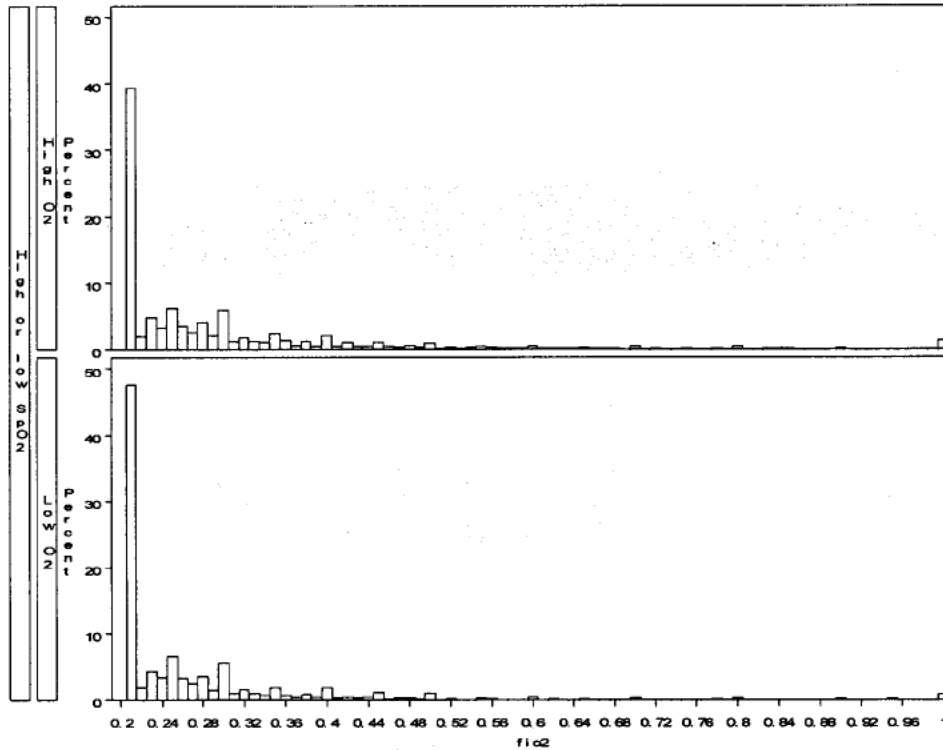


Figure 8. FiO2 on day of life 8 for infants assigned to the high and low SpO2 groups

### Histograms of FiO2 by group and DOL

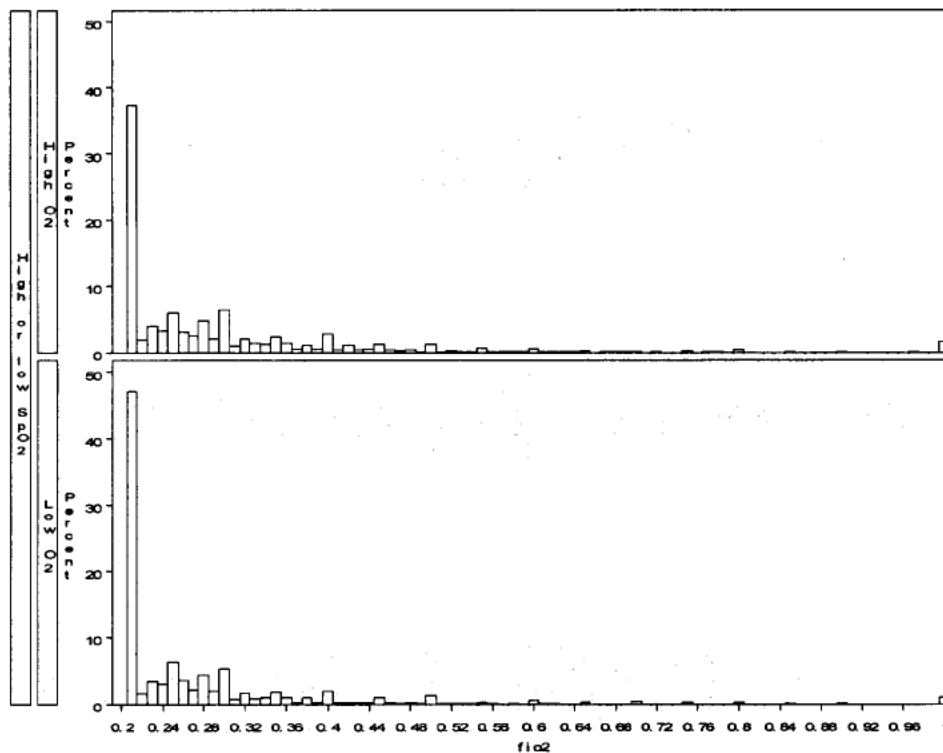


Figure 9. FiO2 on day of life 9 for infants assigned to the high and low SpO2 groups

### Histograms of FiO2 by group and DOL

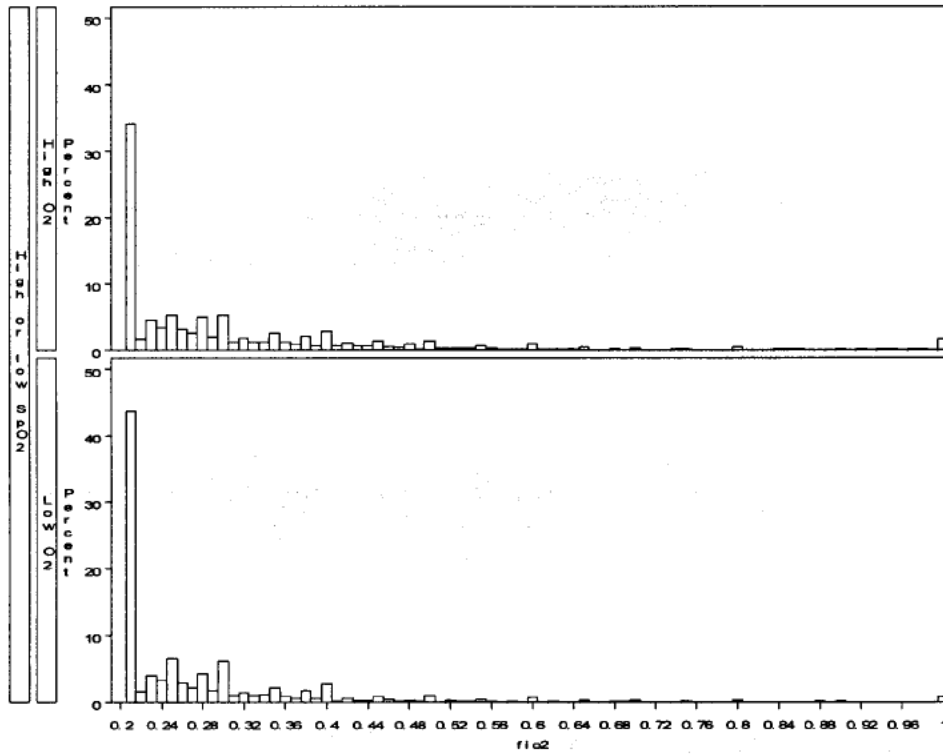


Figure 10. FiO2 on day of life 10 for infants assigned to the high and low SpO2 groups

### Histograms of FiO2 by group and DOL

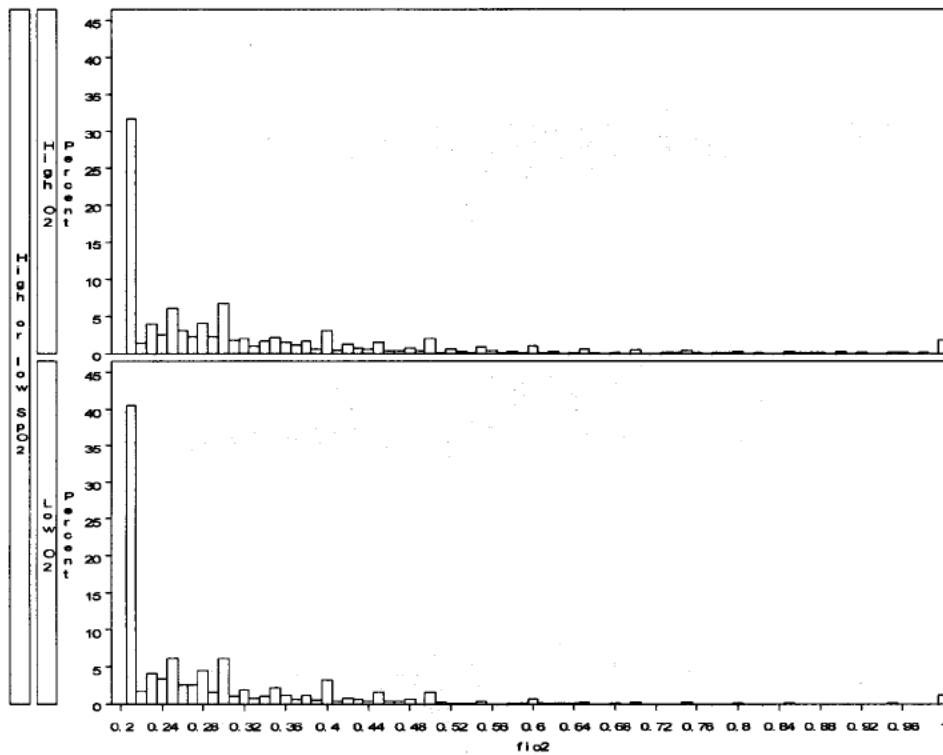


Figure 11. FiO2 on day of life 11 for infants assigned to the high and low SpO2 groups

### Histograms of FiO2 by group and DOL

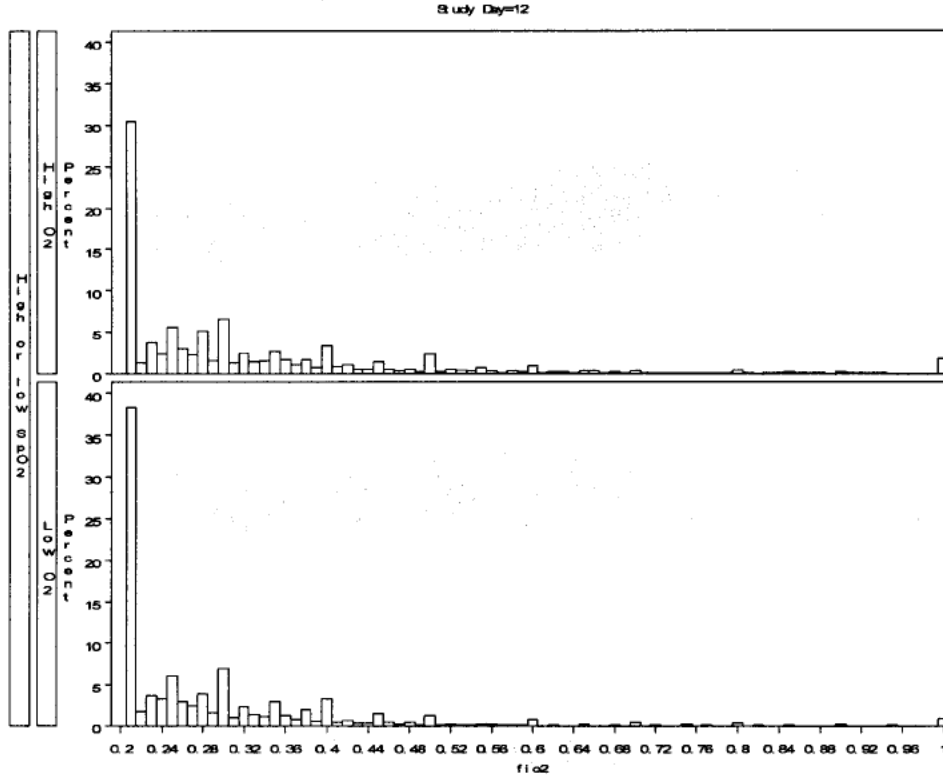


Figure 12. FiO2 on day of life 12 for infants assigned to the high and low SpO2 groups

### Histograms of FiO2 by group and DOL

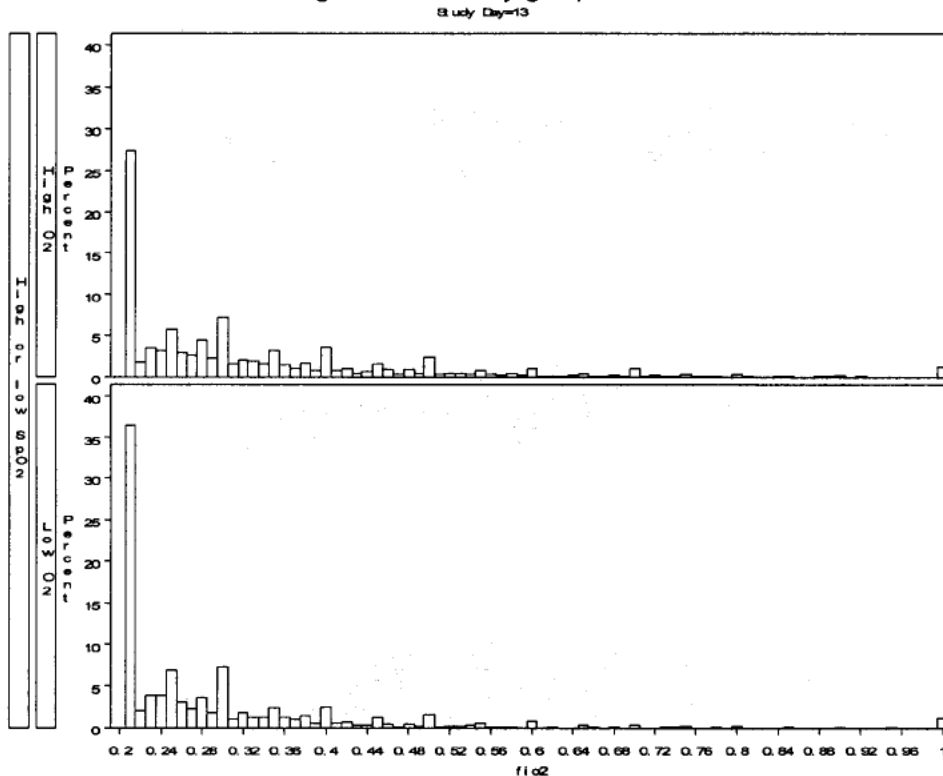


Figure 13. FiO2 on day of life 13 for infants assigned to the high and low SpO2 groups

### Histograms of FIO2 by group and DOL

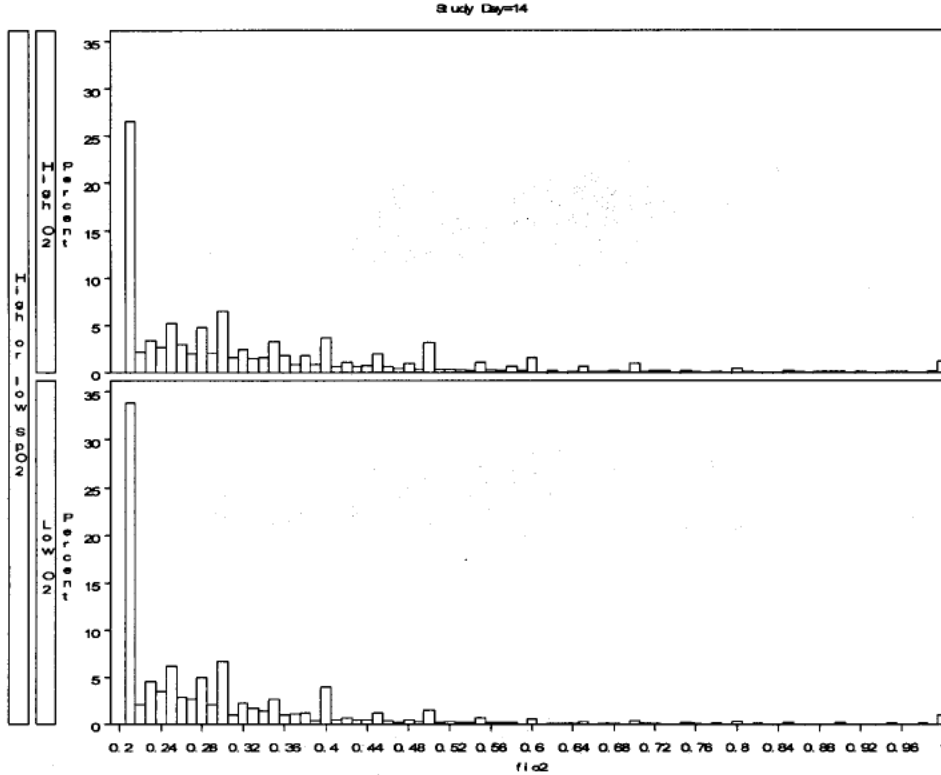


Figure 14. FIO2 on day of life 14 for infants assigned to the high and low SpO2 groups

### FIO2 by day and oximeter group (with spline)

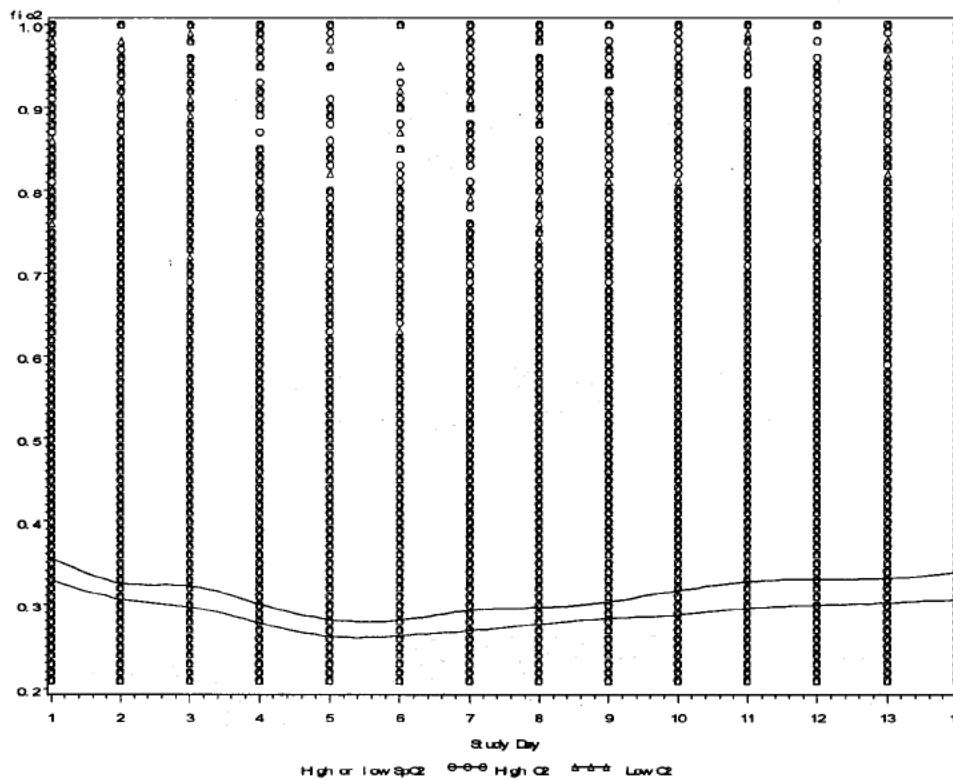


Figure 15. FIO2 by day and oximeter group (with spline)

FiO2 by day and oximeter group (with quadratic regression line)

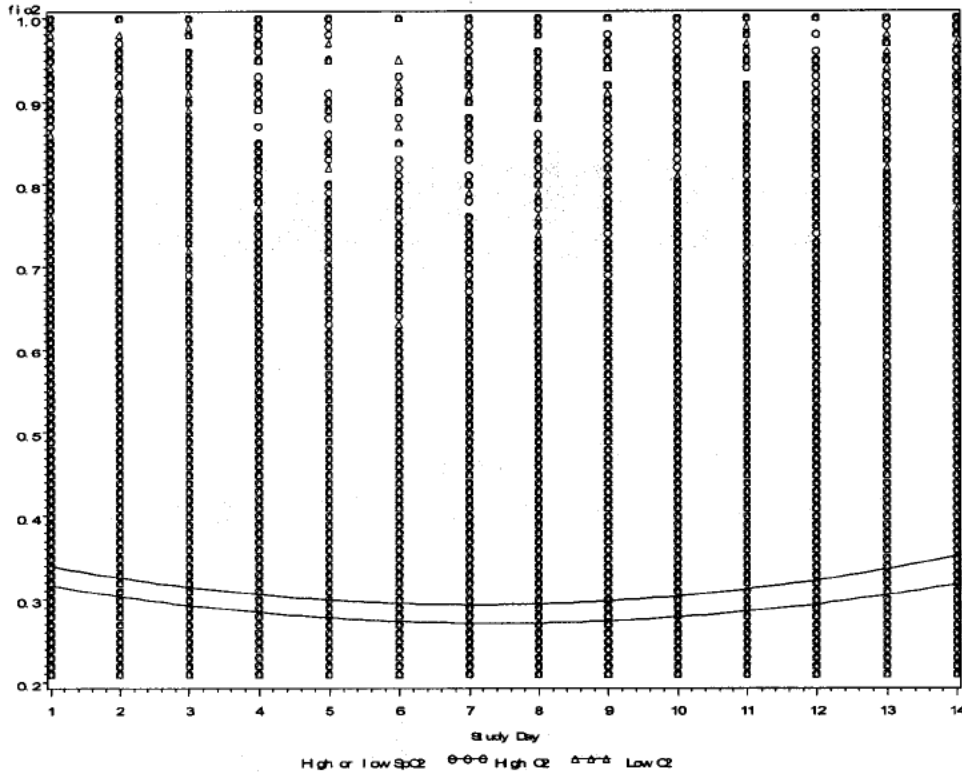


Figure 16. FiO2 by day and oximeter group (with quadratic regression line)

FiO2 by day and oximeter group (with cubic regression line)

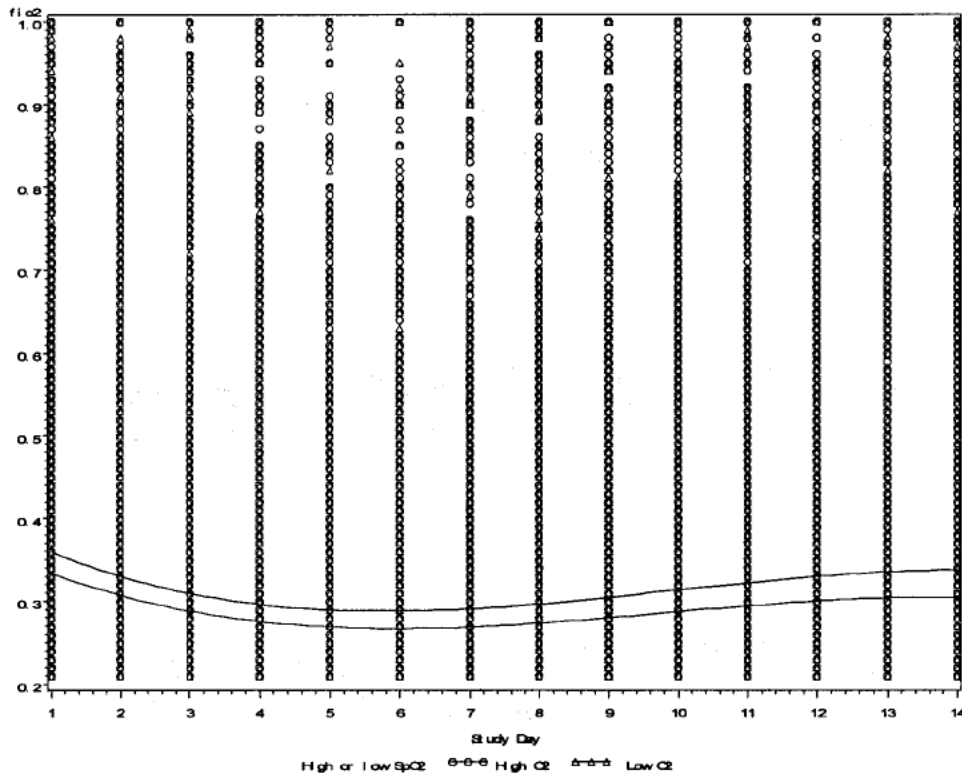


Figure 17. FiO2 by day and oximeter group (with cubic regression line)

Percent of time on oxygen by day and oximeter group (with spline)

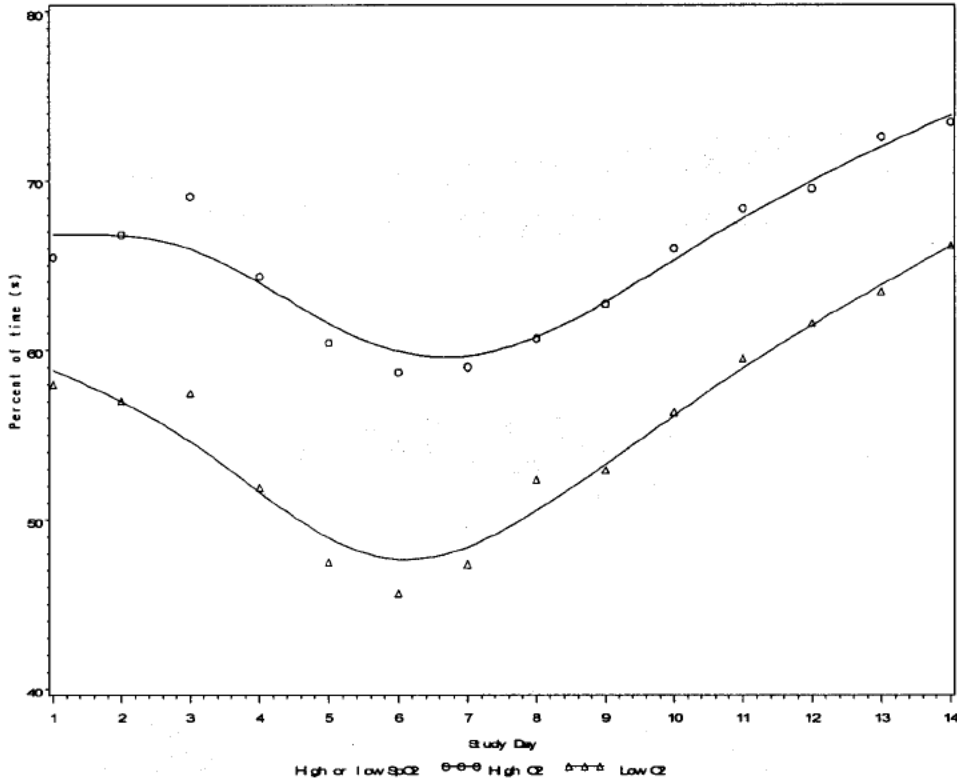


Figure 18. Percent of time on oxygen by day and group (with spline)

Percent of time on oxygen by day and oximeter group (with quadratic regression line)

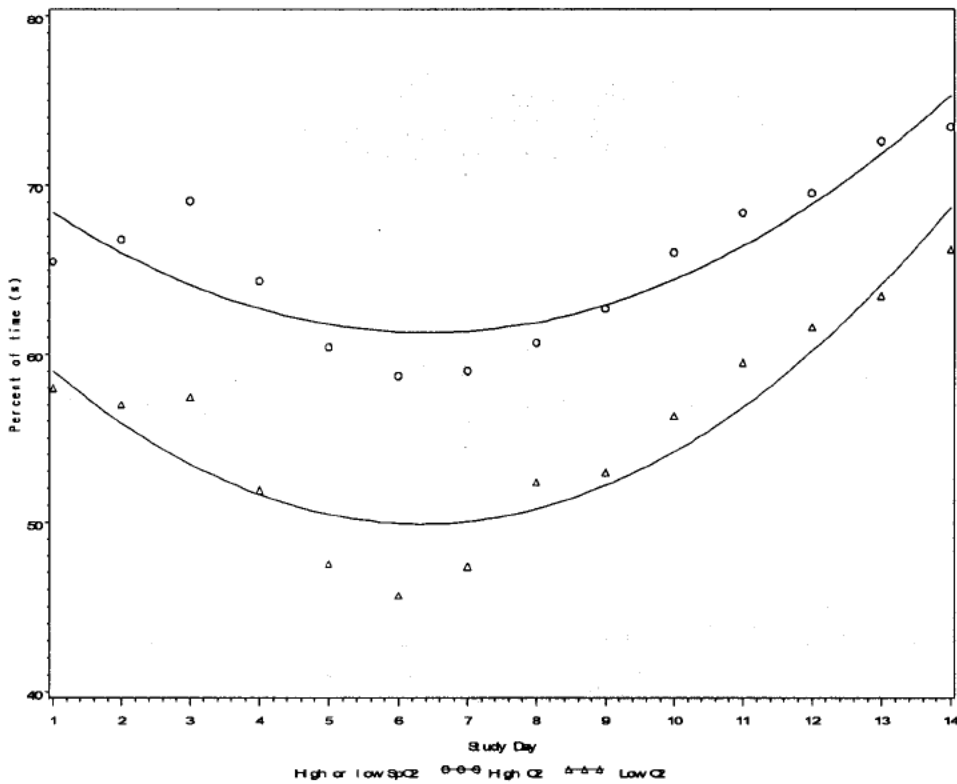


Figure 19. Percent of time on oxygen by day and group (with quadratic regression line)



Percent of time on oxygen by day and oximeter group (with cubic regression line)

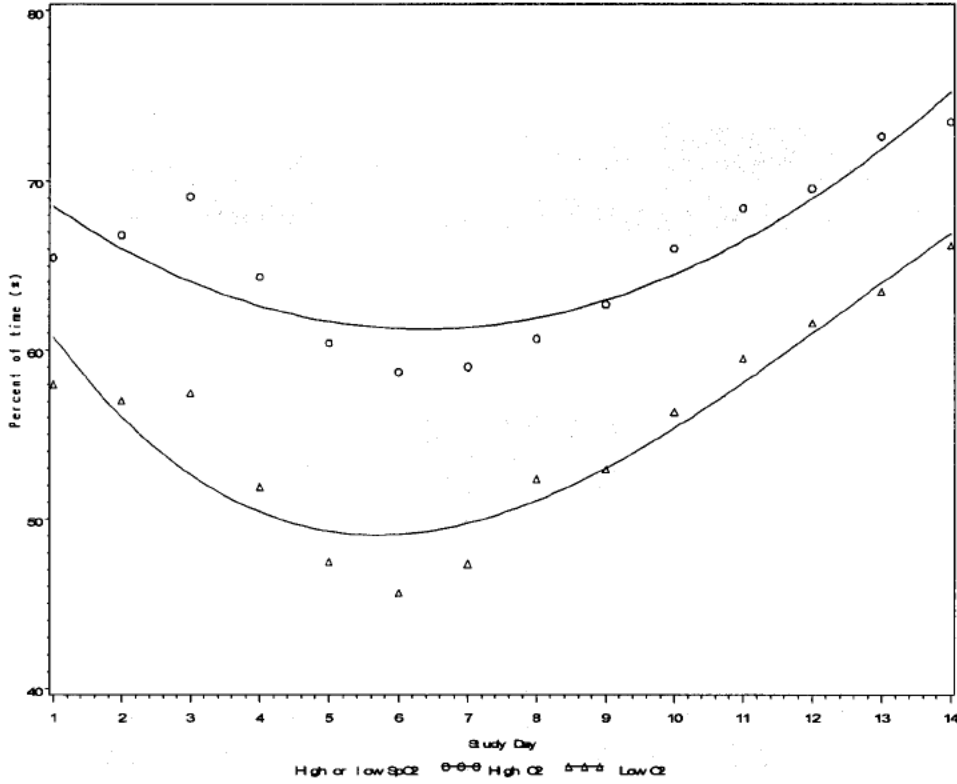


Figure 20. Percent of time on oxygen by day and group (with cubic regression line)

Effect of ROP adjudication for Low vs. High SpO2

Characteristic	Low SpO2 (N=654)	High SpO2 (N=662)	Relative Risk (95% CI)	P-value
ROP/death without adjudication result	171/605 (28.3)	198/616 (32.1)	0.9 (0.76, 1.06)	0.2050
ROP among survivors without adjudication result	41/475 (8.6)	91/509 (17.9)	0.52 (0.37, 0.73)	0.0002
ROP/death with adjudication result (majority rule)*	171/642 (26.6)	198/656 (30.2)	0.91 (0.77, 1.07)	0.2532
ROP among survivors with adjudication result (majority rule)*	41/512 (8.0)	91/549 (16.6)	0.52 (0.37, 0.73)	0.0002
ROP/death with adjudication result ('unknown' set to ROP=Y)**	183/654 (28.0)	204/662 (30.8)	0.93 (0.79, 1.1)	0.4125
ROP among survivors with adjudication result ('unknown' set to ROP=Y)**	53/524 (10.1)	97/555 (17.5)	0.62 (0.45, 0.84)	0.0019

Relative risks are adjusted for GA stratification, center and familial clustering.

Centers with fewer than 10 infants enrolled and those with an incidence of zero for the outcome in question were combined with the geographically closest site for RR calculation.

\* Majority rule: If 2 reviewers determined that the infant 'Probably never had ROP that met criteria for ROP intervention (laser/cryo) in either eye' then ROP=N; if 2 reviewers determined that 'There is no way to know if ROP criteria may have been met' then ROP=missing.

\*\* 'Unknown' set to ROP=Y: If 2 reviewers determined that the infant 'Probably never had ROP that met criteria for ROP intervention (laser/cryo) in either eye' then ROP=N; if 2 reviewers determined that 'There is no way to know if ROP criteria may have been met' then ROP=Y.

**Effect of ROP adjudication for Low vs. High SpO<sub>2</sub>**

Where GA is 24-25 weeks

Characteristic	Low SpO <sub>2</sub> (N=276)	High SpO <sub>2</sub> (N=269)	Relative Risk (95% CI)	P-value
ROP/death without adjudication result	117/256 (45.7)	139/271 (51.3)	0.88 (0.73, 1.05)	0.1648
ROP among survivors without adjudication result	32/171 (18.7)	66/198 (33.3)	0.58 (0.4, 0.85)	0.0046
ROP/death with adjudication result (majority rule)*	117/270 (43.3)	139/286 (48.6)	0.89 (0.74, 1.07)	0.2022
ROP among survivors with adjudication result (majority rule)*	32/185 (17.3)	66/213 (31.0)	0.58 (0.4, 0.85)	0.0051
ROP/death with adjudication result ('unknown' set to ROP=Y)**	123/276 (44.6)	142/289 (49.1)	0.9 (0.75, 1.08)	0.2768
ROP among survivors with adjudication result ('unknown' set to ROP=Y)**	38/191 (19.9)	69/216 (31.9)	0.64 (0.45, 0.91)	0.0130

Relative risks are adjusted for GA stratification, center and familial clustering.

Centers with fewer than 10 infants enrolled and those with an incidence of zero for the outcome in question were combined with the geographically closest site for RR calculation.

\* Majority rule: If 2 reviewers determined that the infant 'Probably never had ROP that met criteria for ROP intervention (laser/cryo) in either eye' then ROP=N; if 2 reviewers determined that 'There is no way to know if ROP criteria may have been met' then ROP=missing.

\*\* 'Unknown' set to ROP=Y: If 2 reviewers determined that the infant 'Probably never had ROP that met criteria for ROP intervention (laser/cryo) in either eye' then ROP=N; if 2 reviewers determined that 'There is no way to know if ROP criteria may have been met' then ROP=Y.

Characteristic	Low SpO <sub>2</sub> (N=378)	High SpO <sub>2</sub> (N=373)	Relative Risk (95% CI) (High vs. Low)	P-Value
ROP/death without adjudication result	54/349 (15.5)	59/345 (17.1)	0.95 (0.67, 1.34)	0.7575
ROP among survivors without adjudication result	9/304 (3.0)	25/311 (8.0)	0.38 (0.18, 0.79)	0.0098
ROP/death with adjudication result (majority rule)*	54/372 (14.5)	59/370 (15.9)	0.96 (0.68, 1.36)	0.8068
ROP among survivors with adjudication result (majority rule)*	9/327 (2.8)	25/336 (7.4)	0.38 (0.18, 0.8)	0.0108
ROP/death with adjudication result ('unknown' set to ROP=Y)**	60/378 (15.9)	62/373 (16.6)	1 (0.72, 1.4)	0.9831
ROP among survivors with adjudication result ('unknown' set to ROP=Y)**	15/333 (4.5)	28/339 (8.3)	0.56 (0.3, 1.02)	0.0597

Relative risks are adjusted for GA stratification, center and familial clustering.

Centers with fewer than 10 infants enrolled and those with an incidence of zero for the outcome in question were combined with the geographically closest site for RR calculation.

\* Majority rule: If 2 reviewers determined that the infant 'Probably never had ROP that met criteria for ROP intervention (laser/cryo) in either eye' then ROP=N; if 2 reviewers determined that 'There is no way to know if ROP criteria may have been met' then ROP=missing.

\*\* 'Unknown' set to ROP=Y: If 2 reviewers determined that the infant 'Probably never had ROP that met criteria for ROP intervention (laser/cryo) in either eye' then ROP=N; if 2 reviewers determined that 'There is no way to know if ROP criteria may have been met' then ROP=Y.

Effect of ROP adjudication for CPAP vs. Surfactant

Characteristic	CPAP (N=663)	Surfactant (N=653)	Relative Risk (95% CI)	p-value
ROP/death without adjudication result	176/620 (28.4)	193/601 (32.1)	0.87 (0.74, 1.03)	0.0971
ROP among survivors without adjudication result	67/511 (13.1)	65/473 (13.7)	0.94 (0.69, 1.28)	0.7140
ROP/death with adjudication result (majority rule)*	176/654 (26.9)	193/644 (30.0)	0.89 (0.75, 1.05)	0.1601
ROP among survivors with adjudication result (majority rule)*	67/545 (12.3)	65/516 (12.6)	0.96 (0.7, 1.31)	0.7969
ROP/death with adjudication result ('unknown' set to ROP=Y)**	185/663 (27.9)	202/653 (30.9)	0.89 (0.76, 1.05)	0.1608
ROP among survivors with adjudication result ('unknown' set to ROP=Y)**	76/554 (13.7)	74/525 (14.1)	0.96 (0.72, 1.28)	0.7599

Relative risks are adjusted for GA stratification, center and familial clustering.

Centers with fewer than 10 infants enrolled and those with an incidence of zero for the outcome in question were combined with the geographically closest site for RR calculation.

\* Majority rule: If 2 reviewers determined that the infant 'Probably never had ROP that met criteria for ROP intervention (laser/cryo) in either eye' then ROP=N; if 2 reviewers determined that 'There is no way to know if ROP criteria may have been met' then ROP=missing.

\*\* 'Unknown' set to ROP=Y: If 2 reviewers determined that the infant 'Probably never had ROP that met criteria for ROP intervention (laser/cryo) in either eye' then ROP=N; if 2 reviewers determined that 'There is no way to know if ROP criteria may have been met' then ROP=Y.

Characteristic	CPAP (N=285)	Surfactant (N=280)	Relative Risk (95% CI)	Adjusted P-Value
ROP/death without adjudication result	112/266 (42.1)	144/261 (55.2)	0.74 (0.62, 0.89)	0.0015
ROP among survivors without adjudication result	44/198 (22.2)	54/171 (31.6)	0.71 (0.5, 1)	0.0525
ROP/death with adjudication result (majority rule)*	112/281 (39.9)	144/275 (52.4)	0.75 (0.63, 0.91)	0.0031
ROP among survivors with adjudication result (majority rule)*	44/213 (20.7)	54/185 (29.2)	0.72 (0.51, 1.02)	0.0663
ROP/death with adjudication result ('unknown' set to ROP=Y)**	116/285 (40.7)	149/280 (53.2)	0.75 (0.63, 0.9)	0.0024
ROP among survivors with adjudication result ('unknown' set to ROP=Y)**	48/217 (22.1)	59/190 (31.1)	0.72 (0.52, 1)	0.0487

Relative risks are adjusted for GA stratification, center and familial clustering.

Centers with fewer than 10 infants enrolled and those with an incidence of zero for the outcome in question were combined with the geographically closest site for RR calculation.

\* Majority rule: If 2 reviewers determined that the infant 'Probably never had ROP that met criteria for ROP intervention (laser/cryo) in either eye' then ROP=N; if 2 reviewers determined that 'There is no way to know if ROP criteria may have been met' then ROP=missing.

\*\* 'Unknown' set to ROP=Y: If 2 reviewers determined that the infant 'Probably never had ROP that met criteria for ROP intervention (laser/cryo) in either eye' then ROP=N; if 2 reviewers determined that 'There is no way to know if ROP criteria may have been met' then ROP=Y.

Characteristic	CPAP (N=378)	Surfactant (N=375)	Relative Risk (95% CI)	P-value
ROP/death without adjudication result	64/354 (18.1)	49/340 (14.4)	1.25 (0.88, 1.77)	0.2153
ROP among survivors without adjudication result	23/313 (7.3)	11/302 (3.6)	2.19 (1.06, 4.53)	0.0343
ROP/death with adjudication result (majority rule)*	64/373 (17.2)	49/369 (13.3)	1.29 (0.9, 1.83)	0.1616
ROP among survivors with adjudication result (majority rule)*	23/332 (6.9)	11/331 (3.3)	2.25 (1.09, 4.67)	0.0287
ROP/death with adjudication result ('unknown' set to ROP=Y)**	69/378 (18.3)	53/373 (14.2)	1.28 (0.91, 1.79)	0.1502
ROP among survivors with adjudication result ('unknown' set to ROP=Y)**	28/337 (8.3)	15/335 (4.5)	1.97 (1.06, 3.66)	0.0332

Relative risks are adjusted for GA stratification, center and familial clustering.

Centers with fewer than 10 infants enrolled and those with an incidence of zero for the outcome in question were combined with the geographically closest site for RR calculation.

\* Majority rule: If 2 reviewers determined that the infant 'Probably never had ROP that met criteria for ROP intervention (laser/cryo) in either eye' then ROP=N; if 2 reviewers determined that 'There is no way to know if ROP criteria may have been met' then ROP=missing.

\*\* 'Unknown' set to ROP=Y: If 2 reviewers determined that the infant 'Probably never had ROP that met criteria for ROP intervention (laser/cryo) in either eye' then ROP=N; if 2 reviewers determined that 'There is no way to know if ROP criteria may have been met' then ROP=Y.

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "wcarlo@peds.uab.edu"  
**Subject:** Re: SC meeting  
**Date:** Tuesday, January 19, 2010 6:20:47 AM

---

Ok  
Thanks  
Rose

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**From:** Wally Carlo, M.D. <WCarlo@peds.uab.edu>  
**To:** Finer, Neil <nfiner@ucsd.edu>; Gantz, Marie <mgantz@rti.org>; Cunningham, Meg <mcunningham@rti.org>; Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik <adas@rti.org>  
**Cc:** Zaterka-Baxter, Kristin <kzaterka@rti.org>  
**Sent:** Mon Jan 18 21:53:50 2010  
**Subject:** RE: SC meeting

Hi Neil and Rose:

I have a conflict on my schedule and the other activity is a press conference about our new NICU and visit to the NICU and I can not be excused as I am the main person representing the Hospital. I am sorry that my secretaries scheduled this and I did not notice the conflict but I have been out of town and the press conference has been on my schedule for a while.

The press conference starts at 11:20 Eastern and is scheduled to finish by 12 so I can join in for the second half of the call. I will call in as soon as it finishes.

Wally

Wally Carlo, M.D.  
Edwin M. Dixon Professor of Pediatrics  
University of Alabama at Birmingham  
Director, Division of Neonatology  
Director, Newborn Nurseries  
619 South 20th Street  
525 New Hillman Building  
Birmingham, AL 35233-7335  
Phone: 205 934 4680  
FAX: 205 934 3100  
Cell: 205 266 (b)

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**From:** Finer, Neil [mailto:nfiner@ucsd.edu]  
**Sent:** Monday, January 18, 2010 8:39 PM  
**To:** Wally Carlo, M.D.; Gantz, Marie; Cunningham, Meg; Rosemary Higgins; Das, Abhik  
**Cc:** Zaterka-Baxter, Kristin  
**Subject:** RE: SC meeting

I agree  
Neil

---

**From:** Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]  
**Sent:** Monday, January 18, 2010 5:17 PM  
**To:** Gantz, Marie; Cunningham, Meg; Finer, Neil; Rosemary Higgins; Das, Abhik  
**Cc:** Zaterka-Baxter, Kristin  
**Subject:** RE: SC meeting



Only 3.5% lost to FU is very impressive.

Wally

Wally Carlo, M.D.  
Edwin M. Dixon Professor of Pediatrics  
University of Alabama at Birmingham  
Director, Division of Neonatology  
Director, Newborn Nurseries  
619 South 20th Street  
525 New Hillman Building  
Birmingham, AL 35233-7335  
Phone: 205 934 4680  
FAX: 205 934 3100  
Cell: 205 266 (b)

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**From:** Gantz, Marie [mailto:mgantz@rti.org]  
**Sent:** Monday, January 18, 2010 2:23 PM  
**To:** Cunningham, Meg; Finer, Neil; Wally Carlo, M.D.; Rosemary Higgins; Das, Abhik  
**Cc:** Zaterka-Baxter, Kristin  
**Subject:** RE: SC meeting

Attached is a document showing FU status for SUPPORT survivors. About 65% of survivors have the FU outcome (completed the FU visit or died following discharge) as of today. FYI, the last SUPPORT FU windows open in December 2010 and close in April 2011.

Marie

Marie Gantz, Ph.D.  
Research Statistician  
RTI International  
mgantz@rti.org  
828-254-6255

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**From:** Cunningham, Meg  
**Sent:** Monday, January 18, 2010 10:51 AM  
**To:** Gantz, Marie  
**Cc:** Zaterka-Baxter, Kristin  
**Subject:** RE: SC meeting

Marie –

Are there any materials about follow-up I should include in my reminder from you? If so, please send along!

Meg

---

**From:** Finer, Neil [mailto:nfiner@ucsd.edu]  
**Sent:** Sunday, January 17, 2010 8:58 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Wally Carlo, M.D.  
**Cc:** Martinez, Fernando; Cunningham, Meg; Gantz, Marie; Das, Abhik  
**Subject:** RE: SC meeting

Hi Rose

For our phone call for Tuesday, Jan 19 2010, I have attached the above for all the subcommittee. Can you circulate with any other material you feel is needed?  
Will you want to hear from Susan Hintz about her study, or from Tim?  
As we have no word from the journal, I suspect that we will have time for these if you want a report I would also like Marie to tell us where we are for the follow-up – how many survivors have had the follow-up evaluation?  
Are there other issues that you want addressed at this time. We have another phone call in about 2-3 weeks  
Let me know  
Be well  
Neil

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**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Wednesday, January 13, 2010 3:53 PM  
**To:** Finer, Neil  
**Cc:** Martinez, Fernando; 'mcunningham@rti.org'  
**Subject:** Re: SC meeting

We will schedule you at 11 am ET (8 am PT).  
Thanks for getting back to me.

Have fun in Palm Springs-  
Rose

---

**From:** Finer, Neil <nfiner@ucsd.edu>  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Martinez, Fernando <fmartinez@ucsd.edu>  
**Sent:** Wed Jan 13 17:52:27 2010  
**Subject:** RE: SC meeting

Hi Rose  
I will do this by phone – My preferred times would be 8:00AM  
Thanks  
Neil

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**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Wednesday, January 13, 2010 9:49 AM  
**To:** Finer, Neil  
**Cc:** 'Cunningham, Meg'  
**Subject:** SC meeting

Neil the next SC meeting is Feb 11-12.

We have the subcommittee meeting in advance by phone. What time would you like to present and will this be by phone or in-person?

We will a lot extra time for you at this meeting (hopefully we will have some good updates)  
Rose

Rosemary D. Higgins, MD  
Program Scientist for the Neonatal Research Network  
Pregnancy and Perinatology Branch  
Center for Developmental Biology and Perinatal Medicine  
Eunice Kennedy Shriver National Institute of Child Health and Human Development  
National Institutes of Health  
6100 Executive Blvd., Room 4B03  
MSC 7510  
Bethesda, MD 20892  
For overnight delivery use Rockville, MD 20852  
301-496-5575  
301-496-3790 (FAX)  
higginsr@mail.nih.gov

## **Higgins, Rosemary (NIH/NICHD) [E]**

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**From:** Finer, Neil <nfiner@ucsd.edu>  
**Sent:** Saturday, January 16, 2010 5:34 PM  
**To:** Gantz, Marie; Rich, Wade; Das, Abhik; Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** Zaterka-Baxter, Kristin  
**Subject:** RE: SUPPORT Analyses

Many thanks Marie  
These are very helpful  
There does not appear to be a major difference between the SpO2 groups for SpO2 < 70% and this may turn out to be very important.  
Neil

-----Original Message-----

**From:** Gantz, Marie [mailto:mgantz@rti.org]  
**Sent:** Friday, January 15, 2010 11:32 AM  
**To:** Finer, Neil; Rich, Wade; Das, Abhik; Wally Carlo, M.D.; Rosemary Higgins  
**Cc:** Zaterka-Baxter, Kristin  
**Subject:** RE: SUPPORT Analyses

Hi all,

The SpO2 analysis Neil requested is attached. Please let me know if you have any questions. Have a good weekend.

Marie

Marie Gantz, Ph.D.  
Research Statistician  
RTI International  
mgantz@rti.org  
828-254-6255

-----Original Message-----

**From:** Gantz, Marie  
**Sent:** Thursday, January 14, 2010 2:31 PM  
**To:** Finer, Neil; Rich, Wade; Das, Abhik; Wally Carlo, M.D.; 'Rosemary Higgins'  
**Cc:** Zaterka-Baxter, Kristin  
**Subject:** RE: SUPPORT Analyses

Hi all,

The FiO2 analysis Neil requested is attached. We do seem to have achieved FiO2 separation between the oximeter groups, at least during the first 14 days of life (which is all I've looked at).

Neil and Wally, let me know if you need anything additional on this. I will work on the SpO2 analysis Neil requested next.

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: Thursday, January 07, 2010 1:37 PM  
To: Gantz, Marie; Rich, Wade  
Subject: Re: SUPPORT Analyses

Hi Marie

The first 14 days which were the intervention days is fine for now.

Lets look at the the SpO2 in a manner which makes it easy at present - ie one group for SpO2 < 70% If this looks important enough and we need to further subdivide we can ask for that later.

Less than 70% should be a good initial place to look.

For the SpO2 at present we should analyze when the infant was on oxygen.

An additional analysis for all times is also helpful. It may be possible that one group - ie - the low reading group, may have increased durations of lower sats when off of oxygen.

Thanks Marie  
Neil

On 1/7/10 9:35 AM, "Gantz, Marie" <mgantz@rti.org> wrote:

> Neil,  
>  
> I have a few questions with regard to your request below.  
>  
> 1) When you talk about the FiO2 analysis, I assume you are referring  
> to  
> the FiO2 values recorded on the SUPP05 (but please correct me if I'm  
> wrong). This is fine for the first 14 days, but as of day 15 when we  
> switch to the SUPP11 we no longer collected FiO2, just oxygen Y/N. So,  
> how would you like me to look at day 15+?  
>  
> 2) For the SpO2 data, do you anticipate looking at any other ranges  
> besides what you have listed below? The reason I ask is that looking  
> at  
> ranges <70% is going to require some re-processing of the data because  
> our current analysis files group all sats <70% together. The  
> programmers  
> can re-process the data, but since this will take some time I wanted  
> to  
> find out if any additional ranges will be needed so that the  
> re-processing can be done just once.  
>  
> 3) For the SpO2 analysis, are you interested in only time on  
> supplemental oxygen or time in room air as well?  
>

> Thanks,  
> 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: Tuesday, December 15, 2009 3:10 PM  
> To: Gantz, Marie; Wally Carlo; Rich, Wade; Das, Abhik; Higgins,  
Rosemary  
> (NIH/NICHD) [E]  
> Subject: SUPPORT Analyses  
>  
> Hi Everyone  
> I would like to ask that we run the following in anticipation of any  
> reviewers questions I would like to see an FiO2 analysis - ie the  
> actual difference in  
FiO2  
> by day for the first 14 days between the 2 SpO2 groups, and after 14  
> days The oximeters were designed to separate the actual FiO2 exposure  
> of these 2 groups.  
> In addition I would like an analysis of the SpO2 durations of < 80% >  
> 96% and durations of SpO2 < 75%, < 70% < 60% and < 50% for the 2  
groups.  
> I suspect this may be helpful in looking at the exposure to severe  
> hypoxia.  
> Marie can you begin these??  
> All the best for Christmas and the New Year to everyone and thanks  
again  
> for a great job!!!!  
> Thanks  
> Neil

**From:** Susan Hintz  
**To:** Susan Hintz  
**Cc:** Higgins, Rosemary (NIH/NICHD) [E]; Das, Abhik  
**Subject:** Re: proportion of enrolled SUPPORT main trial in CUS group and all imaging group of the Neuroimaging secondary  
**Date:** Wednesday, January 13, 2010 9:43:26 AM

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Sorry - keep pressing send by accident. There are more adverse LATE cus combined in cpap than surfactant - which is consistent between central readers. Trying to think ahead to concerns both internal to the NRN and the broader clinical community, I was trying to take a stab at representativeness.

I think we need also to look at the site readings of these late US from GDB . Rose, I know we discussed that we may not have them, but I think we probably have most - we asked the sites to put those in as the "US closet to 36 weeks" in the GDB. Of course, we will end up relying on the Gold Standard central readings anyway, but would be good to have in hand.

Thanks

S

Sent from my iPhone

On Jan 13, 2010, at 6:34 AM, Susan Hintz <srhintz@stanford.edu> wrote:

> Also, agree that the broader clinical community is not truly  
> interested in whether this cohort is representative of trial - but  
> there are a few findings, including more severe adverse findings  
> (combined mod-sev ventric, porenceph cyst, cyst pvl) in CPAP group  
> than  
>  
> Sent from my iPhone  
>  
> On Jan 13, 2010, at 5:57 AM, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov  
>> wrote:  
>  
>> I agree  
>> GOOD POINTS  
>> ROSE  
>>  
>> -----Original Message-----  
>> From: Das, Abhik [mailto:adas@rti.org]  
>> Sent: Wednesday, January 13, 2010 8:55 AM  
>> To: Susan Hintz; Higgins, Rosemary (NIH/NICHD) [E]  
>> Subject: RE: proportion of enrolled SUPPORT main trial in CUS group  
>> and all imaging group of the Neuroimaging secondary  
>>  
>> Susan:  
>>  
>> We can do this, but for the paper the representativeness issue  
>> would be  
>> best sorted out by comparing SUPPORT babies in the neuroimaging  
>> cohort

>> against those not in that cohort by select sociodemographic and  
>> medical  
>> characteristics. For the paper, we could also contemplate a  
>> propensity  
>> score type of model to see if the probability of a SUPPORT baby to  
>> be in  
>> the neuroimaging cohort can be at all predicted using a multivariable  
>> logistic regression model. For the broader community, I doubt they  
>> will  
>> care much if this sub-cohort has equal representation across all NRN  
>> sites.  
>>  
>> Thanks  
>>  
>> Abhik  
>>  
>> -----Original Message-----  
>> From: Susan Hintz [mailto:[srhintz@stanford.edu](mailto:srhintz@stanford.edu)]  
>> Sent: Tuesday, January 12, 2010 5:56 PM  
>> To: Rosemary Higgins  
>> Cc: Das, Abhik  
>> Subject: proportion of enrolled SUPPORT main trial in CUS group and  
>> all  
>> imaging group of the Neuroimaging secondary  
>>  
>> Hi Rose and Abhik,  
>>  
>> I spoke with Rose about this today. I think we need to have a pretty  
>> good handle on the proportion of patients from the SUPPORT main trial  
>> from each of the sites and overall that ended up in the Neuroimaging  
>> secondary. The question will come up re: how "representative" this  
>> secondary cohort is of the trial overall, particularly since some  
>> of the  
>> findings from the CUS group analysis and the main trial differ  
>> slightly  
>> (although, for instance, I think the grade 3-4 IVH rates differ  
>> because  
>> some of those patients with grade 3-4 in the main trial went on to  
>> die,  
>> so they are not in the group of patients we analyzed).  
>>  
>> Attached is a table - I think this can mostly be done by Marie  
>> because  
>> she has most of the pertinent data, although some input from Qing and  
>> from Jenny Auman (who has been maintaining data in the "Master MRI  
>> FU"  
>> spreadsheet with CUS and MRI data, follow-up at 18-22 month  
>> success, and  
>> tracking question for school age follow-up).  
>>  
>> Thanks - and of course, input is welcomed,  
>>  
>> Susan  
>>  
>> --  
>> Susan R. Hintz, M.D., M.S. Epi  
>> Associate Professor of Pediatrics



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- >> Division of Neonatal and Developmental Medicine Stanford University
- >> School of Medicine 750 Welch Road, Suite 315 Palo Alto, CA 94304
- >> ph: 650-723-5711
- >> fax: 650-725-8351

**From:** [Susan Hintz](#)  
**To:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](#)  
**Cc:** [adas@rti.org](mailto:adas@rti.org)  
**Subject:** proportion of enrolled SUPPORT main trial in CUS group and all imaging group of the Neuroimaging secondary  
**Date:** Tuesday, January 12, 2010 5:56:14 PM  
**Attachments:** [Infants Enrolled in Neuroimaging.docx](#)

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Hi Rose and Abhik,

I spoke with Rose about this today. I think we need to have a pretty good handle on the proportion of patients from the SUPPORT main trial from each of the sites and overall that ended up in the Neuroimaging secondary. The question will come up re: how "representative" this secondary cohort is of the trial overall, particularly since some of the findings from the CUS group analysis and the main trial differ slightly (although, for instance, I think the grade 3-4 IVH rates differ because some of those patients with grade 3-4 in the main trial went on to die, so they are not in the group of patients we analyzed).

Attached is a table - I think this can mostly be done by Marie because she has most of the pertinent data, although some input from Qing and from Jenny Auman (who has been maintaining data in the "Master MRI FU" spreadsheet with CUS and MRI data, follow-up at 18-22 month success, and tracking question for school age follow-up).

Thanks - and of course, input is welcomed,

Susan

--

Susan R. Hintz, M.D., M.S. Epi  
Associate Professor of Pediatrics  
Division of Neonatal and Developmental Medicine  
Stanford University School of Medicine  
750 Welch Road, Suite 315  
Palo Alto, CA 94304  
ph: 650-723-5711  
fax: 650-725-8351

Center	# enrolled in SUPPORT main trial	# in SUPPORT who survived to 36 weeks	# in SUPPORT who survived to discharge	# in "CUS group" of Neuroimaging cohort *	# in "all imaging" group Neuroimaging cohort *
3:Case					
4:U Texas D					
5:Wayne					
9:Emory					
12:Indiana					
14:Brown					
15:Stanford					
16: Alabam					
18:U Tex H					
19:Duke					
21: NY					
22:UCSD					
23:Tufts					
24:Iowa					
25:Utah					
26:New M					
<b>TOTAL</b>					

\*Notes:

- 1) "CUS group" of Neuroimaging cohort is defined as patients enrolled in Neuroimaging and Neurodevelopmental Outcomes secondary that had BOTH EARLY and LATE Cranial US done, and read by central readers. **Per Qing's analysis, this number is 570-574** (monthly report describes # late US = 574)
- 2) "All imaging group" of Neuroimaging Cohort is defined as patients enrolled in Neuroimaging and Neurodevelopmental Outcomes secondary that had BOTH EARLY and LATE Cranial US done, AND successful brain MRI. **Per Jenny Auman's numbers, this number is probably ~540-550.**

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Barbara Stoll"; "mcw3@case.edu"; "Laptook, Abbot"; "Bell, Edward"; "Shankaran, Seetha"; "Das, Abhik"; "ellen\_hale@oz.ped.emory.edu"; "Nancy Newman"  
**Cc:** Archer, Stephanie (NIH/NICHD) [E]; "Huitema, Carolyn Petrie"; "Cunningham, Meg"; "Irene, Amanda"; "Zaterka-Baxter, Kristin"  
**Subject:** FW: Application to the GDB and the SUPPORT trial Committees  
**Date:** Tuesday, January 12, 2010 5:01:00 PM  
**Attachments:** Concept proposal 123109 - Luc P Brion.doc  
CPAP poster\_042708\_lpb.ppt

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We will discuss this on the upcoming GDB call - if needed this can be presented to the SC at the Feb. meeting  
Rose

-----Original Message-----

**From:** Luc Brion [mailto:Luc.Brion@UTSouthwestern.edu]  
**Sent:** Thursday, December 31, 2009 5:19 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Cc:** JACLYN LEVAN; Chul Ahn; Mambarath Jaleel; Myra Wyckoff; Pablo Sanchez; Rashmin Savani; Roy Heyne  
**Subject:** Application to the GDB and the SUPPORT trial Committees

Hi Rose:

Thank you for your help in preparing this application.

As discussed, this is concept proposal, which is an application to the Generic Database (GDB) Committee and to the SUPPORT Trial Committee.

I also attach the poster we had presented at the PAS meeting in 2008, in which we presented the preliminary data for this proposal.

Please let me know if you need any additional information.

Best regards and happy New Year,

Luc

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**Application to the Generic Database (GDB) Committee and  
to the SUPPORT Trial Committee**

**Impact of Initiating the SUPPORT trial on  
Management and Outcome  
of Gestational Age-Matched Non-Participants**

Jaclyn LeVan, DO  
Myra Wyckoff, MD  
Pablo Sánchez, MD  
Roy Heyne, MD  
Chul Ahn, PhD  
Mambarath Jaleel, MD  
Luc P Brion, MD (PI)

**For the NICHD Neonatal Research Network**

**Version: 12/31/09**

#### **A. ABSTRACT:**

We propose a retrospective analysis of GDB data to examine the impact of initiating the SUPPORT trial on patient management and outcomes among non-participant gestational age-matched preterm infants.

#### **B. STATEMENT of the PROBLEM**

The SUPPORT trial (Finer, submitted) was a randomized multicenter 2 X 2 factorial trial that enrolled preterm infants of 24 0/7ths weeks to 27 6/7ths weeks. Random allocation of airway management in the delivery room (early continuous positive airway pressure [CPAP], compared with endotracheal intubation and early surfactant), was not blinded. Lack of blinding could have affected health care providers' attitudes for or against CPAP vs. intubation in the delivery room when caring for non-study patients.

In a retrospective study conducted at Parkland Memorial Hospital we found that the frequency of delivery room intubation among gestational age-matched infants, which was high (87%) before the SUPPORT trial, significantly decreased to 52% ( $P < 0.001$ ) after initiation of the SUPPORT trial (Brion 2008), reaching a proportion similar to that in trial participants.

#### **C. HYPOTHESES:**

1. We hypothesize that initiation of the SUPPORT trial significantly reduced the frequency of intubation in the delivery room in non-participant gestational-age-matched preterm inborn infants, and that the decrease in the frequency of delivery room intubation in each neonatal research network (NRN) center depended on baseline rate.

2. We hypothesize that outcomes in non-participant gestational age-matched preterm inborn infants would be similar to those of participants of the SUPPORT trial.

Specifically, we hypothesize that those who were managed with CPAP would be similar to those in the CPAP arm of SUPPORT and those managed by intubation would be similar to the intubation/surfactant in the SUPPORT trial. We hypothesize that initiating the SUPPORT trial did not affect the rates of death or bronchopulmonary dysplasia (BPD, defined by the physiologic definition), death or retinopathy of prematurity (ROP), mortality rate, BPD (defined by the physiologic definition), BPD (defined by oxygen requirement at 36 weeks) and ROP among non-participant gestational age-matched preterm inborn infants, but reduced the frequency of artificial ventilation or death at day 7, the frequency of use of corticosteroids for BPD and mortality rate in the lower gestational age stratum.

#### **D. SPECIFIC AIMS:**

1. To determine the impact of initiating the SUPPORT trial on the incidence of endotracheal intubation in the delivery room in non-participant gestational age-matched preterm inborn infants

2. To determine the impact of initiating the SUPPORT trial on outcomes in non-participant gestational age-matched preterm inborn infants, including: incidence of death or BPD (defined by the physiologic definition), death or ROP, BPD [defined by the physiologic definition], BPD [defined by oxygen requirement at 36 weeks postmenstrual age], ROP, artificial ventilation or death at day 7, use of postnatal corticosteroids for BPD, mortality rate in the whole group and mortality rate in each stratum (24 0/7ths

weeks to 25 6/7ths weeks and 26 0/7ths weeks to 27 6/7ths weeks).

#### **E. RATIONALE/JUSTIFICATION:**

It would be informative to know if the practice of medicine could be affected by conducting a large randomized trial ongoing at a specific institution. Lack of blinding an intervention in a randomized controlled trial (RCT) may affect health care providers' attitudes for or against this intervention and their use of ancillary interventions of supplemental care or treatment (co-interventions) (Shulz 2002).

The intubation rate among extremely low birth weight infants was high (80%) in NRN centers in 1993-1997 (Shankaran 2002) and was still high at Parkland Memorial Hospital in 2005 (Brion 2008). However, there is substantial heterogeneity in therapy and outcome across NRN centers. Therefore, we expected that providers using endotracheal intubation as standard of care in the delivery room before the SUPPORT trial would progressively change their attitudes towards more CPAP and less intubation when they observed surviving trial participants who had been randomly allocated to CPAP. We would expect that the change in practice after initiating the SUPPORT trial would be inversely related with the baseline rate of intubation in each center.

A systematic review has shown that participation in RCTs is associated with similar outcomes to receiving the same treatment outside RCTs (Vist 2008). Therefore, we expect that outcomes in non-participant gestational age-matched preterm infants would be similar to those in trial participants. Thus, those who were managed with CPAP would be similar to those in the CPAP arm of SUPPORT and those managed by intubation would be similar to the intubation/surfactant in the SUPPORT trial.

#### **F. BACKGROUND/PREVIOUS STUDIES:**

Prophylactic and early natural surfactant administration at less than 2 hours of life significantly decreases mortality, air leak, and death or BPD in intubated preterm infants who are either at risk for respiratory distress syndrome (< 30 weeks of gestational age) or with respiratory distress syndrome (Soll 1997, Soll 1999). Several studies have suggested a benefit for early CPAP for preterm infants with respiratory distress syndrome, including a decrease in the need for mechanical ventilation among very preterm infants without an increase in morbidity (Avery 1987, Van Marter 2000, VanPee 2007, Jonsson 1997, Gitterman 1997) except for pneumothorax (summary relative risk 2.36; 95% confidence interval 1.25, 5.54) (Ho 2002). In one observational study, 76% of infants with a birth weight  $\leq$  1250 g who were initially treated with CPAP did not require intubation within 72 hours (Ammari 2005).

The NICHD Feasibility Trial (Finer 2004) was designed to determine the feasibility of randomizing ELBW infants of < 28 weeks' gestation to CPAP/positive end expiratory pressure (PEEP) or no CPAP/PEEP during resuscitation immediately after delivery, avoiding routine delivery room intubation for surfactant administration. Forty-five percent (47 of 104) of infants < 28 weeks' gestation required intubation for resuscitation in the delivery room. CPAP/ PEEP in the delivery room did not affect the need for intubation at birth or during the subsequent week. Overall, 20% of infants did not need intubation by 7 days of life.

Three multicenter RCTs have compared early CPAP with intubation in the delivery room. The IFDAS trial (Thomson 2001) showed no significant difference between 4 groups

(Elective intubation with surfactant administration and extubation within 2 hrs; early nasal CPAP with selective short intubation for surfactant administration; elective intubation with surfactant administration and artificial ventilation; selective intubation with surfactant administration and artificial ventilation based on clinical criteria) in total respiratory support until estimated date of delivery or discharge home (if earlier) and other neonatal complications. However, this study was not powered for any of the outcomes.

The COIN trial (Morley 2008) randomized 610 infants from 25 0/7 to 28 6/7 weeks gestation, who were able to breathe at 5 minutes of age and had evidence of respiratory distress. Infants were randomized, either to intubation and ventilation, or to CPAP at 8 cm H<sub>2</sub>O with intubation for those who met failure criteria. The primary outcome of death or BPD at 36 weeks was similar in the CPAP and in the intubation arms 33.9% vs. 38.9%, (odds ratio=0.58 to 1.12; P=0.19). Infants randomized to CPAP had a higher frequency of pneumothorax (9.1% vs. 3.0%, p=.001) and a lower frequency of death or need for oxygen at 28 days (odds ratio, 0.63; 95% CI, 0.46 to 0.88; P=0.006).

The NICHD SUPPORT trial (Finer, submitted; Carlo, submitted) was a randomized multicenter 2 X 2 factorial trial that enrolled preterm infants of 24 0/7 to 27 6/7 weeks gestation. The trial randomized 1310 infants in the delivery room, either to CPAP at 5 cm H<sub>2</sub>O and a protocol driven limited ventilation strategy, or to intubation and surfactant within 60 minutes of birth. All infants were also randomized to one of 2 blindly set ranges of oxygen saturation while receiving supplemental oxygen. The primary outcome, death or BPD (defined by the physiologic definition [see below]), was 49% in the CPAP group versus 54% in the surfactant group, (RR 0.91, 95% CI 0.82, 1.00, p=0.06 when adjusted for gestational age, center and familial clustering). There was a significantly lower mortality during hospitalization in the 24 to 25 weeks strata for the CPAP infants (24% vs 32%, RR 0.74, 95% CI 0.57, 0.98, p=0.03). More CPAP infants were alive and off mechanical ventilation by day 7 (p=0.019) and fewer required postnatal steroids for BPD (p < 0.001).

A retrospective study (Brion 2008) was conducted at Parkland Memorial Hospital to assess the impact of SUPPORT trial initiation in July 2005 on patient management and short-term outcomes in non-participant preterm infants. We analyzed two prospective databases: the resuscitation registry and the neonatal intensive care unit (NICU) database. We included all inborn infants with gestational age < 35 weeks during 3 epochs: 01/03-07/05, 07/05-12/05 and 01/06-11/07, corresponding, respectively, to 30 months that preceded enrollment into SUPPORT, the first 6 months of SUPPORT enrollment, and the next 23 months of SUPPORT enrollment. We excluded infants who received comfort care only and those enrolled in the SUPPORT trial. Analysis was done separately in 2 gestational age groups: < 28 weeks (i.e., similar gestational age as in the SUPPORT trial) and 28-34 weeks. Initiation of the SUPPORT trial was associated in both gestational age groups with significant decreases in percentage of delivery room intubation, in percentage of intubation in the delivery room or the NICU, and in percentage of surfactant administration. In multivariate logistic regression analysis taking into account gestational age and umbilical cord base excess, the rate of delivery room intubation significantly decreased in July 2005 (odds ratio 0.48, 95% CI 0.37, 0.63, p < 0.001). The percentage of delivery room CPAP increased significantly among infants < 28 weeks. The frequency of pneumothorax did not change significantly.



Infants < 28 wk GA (n=267)				
	1st Epoch N=160	2nd Epoch N=17	3rd Epoch N=90	P
Delivery room intubation	87%	77%	52%	<0.001
Delivery room CPAP	30%	47%	50%	0.004
Early NICU intubation	4%	6%	9%	0.28
Intubation in delivery room or NICU	90%	82%	61%	<0.001
Surfactant	78%	71%	52%	<0.001
Pneumothorax	8%	13%	10%	0.58

## G. METHOD/PROCEDURES:

### Study Design:

We propose a retrospective analysis of the GDB using a before/after design with one cohort of patients born before the date of initiation of the SUPPORT trial in each NRN center (which may vary from center to center from February to approximately July 2005) and a second cohort of patients after initiation of SUPPORT trial.

### Study Population:

#### Cohorts:

We propose to analyze patients in the NRN GDB born between 1/1/02 and 10/30/09, divided into two successive cohorts. The first cohort includes patients born during a 3-year period preceding the SUPPORT trial (from 01/02 until between 02/05 and 07/05 depending on the center). The second cohort includes patients born during the 4-year period of recruitment of the SUPPORT trial (from between 02/05 and 07/05 depending on the center and 02/09) and the 6-month period (02/09 – 10/09) between the end of SUPPORT trial recruitment and the October NRN Steering Committee meeting, when the results of the SUPPORT trial were announced.

#### Eligibility and exclusion criteria:

We will use eligibility and exclusion criteria identical to those in the SUPPORT trial.

Entry criteria: Eligible infants are 24 0/7ths to 27 6/7th weeks at birth by best obstetrical estimate, born without known malformations at an NRN center participating in the SUPPORT trial, for whom a decision had been made to provide full resuscitation. We will include all infants found in the GDB in centers that were included in the NRN during the entire study period.

Exclusion criteria: We will exclude infants enrolled in the SUPPORT trial. We will use the same exclusions as in the SUPPORT trial (as described above in entry criteria): infants with know malformations, outborn infants and those for whom a decision had been made to not provide full resuscitation.

#### Gestational age strata:

We will analyze the same strata as in the SUPPORT trial: 24 0/7ths weeks to 25 6/7ths weeks and 26 0/7ths weeks to 27 6/7ths weeks.

**Study Intervention:**

This is a retrospective study with before/after study design comparing preterm infants before and after the date of initiation of the SUPPORT trial in each participating center.

**Primary/Secondary Outcomes:**

**Primary outcome variables:**

1. The use of intubation in delivery room
2. The incidence of composite of death or BPD (physiologic definition), i.e., a primary outcome of the SUPPORT trial. The Physiologic Definition of BPD assigns the diagnosis of BPD to any infant who received more than 30% oxygen at 36 weeks or who required positive pressure support, but required demonstration of oxygen dependence by an attempt at oxygen withdrawal for infants who required < 30% oxygen at 36 weeks (Walsh 2003, Walsh 2004).
3. The incidence of composite of severe ROP (threshold retinopathy, surgical ophthalmologic intervention, or bevacizumab) or death before discharge from the hospital, i.e., a primary outcome of the SUPPORT trial. This outcome will be used as an internal control. We do not expect any change in this outcome after initiating the SUPPORT trial, because SUPPORT oximeters were blinded.

**Secondary outcome variables:**

1. Relationship between baseline intubation rate in each center and the intubation rate after initiating enrollment into the SUPPORT trial
2. Death or BPD (defined by oxygen requirement at 36 weeks)
3. BPD (defined by oxygen requirement at 36 weeks)
4. Severe ROP (threshold retinopathy, surgical ophthalmologic intervention, or bevacizumab)
5. Mortality rate before discharge
6. Intubation, death or BPD (physiologic definition), death or ROP, mortality rate before discharge in each gestational age stratum (24 0/7ths weeks to 25 6/7ths weeks and 26 0/7ths weeks to 27 6/7ths weeks)
7. Artificial ventilation or death at day 7
8. Use of corticosteroids for BPD
9. Pneumothorax
10. Air leak (pneumothorax, pulmonary interstitial emphysema)
11. Duration of artificial ventilation
12. Duration of supplemental oxygen
13. Proven necrotizing enterocolitis (stage 2 or greater)
14. Severe brain lesions on imaging (cystic periventricular leukomalacia, grade III or IV intraventricular hemorrhage)

Additional variables available in the GDB will be collected, matching as much as possible the tables included in the SUPPORT trial manuscripts (Carlo, submitted; Finer, submitted).

### **Sample Size/Statistical Analysis:**

#### Available sample size:

Data in GDB from January 2002 to December 2004 (DATA AND SAFETY MONITORING PLANS for the SUPPORT Trial) included 4055 infants with a gestational age 24 0/7 – 27 6/7. Assuming 10% exclusions, the first 3-year cohort (1/02-2/05) is estimated to yield approximately 3600 infants for analysis.

The GDB data for 2008 included 1738 inborn infants < 29 weeks gestational age. Therefore we estimate that the second 4 1/2-year cohort (2/05-10/09) would include approximately 1200 yearly infants with 24-27 7/7 weeks gestational age, or 5400 infants. Assuming 10% exclusions, this would yield 4860 infants. The SUPPORT trial enrolled 1316 infants in 4 years. Thus we estimate that the second cohort will yield 4860 – 1316, or approximately 3500 infants for analysis.

#### Uni- or bivariate analyses:

Univariate analyses will be done using chi-square analysis (Mantel-Haenszel chi-square for analyses by gestational age stratum) for categorical variables and using Student t-test for continuous variables.

The sample size calculations were based on available data [which could be updated if more recent data are available from the GDB]:

1. year 2000 NRN baseline occurrence data among 24 0/7 to 26 6/7 week gestational age infants of death or survival with BPD (by physiologic definition) at 36 weeks of 67%,
2. year 2000 NRN baseline occurrence data among 24 0/7 to 26 6/7 week gestational age infants of death or threshold retinopathy of 50%
3. years 1993-1997 intubation rate of rate of 80% among extremely low birth weight infants (Shankaran 2002).

For the primary outcome variables, we calculated power using chi-square analysis, and a conservative 1% level of significance (to account for three co-primary outcomes). The available sample size (n = 7000) gives a power >99% to find a significant change in delivery room intubation from 80% to 60%, a change in death or BPD (by physiologic definition) from 50% to 40% and a change in death or severe ROP from 67 to 57%.

For the analysis of mortality before discharge by gestational age stratum we calculated power using the Cochran-Mantel-Haenszel test, with a 5% level of significance, an odds ratio = 1 for the null hypothesis, an odds ratio = 0.81 for the alternative hypothesis, which was obtained by combining the two tables of the SUPPORT trial, and the software PASS2008. The available sample size (n = 7000) gives a power of 98.5% using these assumptions (Lachin 2000; Nam 1992; Woolson 1986).

The relationship between baseline intubation rate and intubation rate after SUPPORT trial initiation will be analyzed by scatter plot, regression analysis and chi-square analysis.

### Multivariate analyses:

Multivariate analysis of death or BPD (by physiologic definition), death and ROP and death will be done using adjusted odds ratios calculated using logistic regression analysis, taking into account the variables reported in Tyson's analysis in extremely low birth weight infants (Tyson 2008): exposure to antenatal corticosteroids, female sex, singleton birth, and higher birth weight (per each 100-g increment).

A time series analysis by center will be used to assess serial changes in frequency of intubation in the delivery room related to the following:

(1) Changes in the rate of intubation after initiating the Feasibility Trial or after initiating the COIN trial: Five centers participated in the Feasibility Trial from July 2002 to January 2003 (Finer 2004) and at least one center participated in the COIN trial (Morley 2008).

We hypothesize that initiating the Feasibility Trial or the COIN trial may have increased the rate of intubation in these centers and that the initiation of the SUPPORT trial may have had less effect on the rate of intubation. This would be consistent with our first hypothesis (i.e., an inverse relationship between baseline rate of intubation and the change in the rate of intubation after initiation of the SUPPORT trial). For this purpose we will compare the frequency of intubation before, during and after recruitment to the Feasibility Trial or the COIN trial, respectively, in these centers with the corresponding frequency in other centers that did not participate in either of these trials.

(2) Time of initiation of the SUPPORT trial. Based on the data in our preliminary study we anticipate that the frequency of intubation may decrease progressively during the first months after initiating the trial. For our preliminary study we had arbitrarily chosen a 6-month period; the small sample size did not allow us to determine exactly the timeframe of the change in intubation frequency after initiation of the SUPPORT trial. Time series analysis on the large GDB database will allow us to analyze serial changes in the rate of intubation after initiation of the SUPPORT trial, and sensitivity analysis will allow us to compare these changes in centers that did participate in the Feasibility Trial or the COIN trial with those in centers that did not participate in either of these trials.

(3) Time of ending recruitment to the SUPPORT trial. We will compare data during SUPPORT recruitment with those after the end of SUPPORT recruitment to assess possible selection bias due to lower rate of tocolysis and prenatal steroids among non-participants during SUPPORT trial recruitment. We will also conduct a sensitivity analysis, in which we will compare outcome results in centers that did participate in the Feasibility Trial or the COIN trial with those that did not participate in either of these trials. Another approach to check for possible bias (to be discussed with the SUPPORT trial subcommittee) would be to compare patients in the SUPPORT trial with those who were not enrolled.

Some patients who did not participate in the SUPPORT trial and were intubated in the delivery room may not have received surfactant. Based on the literature (Soll 1997, Soll 1999) we expect that those patients may have higher rates of mortality, air leak, and death or BPD than those who were intubated and received surfactant. We will therefore conduct a sensitivity analysis of outcome variables after excluding patients who were intubated but did not receiving surfactant.

**Limitations:**

Before/after study design is limited by confounding variables that may have occurred in addition to the variable of interest. This is why we will do a time series analysis by center and multivariate analyses.

It is possible that patients enrolled into the SUPPORT trial had different characteristics compared to non-participants. The latter may include more patients who were not eligible for tocolysis and prenatal steroids, both of which are associated with lower mortality (Shankaran 2002). For this reason we propose

- (1) To perform a logistic regression analyses including, in addition to variables reported in Tyson's analysis in extremely low birth weight infants (Tyson 2008), other variables known to affect mortality in extremely low birth weight infants (Shankaran 2002), i.e., also including Apgar score at 1 minute and use of tocolytic
- (2) To compare the rates of the primary outcome variables during the last year of SUPPORT trial recruitment with those after SUPPORT trial recruitment using time series analysis. However, sample size may not be sufficient for this analysis.
- (3) To consider a comparison of demographics, therapy and outcomes among patients in the SUPPORT trial with those of patients who were not enrolled.

**Consenting:**

Patients will be selected from GDB using criteria previously explained. We request a waiver for consent form as this research involves minimal risk to patients and collecting data in the GDB has been pre-approved by the IRB in each institution.

**Available Population/compatibility with other ongoing protocols**

The population available will be those patients in the GDB, corresponding to patients born between 1/01 and 10/09.

We are not aware of any conflict with other ongoing protocols.

**Projected Recruitment Time**

Since data collection for the proposed study will not start until after February 2010 (i.e., 4 months after the latest patient's birth), all requested data should already be available in the GDB.

**H. RISKS/BENEFITS:**

The benefit will be mostly for the society in that there is potential quality improvement of patient care in NICU. The risk is minimal and included accidental disclosure of medical information which is unlikely.

**I. BUDGET:**

Cost for access to GDB and SUPPORT database and statistical analysis

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# Delivery Room Practice Change

## Following the Initiation of the NICHD SUPPORT Trial

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### Abstract

**Background:** Conducting randomized trials may affect patient care of non-participants. At Parkland Memorial Hospital, we initiated an 07/01/05 our participation in the SUPPORT trial, a NICHD Neonatal Research Network 302 factorial multicenter trial in which infants with gestational age (GA) 24-27 6/7 weeks (wk) are randomized to 1) CPAP with a permissive ventilatory strategy begun in the delivery room (DR) vs. early surfactant administration and mechanical ventilation, and 2) two levels of oxygen saturation.

**Objective:** We designed this study to analyze whether initiation of the SUPPORT trial would be followed by increased use of CPAP vs. intubation in non-participants and whether these changes would be associated with changes in short-term respiratory outcomes.

**Design/Methods:** This retrospective study analyzed two prospective databases: the resuscitation registry and the NICU database. We selected all newborn infants with GA < 35 wk during 3 epochs: 01/03-07/05, 07/05-12/05 and 01/06-11/07. We excluded infants who received comfort care and those enrolled in the SUPPORT trial. Analysis was done separately in 2 GA groups: < 28 wk (same maximum as the SUPPORT trial) and 28-34 wk.

**Results:** The percentage of DR intubation decreased progressively in both GA groups (Table). In multivariable logistic regression analysis, DR intubation decreased in July 2005 (OR 5.49, 95% CI 0.37, 0.65, p < 0.001) and was associated with low GA, high cord base excess. The percentage of DR CPAP use increased among infants < 28 wk. The percentage of infants intubated within 4 hours of NICU admission did not change significantly, whereas that of surfactant administration decreased in the 3rd epoch in both GA groups. The frequency of pneumothorax did not change significantly.

	< 28 wk GA (n=267)		28-34 wk GA (n=1999)		P
	1 <sup>st</sup> Epoch	2 <sup>nd</sup> Epoch	1 <sup>st</sup> Epoch	2 <sup>nd</sup> Epoch	
DR Intubation	87%	82%	21%	20%	<0.001
DR CPAP	30%; 47%; 50%	0.004	34%; 36%; 36%	NS	
Early NICU Intubation	4%; 6%; 6%	NS	9%; 8%; 8%	NS	
Surfactant	78%; 71%; 62%	<0.001	12%; 16%; 9%	0.001	
Pneumothorax	8%; 13%; 10%	NS	4%; 5%; 4%	NS	

Exact test  
Conclusions: Initiation of the SUPPORT trial in our NICU was followed, for non-participant preterm infants, by more CPAP and less intubation in the DR and less surfactant administration, without a significant change in frequency of pneumothorax.

### Background

• Both insertion of an endotracheal tube (ETT) with IMV and nasal continuous positive airway pressure (CPAP) are considered standard of care in the DR for preterm infants ≥ 24 wk gestational age (GA).

• Previous experience in centers in which CPAP was introduced has shown a reduction in the need for ETT and IMV and in some studies in death or BPD (Wung 79, Jacobsen 93, Gitterman 97, Lindner 99, Poets 99, De Klerk 01, Narendran 03, Lopez 06, Miksch 08).

• In the COIN trial, a recent randomized controlled trial comparing CPAP with intubation in the DR, the group randomized to CPAP had the same odds of mortality or BPD as the control group, but more frequent pneumothoraces (Morley, NEJM 2008).

• Conducting randomized trials may affect patient care of non-participants. Since 1986, UT Southwestern Medical Center has belonged to the NICHD Neonatal Research Network (NRN) and has participated in numerous clinical trials, including the SUPPORT trial (The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants).

• At Parkland Memorial Hospital, on 07/01/05 we initiated our participation in the SUPPORT trial, a 2x2 factorial multicenter trial in which infants with GA 24-27 6/7 weeks (wk) are randomized to

- 1) CPAP with a permissive ventilatory strategy begun in the delivery room (DR) vs. early surfactant administration and mechanical ventilation, and
- 2) two levels of oxygen saturation (85-80% vs. 91-95%).

### Objective

- To analyze whether initiation of the SUPPORT trial was followed by:
  - increased use of CPAP vs. intubation in non-participants, and
  - associated changes in short-term respiratory outcomes.
- The primary hypothesis was that the frequency of intubation in the DR would decrease after initiation of the SUPPORT trial.

### Design/Methods

**Design:** Retrospective cohort study

**Material:** two prospective databases: the Parkland resuscitation registry and the NICU database, which are compliant with the Health Insurance Portability and Accountability Act and have been approved for use by the Institutional Review Board of the University of Texas Southwestern Medical Center at Dallas. The resuscitation registry was created in 1990 to gather information about resuscitation and DR stabilization for all infants admitted to the NICU. The NICU database was created in 1977 to gather information on all infants admitted to the NICU.

**Inclusion and exclusion criteria:** We selected all inborn infants with GA < 35 wk delivery at Parkland between 01/03 and 11/07 (see below, sample size). We excluded infants who received comfort care and those enrolled in SUPPORT.

**Outcome variables:** Main outcome variable: frequency of DR intubation. Secondary outcomes: CPAP in DR, intubation within 4 hours of life, intubation in DR or within 4 hours, surfactant use, pneumothorax

**Pre-planned groups:**

- Three epochs to assess the possibility of transient changes after initiating SUPPORT: before SUPPORT, the first 6 months of SUPPORT, and thereafter
- GA: < 28 wk (same maximum as SUPPORT trial) and 28-34 wk

**Statistical analysis:**

- Chi-square analysis and ANOVA
- Adjusted odds ratios (OR) and 95% confidence intervals (CI) calculated using logistic regression analysis after merging the 2nd and 3rd epochs.

**Sample size:**

For infants < 28 weeks: 97 patients needed in each group to detect a decrease in frequency of intubation from 80% to 40% (a 33% decrease) with a power of 80%.

### Results

**Patient description:**

- Among 2444 infants < 35 weeks GA, 133 received comfort care and 45 infants were recruited into the SUPPORT trial, leading to a total sample size of 2266.
- GA was not different in the 3 epochs (25.7, 25.4 and 25.5 wk for those < 28 weeks, and 32.0, 32.0 and 32.2 wk for those 28-34 weeks, respectively).

**Primary outcome:**

- The percentage of DR intubation decreased significantly in both GA groups (Tables 1 and 2).
- The odds of DR intubation significantly decreased at the initiation of SUPPORT (OR 0.48, 95% CI 0.37, 0.63, p < 0.001), taking into account GA (OR 0.59, 95% CI 0.56, 0.62) and umbilical cord base excess (0.94, 95% CI 0.91, 0.97).

**Secondary outcomes (Tables 1 and 2)**

- The percentage of infants intubated within 4 hours of NICU admission and the frequency of pneumothorax did not change significantly after initiation of the SUPPORT trial.
- < 28 wk GA (Table 1): the % of DR CPAP use increased and the use of surfactant decreased.
- > 28 wk GA (Table 2): the % of DR CPAP did not change significantly. The use of surfactant was higher during the 2<sup>nd</sup> epoch than during the 1<sup>st</sup> one, and lower during the 3<sup>rd</sup> epoch.

Table 1. Infants < 28 wk Gestational Age (n=267)

	1 <sup>st</sup> Epoch N=160	2 <sup>nd</sup> Epoch N=17	3 <sup>rd</sup> Epoch N=90	P
DR intubation	87%	77%	52%*	<0.001
DR CPAP	30%	47%	50%*	0.004
Early NICU Intubation (<4hrs of age)	4%	6%	9%	0.28
ETT in DR or NICU	90%	82%	61%*	<0.001
Surfactant	78%	71%	52%*	<0.001
Pneumothorax	8%	13%	10%	0.58

Table 2. Infants 28-34 wk Gestational Age (n=1999)

	1 <sup>st</sup> Epoch N=956	2 <sup>nd</sup> Epoch N=206	3 <sup>rd</sup> Epoch N=837	P
DR Intubation	21%	20%	12%*	< 0.001
DR CPAP	34%	36%	36%	0.71
Early NICU intubation	5%	8%	6%	0.22
ETT in DR or NICU	26%	27%	17%*	<0.001
Surfactant	12%	18%*	8%*	0.001
Pneumothorax	4%	5%	4%	0.80

First epoch: before SUPPORT; 2<sup>nd</sup> epoch: first 6 months of SUPPORT; 3<sup>rd</sup> epoch: subsequent 11 months; P value refers to chi-square analysis comparing all 3 epochs; \*, significantly different from 1<sup>st</sup> epoch (with Bonferroni correction)

### Conclusion

- Initiation of the SUPPORT trial was followed, in non-participant infants < 35 weeks of GA, by:
- Decreased rate of intubation in the DR and decrease rate of intubation in DR or NICU
  - Decreased use of surfactant (after a transient increase in the 28-34 wk GA group only)
  - Increased use of nasal CPAP in the DR among infants < 28 weeks only.
  - No significant change in frequency of pneumothorax

## **Higgins, Rosemary (NIH/NICHD) [E]**

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**From:** Finer, Neil <nfiner@ucsd.edu>  
**Sent:** Monday, January 11, 2010 5:28 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** Re: Concept proposal 123109 - Luc P Brion

Thanks I'd prefer a rewrite to a long rejection!!!  
Neil

On 1/11/10 1:00 PM, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> wrote:

> Thanks  
> Still no word from NEJM - our papers have been listed as "With editor"  
> for several weeks. I am hoping they are doing their re-write!!!| Rose  
>  
> -----Original Message-----  
> From: Finer, Neil [mailto:nfiner@ucsd.edu]  
> Sent: Monday, January 11, 2010 3:58 PM  
> To: Higgins, Rosemary (NIH/NICHD) [E]; 'Barbara Stoll'; Wally Carlo;  
> Rich, Wade  
> Subject: Re: Concept proposal 123109 - Luc P Brion  
>  
> Hello Rose  
> This trial does not plan to utilize any SUPPORT data but rather GDB  
> data for infants before and during SUPPORT. While it can be conceived  
> of as a SUPPORT related trial, its lack of use of any SUPPORT related  
> data or outcomes would cause me to be hesitant to make any judgment of  
> this proposal. This study is another way of looking at the study effect described by Barbara Schmidt et al.  
> I have no objection and believe that this study should go to the  
> Protocols Committee. I would be OK with having the SUPPORT Comm review  
> it as well. I think that this study will produce interesting data.  
> Neil

>  
>  
> On 1/11/10 10:21 AM, "Higgins, Rosemary (NIH/NICHD) [E]" <higginsr@mail.nih.gov> wrote:

>  
> Can you tell me how you would like this handled??

>  
> Thanks  
> Rose

>  
>  
> \_\_\_\_\_  
>  
> From: Higgins, Rosemary (NIH/NICHD) [E]  
> Sent: Monday, January 04, 2010 9:04 AM

> To: 'Barbara Stoll'; 'Finer, Neil'  
> Cc: Das, Abhik; Wallace, Dennis  
> Subject: Concept proposal 123109 - Luc P Brion  
>  
>  
> Barbara and Neil  
>  
> Here is a proposal from Luc Brion relevant to both GDB and SUPPORT.  
> He is willing to present this as a concept to the SC at the February  
> meeting. How would you like to see this handled? By both  
> subcommittees or by the steering committee??  
> Thanks  
>  
> Rose  
>

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "wcarlo@peds.uab.edu"  
**Subject:** Re: SUPPORT  
**Date:** Wednesday, January 06, 2010 8:27:09 PM

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Great!  
Thanks - I will keep my fingers crossed!!  
Rose

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**From:** Wally Carlo, M.D. <WCarlo@peds.uab.edu>  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; nfiner@ucsd.edu <nfiner@ucsd.edu>  
**Sent:** Wed Jan 06 19:45:30 2010  
**Subject:** RE: SUPPORT

Hi Rose:

I will let you know as soon as they send me any notification.

Wally

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**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Wed 1/6/2010 5:43 PM  
**To:** 'nfiner@ucsd.edu'; Wally Carlo, M.D.  
**Subject:** SUPPORT

Hi

Our papers have been "with the editor" for a little while now (a good sign, no outright rejection). The CPAP paper has had this designation since approximately 12/17 and the oximetry paper since at least 12/31 (I was out of the office from 12/27-30 and did not access the nejm author site during this time). If they are considering publication, the assigned editor usually does significant editorial review including presentation and grammar for the paper (re-write). The NEJM editorial board usually meets on Thursdays. I am currently travelling (b) (6). I am very much available for network issues. Please feel free to send me any correspondence from NEJM via email or to contact by phone if you want to discuss. My cell number is 703-395-(b) (6). I can also be reached at (b) (6) at 520-867-(b) (6) if needed. I am cautiously optimistic! Let's hope for the best!

Thanks for your unending efforts and commitment.

Rose

## Higgins, Rosemary (NIH/NICHD) [E]

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**From:** Finer, Neil <nfiner@ucsd.edu>  
**Sent:** Wednesday, January 06, 2010 8:30 PM  
**To:** Wally Carlo, M.D.; Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** RE: SUPPORT

Hi Rose and Wally

I have heard nothing – I will let you both know as soon as I hear anything at all

Be well

Neil

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**From:** Wally Carlo, M.D. [mailto:WCarlo@peds.uab.edu]  
**Sent:** Wednesday, January 06, 2010 4:46 PM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]; Finer, Neil  
**Subject:** RE: SUPPORT

Hi Rose:

I will let you know as soon as they send me any notification.

Wally

---

**From:** Higgins, Rosemary (NIH/NICHD) [E] [mailto:higginsr@mail.nih.gov]  
**Sent:** Wed 1/6/2010 5:43 PM  
**To:** 'nfiner@ucsd.edu'; Wally Carlo, M.D.  
**Subject:** SUPPORT

Hi

Our papers have been "with the editor" for a little while now (a good sign, no outright rejection). The CPAP paper has had this designation since approximately 12/17 and the oximetry paper since at least 12/31 (I was out of the office from 12/27-30 and did not access the nejm author site during this time). If they are considering publication, the assigned editor usually does significant editorial review including presentation and grammar for the paper (re-write). The NEJM editorial board usually meets on Thursdays. I am currently travelling (b) (6). I am very much available for network issues. Please feel free to send me any correspondence from NEJM via email or to contact by phone if you want to discuss. My cell number is 703-395 (b) (6). I can also be reached at (b) (6) 520-867 (b) (6) if needed. I am cautiously optimistic! Let's hope for the best!

Thanks for your unending efforts and commitment.

Rose

**From:** Susan Hintz  
**To:** [adas@rti.org](mailto:adas@rti.org)  
**Cc:** [Higgins, Rosemary \(NIH/NICHD\) \[E\]](mailto:higgins.rosemary@nih.gov)  
**Subject:** Fwd: 3.2. 05 DSMC Monitoring adrev  
**Date:** Tuesday, January 05, 2010 12:22:21 PM  
**Attachments:** [3.2. 05 DSMC Monitoring adrev.doc](#)  
[Requests for additional info.doc](#)

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Hi Abhik

In preparation for critically evaluating the SUPPORT Neuroimaging data analysis, I wanted to be armed with pre-SUPPORT and SUPPORT trial data to compare with the Neuroimaging sub-cohort. Rose sent me these tables you put together for the DSMC for baseline pre-SUPPORT adverse short term outcomes. However, in order to compare to the Neuroimaging cohort, we will need to look at an even narrower group. So, here are my requests:

- 1) For the group you looked at for the DSMC (inborn, January 1 2002 - December 31 2004), could I see rates of **grade 3 or 4, and grade 3 or 4 or cPVL among only survivors to 36 weeks**. That would more closely reflect what we have in the Neuroimaging cohort.
- 2) For the overall SUPPORT cohort, I have seen the tables from the 2 papers. But again, to more closely reflect what we have in the Neuroimaging cohort, I would like to see rates of **grade 3 or 4, and grade 3 or 4 or cPVL among only survivors to 36 weeks**.

I have attached a mock table.

Thanks Abhik.

Susan

X-IronPortListener: Outbound\_SMTP  
From: "Higgins, Rosemary (NIH/NICHD) [E]" <[higginsr@mail.nih.gov](mailto:higginsr@mail.nih.gov)>  
To: 'Susan Hintz' <[srhintz@stanford.edu](mailto:srhintz@stanford.edu)>  
Date: Tue, 5 Jan 2010 11:33:51 -0500  
Subject: 3.2. 05 DSMC Monitoring adrev  
Thread-Topic: 3.2. 05 DSMC Monitoring adrev  
Thread-Index: AcqOJN5sDd+WbMWsQ42dHaTltxDwfA==  
Accept-Language: en-US  
acceptlanguage: en-US

Content-Type: application/msword; name="3.2. 05 DSMC Monitoring adrev.doc"  
Content-Description: 3.2. 05 DSMC Monitoring adrev.doc  
Content-Disposition: attachment;  
filename="3.2. 05 DSMC Monitoring adrev.doc"; size=49152;  
creation-date="Tue, 05 Jan 2010 11:33:43 GMT";  
modification-date="Tue, 05 Jan 2010 11:33:51 GMT"

## The Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birth Weight Infants

### The SUPPORT Trial

#### DATA AND SAFETY MONITORING PLANS

##### **Adverse Events**

Data on the following potential adverse events that may be related to the study maneuver will be recorded and evaluated as part of continuous safety monitoring during the trial by RTI:

1. Air leak on admission to the NICU, or during the initial 14 days of life
2. The need for chest compressions, and/or epinephrine in the delivery room or NICU
3. The occurrence of severe IVH (Grades 3-4, Papile)
4. Death

As background information to help the DSMC monitor this trial, we are providing the following observational data from the network's generic database from January 1, 2002-December 31, 2004. The proportions listed give the overall rate of an adverse event in the network population for each of the gestational age subgroups. The range of proportions for each adverse event across centers is presented to provide an idea about the variation seen over the sites for these outcomes. It is hoped that this information will provide detailed background statistics regarding the population for study in this trial.

It is suggested by the SUPPORT Subcommittee that consideration for a recommendation to stop the trial based on a safety concern would need to involve a statistically significant difference in an adverse event between the treatment groups, and that the occurrence of the adverse event is outside of the limits of plausibility for that specific event according to the most recent Neonatal Research Network data presented below.

Table 1: Overall proportion, variability and ranges across network centers for infants with gestational age 24-27 weeks at birth

Variable	N	Proportion	SD	Range of proportion across centers
IVH grade (3 or 4)	3753	0.237	0.43	0.108-0.371
DR Chest compressions	4050	0.108	0.31	0.035-0.258
Pneumothorax	3861	0.087	0.29	0.023-0.195
Death within first 14 days	4055	0.159	0.37	0.092-0.325

Table 2: Overall proportion, variability and ranges across network centers for infants with gestational age 24-25 weeks at birth

Variable	N	Proportion	SD	Range of proportion across centers
IVH grade (3 or 4)	1599	0.327	0.47	0.153-0.520
DR Chest compressions	1805	0.133	0.34	0.029-0.340
Pneumothorax	1667	0.116	0.32	0.026-0.239
Death within first 14 days	1808	0.249	0.44	0.124-0.485

Table 3: Overall proportion, variability and ranges across network centers for infants with gestational age 26-27 weeks at birth

Variable	N	Proportion	SD	Range of proportion across centers
IVH grade (3 or 4)	2154	0.170	0.38	0.022-0.263
DR Chest compressions	2245	0.088	0.29	0.034-0.200
Pneumothorax	2194	0.066	0.25	0.022-0.155
Death within first 14 days	2247	0.086	0.28	0.039-0.160

**Note:** The sample includes infants that were born on or after Jan 1, 2002 that have reached status. SD denotes standard deviation.

Comment [h1]:

**Data Safety Monitoring Committee**

The Data Safety Monitoring Committee will review the progress of the study with respect to efficacy and adverse events in a sequential fashion by using interim monitoring boundaries. O'Brien-Fleming<sup>1</sup> boundaries will be used for efficacy monitoring and will be constructed for four looks at the data at 25%, 50%, 75%, and 100% of outcome assessment. Pocock boundaries will be used for adverse event monitoring and will be viewed after every 30 infants have been enrolled. A special adverse event form will collect the information so that it may be entered into the data base in a timely fashion.



Request for additional information re: SUPPORT severe CUS findings

**1) Among inborn, 24-27 week EGA infants born January 1, 2002 to December 31, 2004 ("pre-SUPPORT"), who SURVIVED to 36 weeks PMA**

Overall proportion, variability and ranges across network centers for infants with gestational age 24-27 weeks at birth

Variable	N	Proportion	SD	Range of proportion across centers
IVH grade (3 or 4)				
IVH grade (3 or 4) OR cPVL				

**2) Among SUPPORT overall cohort who SURVIVED to 36 weeks PMA**

Overall proportion, variability and ranges across network centers for infants with gestational age 24-27 weeks at birth

Variable	N	Proportion	SD	Range of proportion across centers
IVH grade (3 or 4)				
IVH grade (3 or 4) OR cPVL				

**From:** Higgins, Rosemary (NIH/NICHD) [E]  
**To:** "Pablo Sanchez"  
**Subject:** RE: SUPPORT data  
**Date:** Tuesday, January 05, 2010 11:16:00 AM

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You ma present the information in a confidential manner

Thanks  
Rose

-----Original Message-----

**From:** Pablo Sanchez [<mailto:Pablo.Sanchez@UTSouthwestern.edu>]  
**Sent:** Tuesday, January 05, 2010 10:38 AM  
**To:** Higgins, Rosemary (NIH/NICHD) [E]  
**Subject:** SUPPORT data

Hi Rose--happy new year! thanks for the card and esp the picture--it was nice to associate your family members with faces...I wanted to ask you if it is OK to present the SUPPORT data to our neo group--I know that they are confidential and will tell them so --thanks--pablo