

NICHD/FDA Newborn Drug Development Initiative

Workshop I

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Workshop Summary

DRAFT

U.S. Department of Health and Human Services

**National Institute of Child Health and Human Development
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Executive Summary

Background

The National Institute of Child Health and Human Development (NICHD) and the U.S. Food and Drug Administration (FDA) convened the first workshop of the Newborn Drug Development Initiative (NDDI) to help frame issues and challenges in the design and conduct of clinical trials of drugs in preterm infants and neonates. Neonatologists, subspecialists, pediatric clinical pharmacologists, biostatisticians, representatives of industry, and representatives of the two sponsoring agencies gathered to provide input in the first step in a continuum of activities designed to help the NICHD and the FDA implement the Best Pharmaceuticals for Children Act (BPCA). This legislation was enacted in 2002 to establish a process for studying on-patent and off-patent drugs for use in pediatric populations and to improve pediatric therapeutics through collaboration on scientific investigation, clinical study design, weight of evidence, and ethical and labeling issues.

As part of the effort to implement BPCA provisions, the NICHD is collaborating with the FDA on the NDDI, which will explore innovative approaches to improving clinical trial design for preterm and full-term neonatal populations with the goal of having more drug therapies studied and appropriately labeled for safe and effective use in these populations. This work is needed because few drugs have been labeled for use in newborns, especially premature infants. More than 90 percent of drugs administered in neonatal intensive care units are administered without adequate labeling of these drugs in this special population. The paucity of suitable, licensed neonatal formulations and their use without bioavailability information can result in dosing errors.

Workshop Objectives

Objectives for the NDDI Workshop I included the following:

- Identify diseases or conditions that are unique to neonates in etiology, pathophysiology, clinical manifestations, and clinical or laboratory measurements.
- Identify newborn conditions in which the response to therapy in newborns or preterm infants differs from that in older children and adults.
- Identify drugs for which no appropriate formulation is available for term and preterm infants.
- Harmonize the design, methodology, performance, and monitoring of academic and industry-sponsored studies to allow the use of data in support of labeling.

An additional objective for the work groups was to develop publications as potential resources for the FDA, industry, and the National Institutes of Health (NIH) and non-NIH networks that might want to conduct clinical trials to study drugs in neonatal populations. The work group publications will serve as the scientific underpinnings of such studies by providing the following information:

- Definitions for the most common neonatal conditions and diseases, with inclusion and exclusion criteria
- Outcome measures (e.g., primary and secondary clinical efficacy endpoints) and potential biomarkers of efficacy and toxicity
- Consideration of extrapolation issues (e.g., the applicability of outcome measures for similar conditions in older children and adults)

Work Group Recommendations

Four work groups focused on the therapeutic areas of pain control, pulmonary, cardiovascular, and neurological conditions. Each therapeutic work group addressed two or more conditions in preterm and/or term neonates. Two additional work groups addressed ethics and drug prioritization. The work groups were asked to propose a framework for potential clinical trial designs based on the background papers. It was acknowledged that not all groups would be able to identify or agree on all of these aspects of clinical trial design for their therapeutic area. However, the goal was to suggest opportunities, strategies, and considerations for designing and conducting clinical trials that would help build a better understanding of therapeutics for both preterm and full-term neonates.

Cardiology

The Cardiology Work Group's mandate was to focus on the use of dopamine (DA) and dobutamine (DOB) in low birth weight neonates. The group considered two neonatal populations—very low birth weight infants with cardiac instability and neonatal postoperative cardiac patients. The work group was unable to propose definitive frameworks for clinical trials, but it reported the following results of its work:

- The work group concluded that it needed more input from neonatologists about the study design issues before it could proceed with the framework of a clinical trial for the study of DA and DOB in low birth weight neonates. The major unresolved issues included whether to design a placebo-controlled study, whether to use steroids in the rescue therapy, and what to use as target blood pressure ranges. However, the work group did conclude that the study of inotropes in neonates would be a prevention trial that would include two different designs with two different interventions studying premature infants with a birth weight of 400 to 1,000 grams.
- Although the Cardiology Work Group did not present a proposed clinical trial framework for neonatal postoperative cardiac patients, members agreed that a design for studying vasoactive agents would be a superiority trial that would compare two established agents (e.g., DA or epinephrine, combination therapy) without using a placebo. The group decided to discuss an appropriate primary endpoint with members of the Pediatric Cardiac Intensive Care Society, which will hold a biannual meeting in December.

Neurology

The Neurology Work Group decided to focus its discussion on two areas—seizures in the newborn and hypoxic-ischemic encephalopathy and neuroprotection. The work group presented the following suggestions about clinical trial frameworks:

- After exploring three possible frameworks for clinical trials of phenobarbital (PB) in the treatment of electroencephalographic neonatal seizures (ENS), the work group proposed a multicenter, placebo-controlled, blinded study of PB versus placebo in a homogeneous population of term infants (≥ 37 weeks chronological age) at high risk for ENS. The study would use continuous video-electroencephalogram monitoring to establish the presence and number of seizures (subclinical or clinical).
- The Neurology Work Group was unable to develop a definitive framework for the study of neuroprotective strategies for neonatal encephalopathy. However, the work group identified key elements for a potential clinical trial framework comparing hypothermia with hypothermia “plus” for moderate to severe encephalopathy.

Pain Control

The Pain Control Work Group identified three prioritized areas of pain control in newborns: pain, procedural pain, and pain associated with mechanical ventilation. Work group recommendations included the following:

- Clinical trials for perioperative pain would include separate designs for postoperative analgesia and general anesthesia. Trials for postoperative analgesia would include one group that is given placebo and one group that is given a single or multiple dose of the drug. Both groups would have immediate access to rescue analgesia with an intravenous opioid in small incremental doses. Studies of general anesthesia would compare old agent(s) with new agent(s), with titration to minimal alveolar concentration.
- The proposed framework for the study of pain control in mechanically ventilated preterm newborns was a randomized, double-blind, placebo-controlled trial of analgesic with or without sedative in premature newborn infants who are stratified into three groups by birth weight, ranging from 500 to 1,500 grams.
- The proposed design for procedural pain was a blinded randomized controlled trial (RCT) of heelstick pain in neonates using current therapies and three study groups stratified according to gestational age (GA).

Pulmonary

The Pulmonary Work Group identified two conditions that were unique to the newborn: apnea of prematurity (AOP) and bronchopulmonary dysplasia (BPD). The work group presented the following recommended frameworks:

- The work group proposed a randomized, blinded, multicenter, placebo-controlled trial to study whether there is any difference in outcome between patients managed with a specific drug (e.g., caffeine) for AOP versus placebo. Neonatal groups would be stratified by birth weight, ranging from < 800 grams to 1,500 grams.
- Components of the work group's proposed BPD clinical trial framework would vary according to the different phases of the disease. However, the overall design would include a placebo-controlled RCT, with no crossover trials, in infants of less than 32 weeks GA.

Ethics

Members of the Ethics Work Group were assigned to the various work groups focused on therapeutic areas. Although issues and proposed study designs varied among the different work groups, the overall impression of the work group members was that the ethical issues involved in designing studies that seek to validate current or emerging medical practice are solvable in one way or another. The Ethics Work Group identified the following major themes emerging from the discussions of the other work groups:

- Whether a clinical trial study is scientifically necessary to conduct the research in neonates
- How to balance risks and potential benefits in neonate clinical trials (e.g., component analysis of risks, equipoise and the choice of control group, ethics of "off-label" practice)
- The process of obtaining parental permission
- Efficiency and effectiveness of review by institutional review boards
- Multicenter collaboration

Drug Prioritization

The goal of the Drug Prioritization Work Group was to determine factors that identify which drugs are most important for study in neonates, especially when resources are limited. A secondary goal was to develop a list of criteria that would help to inform FDA review committees, which often lack pediatric and neonatal input regarding the evaluation of new drugs. The Drug Prioritization Work Group used five categories (i.e., disease/indication, evidence, drug, feasibility, ethics) to describe factors that it considered important for studying drugs in newborns. Within these categories, the work group identified 23 factors that favor studies in neonates. The work group proposed testing the discriminatory value of these criteria for

studying a drug against prioritization by a group of experienced neonatologists, then developing a shorter list of factors that can prioritize drugs effectively.

Conclusion

Workshop participants noted the areas of overlap among clinical trial frameworks that were presented at the meeting. For example, several frameworks identified similar research questions, study design issues, study populations, study drugs, and/or outcomes. These similarities raised questions about the possibility of enrolling the same patients in multiple studies and the scientific and ethical issues related to this practice. One challenge for the NDDI will be to look at common elements among the work groups' proposed frameworks and to use that information to develop an appropriate design that could be applied to a number of different drugs in certain therapeutic areas.

Introduction

On March 29–30, 2004, the National Institute of Child Health and Human Development (NICHD) and the U.S. Food and Drug Administration (FDA) convened the first workshop of the Newborn Drug Development Initiative (NDDI), in Baltimore, Maryland. The workshop was designed to help frame issues and challenges in the design and conduct of clinical trials of drugs in preterm infants and neonates. Workshop participants included neonatologists with expertise in specific subject areas, subspecialists with expertise in specific diseases, pediatric clinical pharmacologists, biostatisticians, representatives of industry, and representatives of the two sponsoring agencies. The workshop is one step in a continuum of activities designed to help the NICHD and the FDA implement recent congressional legislation regarding the testing of drugs given to children.

Donald Mattison, M.D., from the NICHD; Rosemary Roberts, M.D., FAAP, from the FDA; NDDI co-chair George Giacoia, M.D., from the NICHD; and workshop chair Eduardo Bancalari, M.D., welcomed participants and provided information on the background and purpose of the workshop.

The Newborn Drug Development Initiative

The Best Pharmaceuticals for Children Act (BPCA) was enacted into law on January 4, 2002, to establish a process for studying on-patent and off-patent drugs for use in pediatric populations and to improve pediatric therapeutics through collaboration on scientific investigation, clinical study design, weight of evidence, and ethical and labeling issues. The BPCA directs the National Institutes of Health (NIH) to issue contracts to test in children off-patent prescription drugs already approved for adults. Within the NIH, the Director of the NICHD has the lead authority and responsibility for establishing and conducting the pediatric drug development activity.

As part of the effort to implement BPCA provisions, the NICHD is collaborating with the FDA on the Newborn Drug Development Initiative. This initiative will explore innovative approaches to improving clinical trial design for preterm and full-term neonatal populations with the goal of having more drug therapies studied and appropriately labeled for safe and effective use in these populations.

There are several compelling reasons for establishing the NDDI. Perhaps most important is the fact that few drugs have been labeled for use in newborns, especially premature infants. More than 90 percent of drugs administered in neonatal intensive care units (NICUs) are administered without adequate labeling of these drugs in this special population. The paucity of adequate trials in neonatal populations is due in part to the unique physiology and developmental diversity of newborns, as well as differences in neonatal drug responses in terms of efficacy and toxicity. Outcome measures that have been validated in neonatal populations also are lacking. Specifically, the relationship between clinical endpoints and outcomes, particularly outcomes linked to meaningful benefits, has not been characterized. Moreover, variable study designs do not permit comparison and meta-analysis between studies. Finally, few suitable neonatal

formulations have been licensed, leading to their use without bioavailability information as well as to dosing errors.

Several research needs have been identified in the preclinical and clinical phases of the drug development process in neonates and preterm infants. For example, a lack of prior experience in neonates hampers the preclinical process. Although some cell cultures can be used with *in vitro* systems to define the mechanism of action of some drugs, researchers need to determine whether these [cell cultures? systems? mechanisms?] are different from those in adults. In addition, it has been difficult to find juvenile animal models, both mature and premature, that are analogous to human infants. Needs in the clinical process include age-appropriate formulations for both oral and intravenous (IV) drugs, parameters to use in pharmacokinetic (PK) and pharmacodynamic (PD) studies that will correlate with clinical endpoints or outcomes in neonatal populations, efficacy determination, and adverse event characterization.

The design of clinical trials for newborns needs to take into consideration FDA requirements about safety and effectiveness for labeling products for newborns. Safety and effectiveness usually need to be proven by two adequate, well-controlled, and multicenter trials. However, only one trial might be sufficient if other evidence, such as published medical literature or approval of the product for a similar condition in adults, supports safety and effectiveness.

The NICHD and the FDA envision the NDDI as providing a framework for BPCA studies and clinical studies of new drugs in newborns. The initiative also provides a unique opportunity to bridge the gap between academia and Federal regulators, to harmonize academic studies of drugs in newborns, and to promote research and identify areas of discovery in newborn therapeutics.

The NDDI Workshop I

The NDDI Workshop I is the first in a series of meetings that will help examine the state-of-the-science and define research priorities for specific diseases or conditions in neonates. The 5-year plan for the NDDI involves five phases. The first phase of the initiative began with the formation of work groups in February 2003 and concludes with the current workshop. This first phase has addressed ethics and drug prioritization as well as the four therapeutic areas of pain control and pulmonary, cardiovascular, and neurological diseases or conditions. Subsequent phases will involve additional work groups and workshops focused on other therapeutic areas as well as a final evaluation phase.

Objectives for Workshop I included the following:

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- Identify newborn conditions in which the response to therapy in newborns or preterm infants differs from that in older children and adults.
- Identify drugs for which no appropriate formulation is available for term and preterm infants.

- Harmonize the design, methodology, performance, and monitoring of academic and industry-sponsored studies to allow the use of data in support of labeling.

An additional objective for the work groups was to develop publications as potential resources for the FDA, industry, and NIH and non-NIH networks that might want to conduct clinical trials to study drugs in neonatal populations. The work group publications will serve as the scientific underpinnings of such studies by providing the following information:

- Definitions for the most common neonatal conditions and diseases, with inclusion and exclusion criteria
- Outcome measures (e.g., primary and secondary clinical efficacy endpoints) and potential biomarkers of efficacy and toxicity
- Consideration of extrapolation issues (e.g., the applicability of outcome measures for similar conditions in older children and adults)

The clinical trials issue papers developed by work group members over the previous 14 months constitute the foundation for the work group publications and workshop discussions. The work groups were asked to propose a framework for potential clinical trial designs based on those background papers. The proposed clinical trial frameworks were to include information such as the suggested study population (e.g., stratification, age at study), biomarkers (e.g., for diagnosis, efficacy, and toxicity), drug prioritization and formulations, ethical and feasibility issues, treatment endpoints, outcome variables, and long-term outcomes. However, it was acknowledged that not all groups would be able to identify or agree on all of these aspects of clinical trial design for their therapeutic area. Moreover, the goal was not to achieve consensus but to suggest opportunities, strategies, and considerations for designing and conducting clinical trials that would help build a better understanding of therapeutics for both preterm and full-term neonates.

On the first day of the workshop, each therapeutic work group gave a plenary presentation on the clinical trial issues and potential clinical trial frameworks it would address. Then each group met in concurrent breakout sessions that also included reactors to the clinical trial issue papers, representatives of the Ethics Work Group and the Drug Prioritization Work Group, co-facilitators from the NIH and the FDA, and members of the general public. The Pulmonary Work Group divided into separate breakout sessions on apnea and bronchopulmonary dysplasia (BPD).

On the second day of the workshop, the four therapeutic work groups presented highlights of their discussions of clinical trial issues. The Ethics Work Group summarized major themes that emerged from the breakout discussions. The Drug Prioritization Work Group suggested factors that could help identify which drugs are most important for study in neonates.

This report summarizes the issues, proposed clinical trial frameworks, and other suggestions presented by the work groups to the full assembly of workshop participants. Appendices A–D contain summaries of the breakout discussions, which provide additional details on work group

deliberations and rationales for their recommendations. Appendix E contains the Participant List. Appendix F presents a list of abbreviations and acronyms used in the workshop summary.

The views presented in the workshop did not necessarily reflect those of the FDA. The workshop discussions about designing clinical trials in newborns should not be construed as an agreement or guidance from the FDA. Drug development and clinical trial design should be discussed with the relevant review division within the FDA.

Therapeutic Areas

Cardiology

The Cardiology Work Group's mandate was to focus on the use of dopamine (DA) and dobutamine (DOB) in low birth weight neonates. The group focused on two neonatal populations—very low birth weight (VLBW) infants with cardiac instability and neonatal postoperative cardiac patients.

Preterm Infants and Cardiac Instability

Presented by Billie Lou Short, M.D.

Background

Neonates with extremely low birth weight can experience cardiovascular instability brought on by cardiovascular changes or illnesses in the first month after birth. This instability, evidenced by low blood pressure, is most often treated with inotropes, although little is known about the mechanisms by which these drugs work in neonates. In fact, definitive data are lacking on normative values of blood pressure as well as other hemodynamic measures in neonates.

The patient population with cardiovascular instability generally comprises VLBW infants who are less than 28 weeks gestational age (GA) with a birth weight of less than 1,000 grams and a normal heart structure. These infants have significant cardiac and respiratory instability in the first 2 to 3 weeks of life, with clinical manifestations such as hypertension, hypoxia, acidosis, and end organ failure.

Although there is empiric use of inotropes in treating neonates, the labeling of these drugs is inadequate for this population. Inotropes such as DA and DOB raise blood pressure in neonates, but it is unclear whether blood pressure always correlates with cardiac output or tissue perfusion. Use of inotropes also carries some risk of intraventricular hemorrhage (IVH) and necrotizing enterocolitis (NEC).

Study Design Issues

The Cardiology Work Group identified the following key issues that must be taken into consideration when designing studies of inotropes in preterm infants:

- The cause of cardiovascular instability in VLBW infants is not fully understood and can be multifactorial, including factors such as poor ventricular function and immature myocardium, poor peripheral vasoregulation, and acute blood loss.
- Definitive data for normative values for hemodynamic measures in VLBW infants are lacking.
- Most measures of cardioinstability (e.g., cardiac output) have not been validated in neonates, have limited availability, or may not be feasible with current techniques (e.g., pulmonary arterial catheterization). Consequently, blood pressure remains one of the major parameters to follow. However, it is unclear whether blood pressure reflects cardiac output and adequate tissue perfusion.
- Information is lacking on what constitutes adequate blood pressure for neonates, especially VLBW infants.
- Surrogate markers of cardiovascular instability and end organ injury include NEC, IVH, retinopathy of prematurity (ROP), neurodevelopmental outcome, and death.
- None of the current treatments for hypotension, including inotropic agents (e.g., DA, DOB), have been well studied in the VLBW population. Safety and efficacy studies in this group are lacking.
- Labeling for the use of inotropic agents as therapeutic agents is inadequate.
- Research data are lacking on the cardiovascular response to commonly used therapies, including inotropic agents.
- Although DA and DOB are commonly used, studies of treatment with both drugs are needed to answer important questions. Results from small trials indicate that DA improves blood pressure. Recent studies indicate that DOB improves cardiac output and may improve outcome, even though it does not have as great an effect on blood pressure as achieved by DA.
- Some data suggest that hypotension (low superior vena cava [SVC] flow) is associated with IVH or periventricular leukomalacia (PVL). Other data suggest that hypotension therapy is associated with increased IVH/PVL.
- Data from randomized trials in adults treated with vasoactive agents show unexpected adverse outcomes, including mortality.
- The key research question was whether treatment in neonates is protective or harmful.

Proposed Clinical Trial Framework

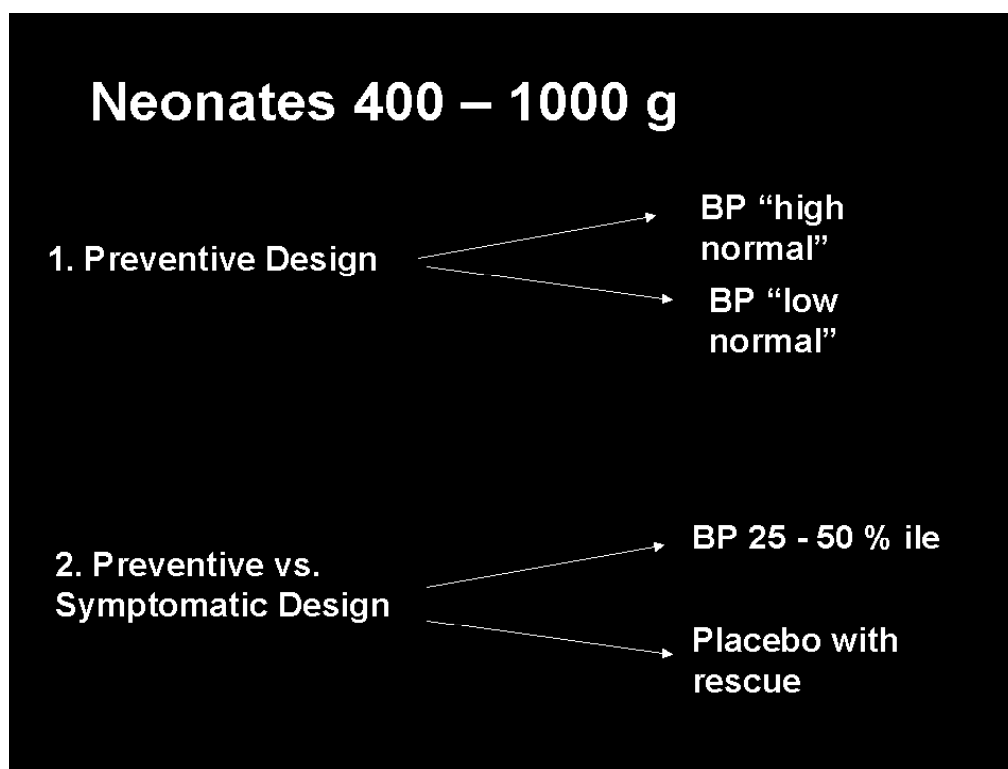
The Cardiology Work Group decided that it was not ready to finalize a clinical trial design. The major unresolved issues included whether to design a placebo-controlled study, whether to use steroids in the rescue therapy, and what to use as target blood pressure ranges. However, the work group did conclude that the study of inotropes in neonates would require a complicated trial design that would need to include the elements listed in the text box below.

FRAMEWORK FOR THE STUDY OF INOTROPES IN PRETERM INFANTS WITH CARDIAC INSTABILITY

- **Hypotheses**—The following hypotheses should be studied:
 - Hypotension in neonates is associated with increased risk of adverse outcomes.
 - Preventing hypotension is protective.
- **Pilot study**—A pilot study in one or two centers would be needed to work out issues (e.g., bedside monitoring) and finalize the design.
- **Study population**—Premature infants with a birth weight of 400 to 1,000 grams
- **Enrollment**—Because the trial would be preventive (i.e., prevent hypotension in one group), prenatal enrollment of infants would be essential.
- **Procedures**—An arterial line would be needed to determine effects on blood pressure.
- **Exclusion criteria**—The work group proposed the following exclusion criteria:
 - Severe congenital anomaly
 - Congenital heart diseases (except patent ductus arteriosus [PDA])
 - Small for gestational age (SGA) or intrauterine growth retardation (IUGR)
- **Primary outcome**—The primary outcome would be the combined endpoint of mortality or a severe neurological outcome such as IVH at day 7 or PVL at day 28 or discharge.
- **Secondary outcomes**—The following indicators of end organ perfusion abnormality would be secondary outcomes:
 - NEC
 - ROP
 - BPD
 - Long-term neurodevelopmental outcomes (at 2 years)
 - Other adverse events that could be caused by the drugs (e.g., arrhythmia, hypertension, seizures)

- **Additional Outcomes**—Additional measures that would be interesting to study include the following:
 - SVC flow
 - Cerebral oxygenation
 - Magnetic resonance imaging (MRI) scans of brain development
 - Pulse oxygen perfusion index
 - PK/PD data
- **Intervention**—The prevention trial would include two different designs with different interventions. (See Figure 1.)
 - A preventive design would be randomized to groups with high normal blood pressure and low normal blood pressure, with values for the blood pressure categories to be determined. These groups would then be treated with either DA or DOB.
 - A prevention versus symptomatic design would include one arm that would target blood pressure as a preventive measure (i.e., keep blood pressure stable within a range to be determined, probably between 10th and 20th percentile of data in the literature) and the other arm that would titrate with a placebo with

Figure 1. Prevention Trial Designs



Unanswered Study Design Questions

The Cardiology Work Group was left with the following unanswered ethical questions about the study design:

- After consideration, the “high entry group” was too high and had the potential to cause harm. This level will need to be adjusted after further discussion.
- The issue of whether a placebo-controlled trial is ethical when therapy is well accepted needs further consideration. If equipoise exists in the field of neonatology, it would provide an opportunity to do a cleaner study using a placebo.
- Obtaining informed consent will involve dealing with mothers who are going into premature labor and probably obtaining consent from both parents.

Questions for Workshop Participants

The Cardiology Work Group concluded that it needed more input from neonatologists about the study design issues before it could proceed with the framework of a clinical trial for drug study in this area. The work group decided to seek information from other neonatal colleagues around the country. As a first step, the work group posed a set of questions to the assembly of workshop participants. Input from neonatologists in the audience addressed the following questions:

- **What drug do you use first line—epinephrine, dopamine, or dobutamine?** Dopamine appeared to be more acceptable as a first-line drug than dobutamine. Most of the audience thought that epinephrine would be an acceptable rescue drug. No one thought that epinephrine would *not* be acceptable as a rescue drug.
- **Would you use hydrocortisone to treat refractory hypotension?** A great number of neonatologists would use hydrocortisone to treat refractory hypotension. About half of the responders would be comfortable following a protocol for a hydrocortisone treatment.
- **Would you perform a placebo-controlled trial in this setting if rescue occurred with a blood pressure below 20 mm Hg (400–750 gm)?** Participants were nearly evenly divided regarding whether they would be willing to perform a placebo-controlled trial that would randomize to saline versus DA or DOB.
- **Would you conduct a trial that used clinical signs only (e.g., poor cap refill, oliguria, acidosis) as the determining factor for study entry with no use of an arterial line/blood pressure measurement?** More neurologists than anticipated indicated they would feel comfortable with a clinical-signs-only trial design. Many participants were undecided on this issue.
- **Would you allow blood pressure in 400- to 750-gram babies to drop below 20 mm Hg before starting a rescue drug?** “A handful” of neurologists would allow blood pressure to drop to this level. Many participants were undecided on this issue.

Next Steps

The Cardiology Work Group plans to send a questionnaire to members of the Neonatal Network and poll people who come to the “Shock Club.” After receiving input from these neonatologists, the work group will determine which clinical trial framework it will recommend.

Cardiac Dysfunction in Postoperative Neonates

Presented by Stephen Roth, M.P.H.

Background

The second population studied by the Cardiology Work Group was the approximately 32,000 babies born yearly in the United States with congenital heart disease. About one-third of the neonates with this disease need some kind of intervention—usually reparative or palliative surgery with cardiopulmonary bypass. However, cardiopulmonary bypass can cause significant postoperative cardiovascular dysfunction and arrhythmia in neonates. The issue of hypovolemia usually arises in these patients because of problems with bleeding and capillary leak syndrome. Vasoactive agents such as inotropes and afterload-reducing drugs are used most often to treat neonates in these cases. The rationales for a focus on vasoactive agents in postoperative cardiac patients include:

- The scientifically established association between low cardiac output and increased morbidity and mortality after cardiac surgery
- Evidence that inotropic agents (e.g., DA, epinephrine) and afterload-reducing agents (e.g., milrinone, nitroprusside) increase cardiac output
- Routine use of these agents, based on a belief in a favorable benefit-to-risk ratio, despite a lack of scientific proof regarding their efficacy and safety

Compared with babies being treated for cardiovascular instability, neonates undergoing cardiac surgery tend to be more mature and larger (1.5–2.0 kg), especially those undergoing surgery with cardiopulmonary bypass. Low systemic blood pressure in these patients is more likely to be related to postoperative myocardial dysfunction with vasoconstriction, rather than vasodilation. Hypovolemia related to both blood loss (e.g., chest bleeding) and capillary leak is common in these postoperative cardiac neonates. Because cardiac output in neonates is very difficult to measure, cardiologists look at blood pressure as an indicator of this condition.

Study Design Issues

The Cardiology Work Group identified the following issues as being important in the consideration of clinical trial design:

- The clinical use and assumption of the efficacy and safety of vasoactive agents, including their use in neonates, is widespread.

- There is general agreement that randomized, placebo-controlled clinical trials will not be feasible for the established individual agents (e.g., DA, epinephrine, milrinone).
- It is important to appreciate developmental differences in preterm versus term neonates (e.g., maturity of adrenergic receptors).
- It is essential to incorporate the physical differences in single-ventricle versus two-ventricle patients into the trial design.
- Combined therapy regimens, such as an inotrope used with an afterload-reducing agent (e.g., DA plus milrinone), should be studied.
- It is difficult to identify primary efficacy endpoints for labeling due to the current low mortality and morbidity rates, particularly for patients with two-ventricle repair.

Potential Clinical Trial Frameworks

The Cardiology Work Group decided to consider potential clinical trial frameworks that have the following characteristics:

- Randomized trials of goal-directed management (e.g., comparison of two established agents, comparison of a new agent to an established agent, comparison of two combination therapy regimens)
- No placebo-controlled trials
- Dose-ranging studies of new or established agents for PK/PD data
- Hemodynamic targets that include the following:
 - Target cardiac index of more than 2.0 liters/minute/m²
 - Target systemic arteriovenous oxygen saturation difference of less than 35 percent
- A study population of preterm (less than 34 weeks) and term neonates with a diagnosis of congenital heart disease either for palliation or repair with cardiopulmonary bypass and planned postoperative use of a vasoactive agent
- Exclusion criteria, including patients with complicating features that would make it difficult to assess cardiac performance (e.g., preoperative infection, severe noncardiac anomaly)
- Randomization and study drug initiation in the operating room or NICU
- Stratification by cardiac diagnosis and study center
- Primary endpoints that vary by type of surgery, as follows:

- Palliative surgery—early postoperative mortality or the need for extracorporeal membrane oxygenation (ECMO) as a rescue modality for cardiovascular dysfunction plus selected serious adverse events (e.g., cardiopulmonary resuscitation [CPR], NEC, IVH, renal failure)
 - Reparative surgery—a composite endpoint that includes early postoperative mortality or the need for ECMO, selected serious adverse events, use of a vasoactive agent, and health care utilization parameters
- Other endpoints, including similar secondary endpoints and PK/PD studies.

Work Group Decisions

Although the Cardiology Work Group did not present a proposed clinical trial framework, members agreed on the following aspects of a design for studying vasoactive agents in neonatal postoperative cardiac patients:

- Modified proposed inclusion/exclusion criteria
- The mechanism for enrolling and randomizing patients while they were in the operating room
- A short-term duration for the application of inotropes in the early postoperative period, although patients would be followed until the time of discharge or perhaps a set number of days (e.g., 30 days) for adverse events and safety reasons
- A decision to proceed with goal-directed therapy
- A superiority trial that would compare two established agents (e.g., DA or epinephrine, combination therapy) without using a placebo
- Acknowledgment that buy-in and input on study design would need to be obtained from pediatric/cardiac surgeons
- A decision to discuss an appropriate primary endpoint with members of the Pediatric Cardiac Intensive Care Society, which will hold a biannual meeting in December. No validated or agreed-upon endpoint currently exists, especially for patients with reparative surgery, who have a low mortality rate. A panel discussion at the meeting might help the work group determine the study's primary endpoint.

Plenary Discussion

During the plenary session discussion, Cardiology Work Group members and other workshop participants made the following remarks about the study of cardiology issues in neonates:

- The work group discussed methods for measuring blood pressure in premature neonates and determined that an arterial line was necessary because cuff blood pressure would not be

correlative with an arterial line. Procedures for taking arterial blood pressures that might affect values (e.g., transducer calibration and placement) will need to be standardized.

- The work group did not discuss the use of milrinone in the trials of premature infants because the focus was on existing therapies (e.g., DA, DOB). Milrinone probably would fall in the category of a new drug and would need a straightforward randomized controlled trial (RCT). PK studies in premature infants would have to be conducted first.
- A suggested model to consider is the randomized withdrawal study in which investigators increase blood pressure or rescue all babies at the beginning of the trial and then randomly withdraw babies to placebo or continue with the drug under study. There would be very strict criteria about when to rescue babies back to therapy to get an idea of efficacy. Because the pharmacological half-life of the drugs is in minutes, responses should occur in minutes, allowing quick rescue. The randomized withdrawal approach might be more acceptable than allowing a baby to remain at a blood pressure level below 20 mm Hg.
- The combination design first proposed for studying premature neonates has the potential to answer both the question of drug efficacy versus placebo and the question of the effect of higher versus lower blood pressure on long-term outcomes. The design would include randomization to high normal blood pressure or low normal blood pressure, with each group being randomized to DA or DOB. This approach would avoid the ethical issues associated with using a placebo. However, including a placebo in the trial might allow a reduction in the estimated study size from 800 to 300 infants. The work group hopes that its poll of neonatologists will indicate whether these professionals would be interested in a placebo-controlled trial.
- Concerning methods for controlling for the adequacy of surgical repair, the work group noted that many large centers conduct an assessment of the adequacy of repair in the operating room using transesophageal echocardiography as the patients are being weaned off cardiopulmonary bypass. In the absence of this assessment, NICU staff would use stethoscopes and bedside monitoring to determine whether the patient had any important lesions. Because lesions might not be immediately detectable by the latter method, investigators would need to determine a way to deal with this outcome within several days of starting the trial. Another possibility is to stratify randomization by surgeon rather than by center. One concern was the additional number of stratifications that would be necessary to use the surgeon approach.
- Work group members expressed concerns about whether the proposed treatment algorithm for the trial of inotropes in premature newborns took into account the possibility of failing to distinguish between cardiac failure and vascular failure. A different sequence of drugs might be more effective for babies who were in cold shock and already underperfused. The work group discussed this issue and debated various approaches. The fact that the actual cause of hypotension in these infants is not clear but probably is multifactorial complicates the issue. The question of whether the primary use of fluid boluses versus the primary use of DA affects the occurrence of IVH has not been studied. However, the proposed design calls for using only two fluid boluses before moving the patient to an inotrope.

- Given that the proposed clinical trial frameworks of many of the work groups target the same populations, it will be important to consider the possibility for combining certain studies with similar outcomes. The involvement of a statistician will be crucial to looking at crossover groups and potential combinations of groups.

Neurology

The neurological issues facing newborns are many and varied. The Neurology Work Group decided to focus its discussion on two areas—seizures in the newborn and hypoxic-ischemic encephalopathy and neuroprotection.

Electrographic Neonatal Seizures

Presented by Robert Clancy, M.D.

Background

Seizures occur in 1 to 2 percent of babies during the first 30 days of life, the neonatal period, which is one of the highest risk periods for seizure during the human lifespan. Most neonatal seizures are triggered by an acute illness, such as hypoxic-ischemic encephalopathy (HIE), stroke, and infection, but rarely by epilepsy. The presence of seizures is the most common and important sign of acute neonatal encephalopathy. Customary clinical practice is visual monitoring of high-risk neonates for seizures, performance of electroencephalogram (EEG) upon noting suspicious clinical activity, and empirical treatment with phenobarbital (PB).

Growing evidence from research in newborn animal models supports the view that neonatal seizures by themselves contribute to an adverse neurodevelopmental outcome. However, clinical studies demonstrating the danger of seizures to neonates have not been reported. The customary clinical practice of using PB to treat neonatal seizures is based entirely on studies without placebo controls. Although PB is the most commonly used treatment for neonatal seizures and is the best studied, there is no clinical evidence supporting the view that it is safe for use in neonates. Accordingly, there is a pressing need for a randomized, placebo-controlled, ethically acceptable trial of the efficacy and safety of PB in the treatment of neonatal seizures.

Potential Clinical Trial Frameworks

Prior to the workshop, the Neurology Work Group explored three possible frameworks for clinical trials of PB in the treatment of neonatal seizures. The group focused on a blinded study of PB versus placebo in a homogeneous high-risk group of newborns who are anticipated to develop early subclinical electroencephalographic neonatal seizures (ENSs), for which video-EEG monitoring or early PB treatment is not customary clinical care.

High-risk infants include neonates who have meningitis, a hemorrhage, or hypoglycemia. Data indicated another high-risk group—newborns undergoing heart surgery, about 11 percent of whom have postoperative, usually subclinical, ENSs. Because subclinical ENSs would not be

diagnosed and treated if infants were not participating in the study, these newborns could be studied ethically, at least for a few hours, using either PB or placebo, to assess seizure reduction.

Clinical seizures would constitute escape criteria, and the criteria for the number of subclinical seizures required before random administration of PB or placebo would be determined.

The work group decided to use the FDA definition of efficacy for seizure-reducing drugs (i.e., a 50-percent reduction of ENSs in at least half of the treated patients, adjusted for the controls). Based on data from newborn cardiac surgery patients at the Children's Hospital of Philadelphia, the work group estimated that 46 patients in multiple centers would need to be enrolled in the proposed study to demonstrate efficacy.

Study Design Issues

The Neurology Work Group reported the following conclusions it had made about the study design issues:

The Need for Study. The customary clinical practice of using PB to treat neonatal seizures is based on data-derived studies with no placebo controls, studies using only clinical or EEG endpoints, and heterogeneous patient populations. Consequently, the work group agreed that the issue of the efficacy and safety of PB in the treatment of neonatal seizures needs to be studied in a formal, placebo-controlled, randomized trial.

Clinical Endpoints. Clinical endpoints for treatment of ENSs are notoriously elusive but are still important to clinicians. The customary clinical practice is to *visually* monitor high-risk neonates for the emergence of clinical seizures, perform routine EEG exams when suspicious clinical activity appears, and empirically treat with PB. Video-EEG monitoring allows examination of the traditional endpoint of treatment (i.e., cessation of clinical seizures). Although EEG endpoints are *more* objective, there are no data that demonstrate inter-observer agreement; however, disputes can be adjudicated post hoc. The group decided that cessation of EEG seizures should be the endpoint, rather than the previously noted FDA definition of efficacy.

Selection of the First Drug To Study. The work group agreed that PB should be the first drug studied, based on the following considerations:

- PB is the traditional agent selected to treat neonatal seizures.
- The best scientific data that exist in animals are based on PB.
- Good safety data exist. However, pre-administration testing would need to include an *in vitro* binding study to determine the dose. This study is needed because the portion of PB that is unbound, and thus available to enter the brain and produce the desired effects, is highly variable. The work group concluded that the goal of treatment is a free ("unbound") level of ~25mg/liter, which has been shown to be safe in the target group. This level corresponds to a loading dose of approximately 35 to 45mg/kg/dose. It is hoped that

participating clinicians will accept this dose, which comes close to, but exceeds, the often-cited clinical convention of 20mg/kg loading dose.

- An efficacy trial of PB would have an immediate impact on phenytoin, another antiepileptic drug commonly used for neonatal seizures. Phenytoin may be an important consideration because a comparative study showed that total cessation of seizures is the same whether an infant is randomized first to PB or phenytoin.
- Evidence is insufficient to recommend the primary study of benzodiazepines and other putative antiepileptic drugs; these drugs must await secondary confirmation in circumstances of primary treatment failure.

Exclusion of Preterm Infants. The underlying causes of seizures in preterm infants are not as well understood as those for term infants. The preterm group is etiologically heterogeneous, with different mechanisms triggering seizures. No consensus exists for an *epileptic* basis of paroxysmal clinical “seizures” (variable occurrence of electrographic seizures). Theoretically, gamma-aminobutyric acid (GABA)ergic drugs may paradoxically depolarize neurons and lower the seizure threshold in very young babies (although this effect is not consistent with typical clinical observations). Consequently, the work group concluded that the PB study should focus on children 37 weeks of chronological age (CA) or older.

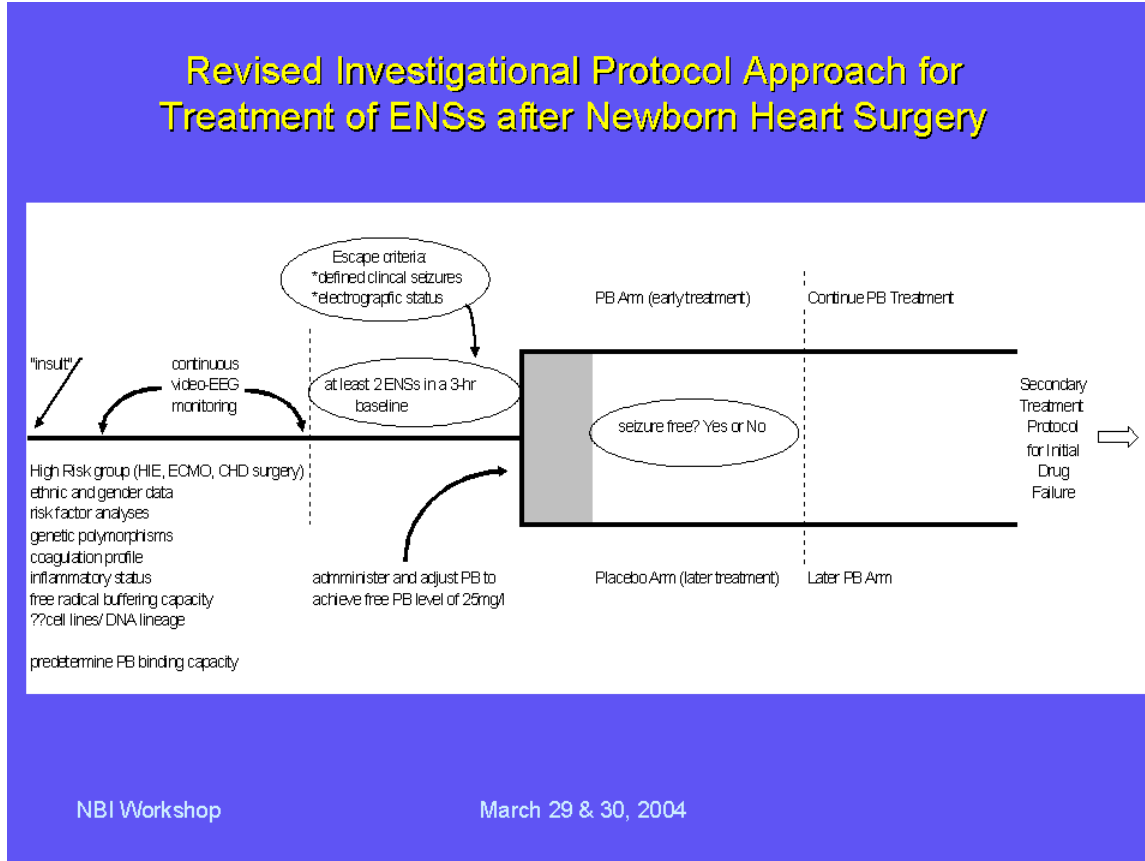
Proposed Clinical Trial Framework

The Neurology Work Group had sought an RCT study design that would be sensitive to and respectful of customary clinical practices. After examining three different study designs, the work group proposed a PB efficacy trial for ENSs (see Figure 2) that would include the elements described in the text box below.

FRAMEWORK FOR THE STUDY OF PB TREATMENT OF ELECTROGRAPHIC NEONATAL SEIZURES

- **Type of Study**—Multicenter, placebo-controlled, EEGer-blinded study of PB versus placebo
- **Study Population**—A homogeneous population of term infants (≥ 37 weeks CA) at high risk for ENS (e.g., congenital heart disease surgery, HIE, ECMO). Potential study populations with conditions other than congenital heart disease would need extensive preliminary data and individual study.
- **Enrollment**—Preoperative enrollment for infants undergoing congenital heart disease surgery
- **Monitoring**—Continuous video-EEG monitoring to establish presence and number of seizures
- **Entry Criteria**—Two or more ENSs in a 3-hour period
- **Intervention**—The study would include the following two arms, with PB administered and adjusted to achieve a free PB level of ~ 25 mg/liter:
 - PB (early treatment)
 - Placebo (later treatment)
- **Endpoint**—Cessation of EEG seizures, adjusted for the controls
- **Escape Criteria**—Criteria for escape from the study to treatment would include the following events:
 - Presence of clinical seizures (specifically defined as focal clonic, focal tonic, or sustained eye deviation) verified by EEG
 - Electrographic status epilepticus appears during the study. (No formal definition of status exists.)
- **Secondary Treatment Protocol**—The work group needs to determine the secondary treatment protocol for initial drug failure.
- **Followup**—Careful followup to 8 years of age. However, there was consensus that it will not be possible to demonstrate subtle PB effects on long-term neurodevelopmental outcomes.

Figure 2.



Future Directions

The Neurology Work Group agreed that the next steps should include the following:

- Obtain pilot data in other groups at high risk for ENSs (e.g., infants in the HIE hypothermia trial, infants who had received ECMO).
- Obtain values for specific entry criteria and the effects of these values on sample size calculations.
- Consider adding an additional study arm to include a benzodiazepine drug.
- Consider what to do about high-risk premature infants.

Hypoxic-Ischemic Encephalopathy

Presented by Jeffrey Perlman, M.B., Ch.B.

Background

Hypoxic-ischemic brain injury is an evolving process. It begins *in utero* with interruption of placental blood flow, and extends *in utero* and postnatally into a recovery period known as the reperfusion period. The fetal events that predispose to neonatal encephalopathy are not understood. A search for a biological marker of the development of neonatal encephalopathy is needed.

Cellular injury takes two forms—necrosis and apoptosis. Tissue swelling, membrane disruption, and an inflammatory cellular response characterize necrosis. Apoptosis, “programmed cell death,” is characterized by cellular and nuclear shrinkage, chromatin condensation, and DNA fragmentation. Necrosis and apoptosis can be distinguished by electron microscopy. A less severe and prolonged insult results in apoptosis. A more severe and prolonged insult leads to necrosis, which might not benefit from intervention strategies.

Interventions are directed chiefly at managing reperfusion injury in the delivery room during the first 6 hours of a neonate’s life. It is conceivable that protection could be started before labor, but identifying an affected fetus remains difficult.

Key Questions

The Neurology Work Group needs to address several key questions before exploring possible study designs for the management of HIE. These questions include the following:

- Which pathways contribute to brain injury?
- What mechanisms contribute to fetal resistance to hypoxia-ischemia?
- How can infants at highest risk for brain injury be identified early?
- What animal models of hypoxia-ischemia are appropriate for study?
- What neuroprotective strategies should be implemented?

Study Design Issues

The study design also needs to take into account the following key issues:

- Hypoxic-ischemic cerebral injury is rare, occurring in no more than 1 in 1,000 live term deliveries. Consequently, a multicenter trial design will be necessary.
- Early identification of infants at highest risk for evolving brain injury is critical. The therapeutic window for intervention is short—considered to be less than 6 hours.

- Novel therapies carry the potential for significant side effects.
- Treatment strategies are likely to vary, depending in part on the severity of initial presentation.

Various models of events that occur during the process of hypoxia-ischemia in the human neonate indicate points for potential neuroprotective intervention. Given the various pathways that may predispose infants to hypoxia-ischemic cerebral injury, it becomes critical to identify early the patients characterized by sentinel events (e.g., delivery room depression, initial abnormal clinical examination and abnormal EEG) and to implement therapies.

General Principles for Treatment Strategies

The Neurology Work Group discussed the following general principles that need to be considered in developing treatment strategies.

- Treatment strategies will likely depend on the severity of the initial encephalopathy.
- Multiple interventions may be necessary.
- Potential genetic and gender influences are likely and will need to be delineated.
- The importance of placental abnormalities and their contribution to the evolving encephalopathy (i.e., inflammation, thrombosis) is a critical factor.
- The importance of other factors such as ischemic preconditioning needs to be considered.

Potential Treatment Strategies

Using the models of hypoxic-ischemic cerebral injury, the Neurology Work Group identified certain potential strategies for preventing reperfusion injury. Data from studies of modest hypothermia in term infants at highest risk for perinatal hypoxic-ischemic brain injury suggest that this therapy may be neuroprotective with early and moderate, but not severe, encephalopathy. The group identified the following treatment strategies for consideration during the workshop:

- Treatment for moderate encephalopathy (defined clinically and with an amplitude EEG) would start with modest hypothermia. Possible adjunctive strategies could include PB for infants with EEG seizures and other neuroprotective strategies.
- Treatment for severe encephalopathy (defined clinically and with an amplitude EEG) would include hypothermia and other strategies, the possible use of PB even in the absence of seizures, and other neuroprotective strategies.

Neuroprotective Strategies

During the breakout discussion, the Neurology Work Group's original focus on management strategies for HIE shifted to neuroprotective strategies for neonatal encephalopathy. As a result of the discussion, the group identified the following key elements of a neuroprotective strategy:

- **Who to treat**—Infants at highest risk as indicated by a combination of markers that would identify an intrapartum event (e.g., sentinel event, delivery room resuscitation, 5-minute Apgar score ≤ 5 , cord arterial pH ≤ 7.00) and postnatal evidence of moderate to severe encephalopathy (e.g., using both abnormal clinical exam and abnormal EEG)
- **When to treat**—The earlier the better during the short therapeutic window, preferably less than 6 hours after reperfusion
- **How long to treat**—Optimal duration is unclear; 72 hours is recommended, but treatment may need to be extended beyond this time, depending on severity or other factors of the initial presentation.
- **What to treat with**—Hypothermia appears to be the most attractive strategy because it may act at all levels within different pathways to reduce deleterious effects.

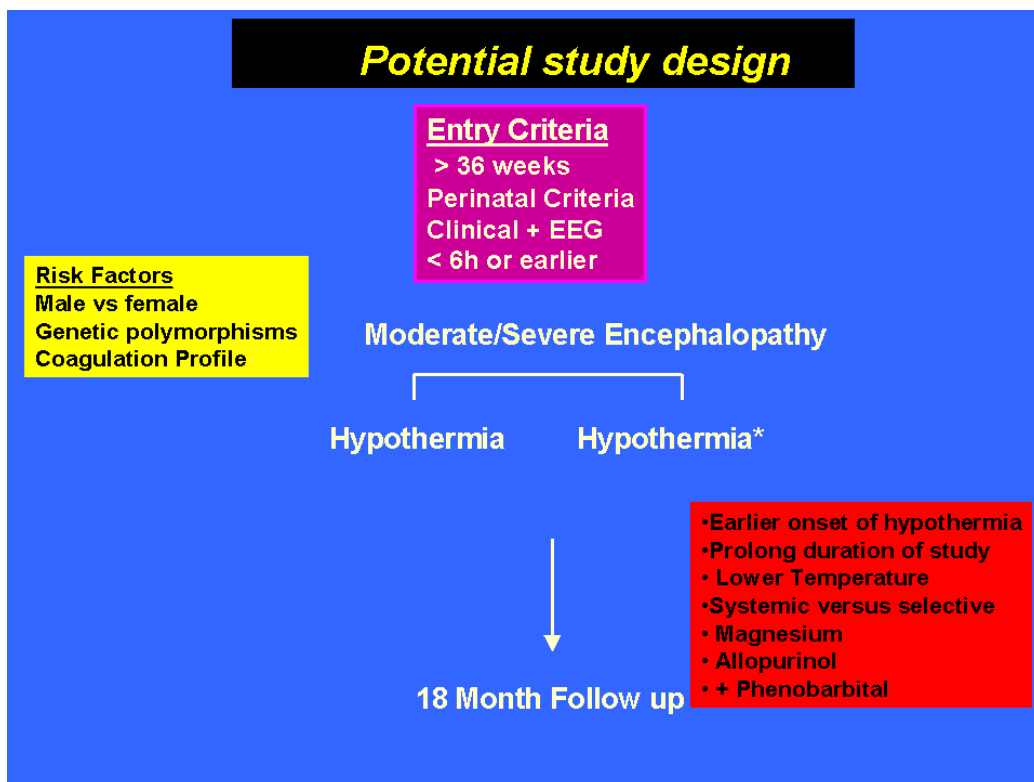
Proposed Clinical Trial Framework

The Neurology Work Group was unable to develop a definitive framework for the study of neuroprotective strategies for neonatal encephalopathy. However, the group identified key elements for a potential clinical trial framework comparing hypothermia with hypothermia “plus” for moderate to severe encephalopathy. These elements are listed in the following text box and depicted in Figure 3.

**FRAMEWORK FOR THE STUDY OF
NEONATAL ENCEPHALOPATHY NEUROPROTECTIVE STRATEGIES**

- **Entry Criteria**—Criteria for entry to the study would include the following:
 - Term infants older than 36 weeks of age
 - Perinatal depression
 - Clinical plus EEG criteria at less than 6 hours for moderate or severe encephalopathy
- **Intervention**—Hypothermia would be the first drug used. The study would include the following two groups:
 - Hypothermia
 - Hypothermia plus (Possibilities include earlier onset of hypothermia; prolonged duration of study; lower temperature; systemic versus selective; other drugs such as PB, magnesium, and allopurinol)
- **Risk Factors**—Blood would be saved to examine the following potential risk factors:
 - Male versus female
 - Genetic polymorphisms
 - Coagulation profile
- **Followup**—At 18 months

Figure 3.



The work group recognized that the clinical trial framework also needed to address the following additional considerations:

- Drug interactions
- The effect of comorbid conditions
- Ethical issues
- Feasibility
- Treatment endpoints
- Outcome variables (e.g., delay or reduce severity of EEG seizures, death, cerebral palsy, mental retardation)
- Long-term outcomes at 18 months

Gaps in Knowledge

The Neurology Work Group identified the following gaps in knowledge that still need to be addressed:

- What is the contribution of the fetal inflammatory response?
- Are there gender and genetic influences?
- Does ischemic preconditioning contribute to the resistance of the infant to hypoxia-ischemia, and can it be modulated in any way?
- How can all drugs be delivered effectively across the blood brain barrier?
- What additional evaluations should be performed at the time of delivery to enhance therapy?
- What are potential treatment strategies for infants who initially present beyond 6 hours of age?

Plenary Discussion

During the plenary session discussion, Neurology Work Group members and other workshop participants made the following point about neurological studies in the newborn. Because Dr. Perlman mentioned a potential synergistic effect of PB and cooling, it was suggested that a study design could include the administration of PB as early as the intrapartum period. The design would include four arms: treatment with PB versus placebo administered to the mothers of high-risk infants, then randomization of the infants with HIE to cooling versus control. Dr. Perlman thought that the proposal was interesting and should be considered. However, he

was concerned that such a study would entail giving too many mothers PB. Dr. Perlman's bias was to start PB treatment postnatally.

Additional comments addressed ethical issues and are included under the plenary discussion on ethics.

Pain Control

Presented by K.S. Anand, D.Phil., MBBS

Background

Until 1960, it was not recognized that the fetus and newborn feel pain. Since then, much effort has been made to determine the best way to control pain in the neonate. The issue of pain in neonates is complex, involving different sources of pain and different types of pain, each with its own specific receptors and mechanisms within the developing nervous system. Pain can be classified as acute, established, and chronic, with each of these categories further classified according to the degree of invasiveness. Once pain occurs, a series of sequential neurobiological changes involves activation and modulation of the pain system. If pain is prolonged or repetitive, the pain system will become modified, resulting in altered pain processing at the spinal and supraspinal levels. Pain also is a multi-layered phenomenon that is associated with different clinical and neurophysiological states, such as primary and secondary hyperalgesia, in which the processing of pain stimulus is accentuated and pain is magnified.

Over the last several years, findings from both clinical and preclinical research have shown that newborns are more sensitive to pain than older infants, children, or adults. Studies also have documented the vast number of procedures that are performed in newborn infants, often without analgesia. One 2003 study found that less than 35 percent of the nearly 20,000 procedures performed on 151 neonates were accompanied by analgesia, although many of the procedures seemed to produce moderate to severe pain.

The Pain Control Work Group identified three prioritized areas of pain control in newborns:

- **Procedural Pain**—Neonates experience 5 to 15 invasive procedures a day that cause pain. Important procedures to address include heelsticks, venepuncture, venous or arterial cannulation, tracheal intubation/suction, spinal tap, and circumcision. Research is needed to assess the safety and efficacy of repeated dosing as well as the long-term effects of regular analgesic use versus repetitive pain on the global development of the child. Potential therapeutic drug groups include opioids, nonopioids (e.g., nonsteroidal anti-inflammatory drugs [NSAIDs]), local anesthetics, and other agents such as sucrose.
- **Perioperative Pain**—Nearly 1.3 million infants in the United States undergo operative procedures each year. Pain management for these infants must include intraoperative and postoperative interventions. This type of pain has somewhat similar physiological characteristics that may allow researchers to extrapolate from one patient group to another. Tolerance and withdrawal may occur, but an opportunity exists to use multiple types of

analgesic interventions. Potential drug therapeutic groups include opioids and opioid antagonists, sedatives/hypnotics, vapor anesthetics, local anesthetics, and NSAIDs.

- **Pain Associated With Mechanical Ventilation**—Mechanical ventilation occurs in 35,000 preterm neonates and 20,000 term neonates per year. The indications for sedation and analgesia in these infants remain unclear, and questions about the effects of sedation and analgesia on morbidity and mortality and the developing nervous system have not yet been answered. Additional research challenges include the need to incorporate behavioral and environmental interactions into pharmacological study designs; the need for information on safety, efficacy, and drug interactions in these neonates; and the lack of validated pain assessment tools to evaluate ongoing pain and discomfort rather than acute pain. Potential drug therapeutic groups include opioids, NSAIDs, and sedatives.

Ethical Issues

Ethical constraints that need to be considered in the design of pain studies include the following potential costs to the patient:

- Withholding of analgesia in placebo-controlled trials
- Unknown side effects that have not been documented in older children or adults
- Burdens related to monitoring for routine laboratory tests and PK studies
- Potential for sampling to be invasive

Future Directions for Research

The Pain Control Work Group identified the following needs for future neonatal pain research:

- Prioritize the drugs to be used.
- Articulate drug formulation concerns.
- Evaluate pain as a valid endpoint in RCTs.
- Identify potential biomarkers of pain.
- Address safety issues from a global neonatal perspective.
- Go beyond pain assessment to the assessment of intermediate and long-term outcomes.
- Stimulate the study of developmental neurobiology, pharmacology, pharmacogenomics, pharmacogenetics, medical effectiveness, and cost-utility analyses.

Treatment of Perioperative Pain

Presented by Charles Berde, M.D., Ph.D.

Study designs for postoperative analgesia, general anesthesia, and regional anesthesia will involve different issues. A common challenge to developing study designs for the treatment of pain in neonates is determining whether investigators need to make the baby experience pain in order to measure pain relief. Unlike adult studies, neonate studies face the ethical constraint of not being able to have a placebo that withholds analgesia for extended periods of time. Many studies on methods for measuring pain/distress in neonates have looked at behaviors, physiologic parameters, and other measures. However, the measures for neonates do not have the same scaling properties as measures used in adults, and it is not as well understood how to use them as a basis for clinical action.

Postoperative Analgesia

Study Design Issues

- Study design issues include how to delineate the interactions between rescue analgesics and the drug being studied and how to study the time course of each incremental dose.
- A major unsolved issue in this area is the criteria for extubation and reintubation. Virtually no data exist on a morphine or fentanyl dosing regimen that uniformly relieves pain in nonintubated neonates. Measures of respiratory effect and efficacy are very different in intubated and nonintubated populations. A goal of the studies should be to look at the influence on timing of extubation and respiratory function.
- Standardization of intraoperative management would be crucial to the study design. Standardization would need to include everything from analgesics, anesthetics, and relaxants to fluid management, glucose, and temperature.

Proposed Clinical Trial Frameworks

Clinical trial frameworks for postoperative analgesia would have the following common features:

- **Intervention**—The trials would include one group that is given placebo and one group that is given a single or multiple dose of the drug. Both groups would have immediate access to rescue analgesia with an IV opioid in small incremental doses.
- **Study drugs**—Examples of drugs to study include NSAIDs or cyclooxygenase (COX)-2 inhibitors and epidural analgesia (e.g., local anesthetics, opioids, clonidine).
- **Patient groups**—Patient groups that are easily available for these types of studies often include term neonates having elective surgeries; infants less than 3 months of age; infants undergoing major abdominal, pelvic, or urologic surgeries; and infants capable of early extubation.

- **Outcomes**—In addition to analgesia, outcomes could include side effects, respiratory function, time to extubation, time to recovery of gastrointestinal function, bleeding, nephropathy, IVH, PVL, and ductus closure.

General Anesthesia

In adult studies, general anesthesia means unconsciousness (lack of implicit recall and lack of awareness of surgery), analgesia (suppression of autonomic responses to noxious stimuli), and immobility.

Study Design Issues

Issues for the design of general anesthesia studies include the following:

- Studies of new agents should address whether those agents are safer in the short run than existing agents and what their long-term effects are on neurodevelopment.
- Studies cannot withhold general anesthesia from a placebo group. However, one way to study minimal effective dose in the case of volatile anesthetics is to use a minimal alveolar concentration (MAC) that suppresses movement. A partial neuromuscular blockade and electromyography recording can be used.
- An unresolved question is how to interpret results from animal model studies on the short- and long-term effects of various methods of general anesthesia on the nervous system. Infant animal studies showing neurodegeneration from repeated administration of a variety of general anesthetics may or may not be applicable to human neonates and infants.

Proposed Clinical Trial Frameworks

Clinical trial frameworks for general anesthesia generally have the following features:

- **Intervention**—Studies usually compare old agent(s) to new agent(s), with titration to MAC.
- **Outcome measures**—These measures include suppression of movement, intraoperative hemodynamic stability, postoperative respiratory function, and time course of recovery.
- **Patient groups**—The studies eventually will need to be conducted in all age groups, including the full range of preterm neonates, term neonates, and infants younger than 3 months of age. For the use of pure regional versus pure general anesthesia, the ideal patient groups over the whole range are infants undergoing inguinal hernia repairs.

In general, studies of the treatment of perioperative pain can use surrogate measures of efficacy, cannot withhold anesthesia and analgesia, and need to assess immediate and long-term postoperative outcomes.

Pain Associated With Mechanical Ventilation

Presented by Jacob Aranda, M.D., Ph.D., FRCPC

Study Design Issues

- The literature includes many RCTs of pain control in mechanically ventilated newborns, but most of these studies have been underpowered. Two recent, well-powered studies with a total of 1,000 babies (Simons 2003, Anand 2004) showed no difference in primary outcome between morphine and placebo.
- Drug options for pain control in mechanically ventilated preterm newborns include opioids and IV NSAIDs for analgesia and midazolam, lorazepam, and various combinations for sedation. NSAIDs are good candidates for analgesia in newborns because they have the potential to provide good IV analgesia in newborns, spare the use of opioids, and obviate the potential for addiction. NSAIDs also have been used extensively in newborns for PDA closure and IVH prevention, and they have defined PK/PD profiles.

Proposed Clinical Trial Framework

The Pain Control Work Group proposed a randomized double-blind placebo-controlled trial of analgesic with or without sedative for pain control in mechanically ventilated preterm newborns. The study would have the features listed in the text box below.

FRAMEWORK FOR THE STUDY OF PAIN CONTROL IN MECHANICALLY VENTILATED PRETERM NEWBORNS

- **Objectives**—The proposed study would have the following objectives:
 - The primary objective would be to determine the safety and efficacy of an IV analgesic and sedative in the management of pain and stress during mechanical ventilation in preterm newborns.
 - The secondary objective would be to determine the population PK profile of an IV analgesic and sedative in this patient group.
- **Hypothesis**—Daily IV analgesia with or without sedation decreases pain experience and opiate need in mechanically ventilated preterm newborns.
- **Patient group**—The study would look at premature newborn infants whose birth weight is 500 to 1,500 grams and who are less than 7 days postnatal life.
- **Stratification**—The study population would be stratified into three weight categories:
 - 500 to 750 grams
 - 751 to 1,000 grams
 - 1,001 to 1,500 grams
- **Interventions**—The intention-to-treat study would have four arms:
 - Group 1: placebo
 - Group 2: IV analgesic
 - Group 3: IV sedative
 - Group 4: IV analgesic plus IV sedative
- **Duration of treatment**—The treatment would last 14 days while the infants were ventilated.
- **Study population and sample size**—To have a meaningful subset analysis, the study would seek to enroll 224 infants per study arm, for a total of 896 infants. However, meaningful analysis of secondary outcomes could be achieved with fewer patients (189 per arm, 756 total).
- **Stopping and weaning criteria**—Treatment would be continued until infants meet the following criteria:
 - Expected extubation within 24 hours
 - No spontaneous breathing at PaCO₂ of 5.3 to 6.7 kPa Rapid clinical deterioration
 - Continued use of the study drug for 14 days
- **PDA rescue criteria**—If NSAIDs are used, the rescue criteria would be indomethacin (0.1 mg/kg/day x 3). The pain rescue will be open-label fentanyl.
- **Inclusion criteria**—The study would include preterm newborns with birth weights of 500 to 1,500 grams who needed mechanical ventilation for more than 24 hours.
- **Exclusion criteria**—The study would exclude infants with the following conditions:
 - Severe congenital malformations
 - Severe IVH grade 3 to 4

- Thrombocytopenia < 50,000
- Maternal opioid dependence
- Asphyxia (Apgar < 3 at 5 min or cord pH < 7.00)
- Intrauterine growth restricted (birth weight < 5th percentile for GA)
- **Primary outcome**—The study’s primary outcome would be the Neonatal Pain Agitation Sedation Score (N-PASS) for chronic pain.
- **Secondary Outcomes**—The secondary outcomes would include the following:
 - Composite of severe IVH (grade 3 to 4) or death
 - Premature Infant Pain Profile (PIPP) score during acute pain stimulus (intratracheal suctioning)
 - Need for open-label opiate (fentanyl)
- **Safety outcomes**—Additional secondary outcomes would include the following safety outcomes:
 - Renal function (urine flow rate and serum creatinine)
 - Hepatic function
 - Serum bilirubin
 - Platelet count
 - Bleeding from any site
 - Arterial blood pressure for the first 3 days
- **Other neonatal morbidity issues**—Additional secondary outcomes would include the following neonatal morbidity:
 - NEC
 - Systemic infections (sepsis)
 - PDA
 - IVH
 - ROP
 - PVL
 - BPD
- **Other secondary outcomes**—The study also would assess the following secondary outcomes:
 - Days to full oral feeding
 - Length of stay in the hospital
 - Lung function according to the following parameters:
 - ◇ Duration of mechanical ventilation (days)
 - ◇ Duration of oxygen therapy > 0.21 (days)
 - ◇ Duration of oxygen therapy > 0.40 (days)
- **Exploratory outcomes**—The study would explore the following exploratory outcomes:
 - Cytokines (e.g., IL-1, IL-4, IL-6, IL-10)
 - PGF1a (prostaglandin F1 alpha)
 - Plasma cortisol
 - Plasma adrenalin/noradrenalin
 - Plasma concentrations of drugs and metabolites.
- **Long-term followup**—The study would conduct followup with the infants until they are 18 months of age. Investigators would examine neurodevelopment outcomes as measured by the Bayley Scales of Infant Development or another test, neurological exam, and pain perception (e.g., response to vaccination).

Treatment of Pain Associated With Medical Procedures

Presented by Dr. K.S. Anand

The Pain Control Work Group considered a variety of clinical trial designs that could be applied to the study of pain in the neonate. The group also considered a randomized “play the winner” design, which involves testing two different types of treatment. After reviewing the literature on the epidemiology of pain in newborns, the work group decided that suctioning, heel lancing, and IV insertion were the three neonatal procedures that warranted prioritized study. Because heel lancing is the most common painful, invasive procedure performed in the NICU, the work group proposed a design to study heelstick pain in neonates.

Pilot Study

Pilot data would be needed to design a RCT for this intervention. The Pain Control Work Group identified two populations in which heelstick is most common: the smallest and sickest babies that stay in the NICU and get multiple heelsticks, and relatively healthy babies that get heelsticks for metabolic monitoring. Consequently, the group proposed to stratify the study group by the following GAs: 23 to 26 weeks, 27 to 30 weeks, and 37 to 42 weeks. Selected babies would be younger than 2 weeks of age, have no hemodynamic instability, and have indwelling catheters for blood sampling. The pilot study would test the efficacy of S-caine for placement of peripherally inserted central catheter (PICC) lines, which occur commonly in NICU patients of the proposed GAs. The sample size would be 30 neonates, with 10 babies in each GA group. The time of application of the therapy would be 30 minutes, with plasma samples taken at 15 minutes, 30 minutes, 60 minutes, 6 hours, and 12 hours for measurement of the drugs and their metabolites. The pilot study would provide toxicity and PK data as well as preliminary efficacy using PIPP scores, and would identify any technical difficulty with PICC line placement.

Proposed Clinical Trial Framework

After the completion of the pilot study, an RCT would be designed with the characteristics listed in the text box below.

FRAMEWORK FOR A STUDY OF HEELSTICK PAIN IN NEONATES

- **Objectives**—The study would have the following objectives:
 - To investigate the efficacy, safety, and toxicity of therapies for heelstick pain in neonates using current therapies (e.g., sucrose 24 percent and S-caine, a eutectic mixture of lidocaine and tetracaine)
 - To evaluate the PK and toxicity of tetracaine and lidocaine in preterm and term neonates (secondary)
 - To evaluate the long-term hypersensitivity following multiple neonatal heelsticks in children at age 18 and 24 months

- **Hypotheses**—The study would assess the following hypotheses:
 - The primary hypothesis is whether S-caine provides adequate topical analgesia in preterm or term neonates undergoing heelsticks.
 - The secondary hypothesis is whether repeated heelsticks in preterm neonates are associated with long-term developmental consequences.
- **Inclusion criteria**—The inclusion criteria would include the following:
 - Infants 23 to 30 weeks GA and 37 to 42 weeks GA
 - Less than 2 weeks of age (selected babies)
 - No indwelling lines from which blood can be drawn
 - Clinical need for blood sampling from heelstick
 - Parental consent
- **Exclusion criteria**—The RCT would exclude neonates with the following conditions:
 - Severe IVH or PVL
 - Severe birth asphyxia, as indicated by the following:
 - ◇ Apgar score ≤ 3 at 1 or 5 minutes
 - ◇ Cord pH ≤ 7.00 (umbilical artery or umbilical vein)
 - ◇ True knot of the cord, tight nuchal cord
 - ◇ Evidence of fetal distress, emergency cesarean section delivery
 - Inadequate blood pressure or perfusion
 - Major congenital anomalies
 - Neonatal seizures
 - Infusions for preemptive analgesia
- **Standardized procedures**—The study would standardize the following procedures:
 - Preparation and positioning
 - Cleaning with antiseptic
 - Method of heelstick using an automated device
 - Duration of squeezing
 - Amount of blood sampled
 - Postsampling care
- **Interventions**—The blinded RCT would use the following interventions for three study groups, stratified according to GA:
 - 23 to 26 weeks: placebo, S-caine, 24 percent sucrose
 - 27 to 30 weeks: sucrose, S-caine + sucrose, S-caine
 - 37 to 42 weeks: sucrose, S-caine + sucrose, S-caine
 - Preterm neonates would be allowed up to three applications per day, each at least 6 hours apart, from birth to 14 days postnatal age.
- **Concealment techniques**—The study would use the following techniques to conceal which intervention was being administered:
 - Similar patches or paste for the placebo group
 - Blinded neonatal assessments and data analysis
 - Centralized randomization for multicenter RCTs using the following techniques:
 - ◇ Sealed, opaque, numbered envelopes
 - ◇ Automated telephone response system
 - ◇ Web-based randomization system

- Balanced randomization in blocks
- Randomization tables for each stratum
- Faxed confirmation to pharmacy and NICU
- **Short-term outcomes**—Ideally, the study might measure the following short-term outcome measures:
 - Pain (measured by a change in the PIPP score of 2 or more points)
 - Changes from baseline in heart rate, blood pressure, and oxygen saturation
 - Time taken for the recovery of heart rate, and blood pressure, oxygen saturation, and heart rate variability
 - Total time required for blood sampling
 - Number of heelsticks required
 - Stress parameters (e.g., salivary cortisol in term neonates)
 - Palmar sweating/transdermal conductance (to measure autonomic activation as a result of pain)
 - Skin blood flow (laser Doppler flowmetry) at the site of application before and after patch application to determine whether there is vasodilation associated with the preparation
- **Long-term outcomes**—Long-term outcome measures are particularly important in the extremely preterm child. Investigators would need baseline data on the severity of illness in the infants (which can be obtained from Support for the Sick Newborn and their Parents [SSNAP], a charity in Oxford, England, or from Clinical Risk Index for Babies [CRIB] scores). Followup in the infants would include the following outcome measures:
 - At 4 to 6 months: Response to vaccination (PIPP, heart rate, salivary cortisol)
 - At 18 to 24 months:
 - ◇ Neurological examination (to exclude cerebral palsy)
 - ◇ Dorsal cutaneous flexor reflex (Von Frey filaments) to test pain threshold or tactile sensitivity
 - ◇ Developmental milestones (e.g., age to standing, coasting, walking without support)
 - ◇ Developmental assessment (e.g., Bayley Scales of Infant Development, Third Edition)
 - ◇ Visual motor integration (Beery-Buktenica Developmental Test of Visual-Motor Integration)
 - ◇ Regulation of attention, behavioral state, response to novelty
- **Safety and Adverse Effects Parameters**—Investigators would assess local and systemic toxicity, as indicated by the following parameters:
 - Rash, erythema, petechiae, and other local reactions
 - Lidocaine and tetracaine toxicity, as indicated by cardiac arrhythmias and generalized seizures
 - Tachycardia of more than 5 minutes
 - Prolonged hypoxemia
 - Excessive bleeding from the site of the heelstick
 - Allergic reactions

Research Needs and Future Directions

The Pain Control Work Group identified needs and resources for the field of neonatal pain research during the Decade for Research on Pain, 2001–2010.

The work group identified the following research needs:

- Empiric foundations for composite measures in the youngest neonates (i.e., 23 to 26 weeks)
- Understanding of autonomic responses and how they change in the youngest neonates
- Need assessment scales for ongoing and chronic pain
- PK and PD data for all analgesic drugs used in neonates
- Incorporation of models for examining patterns of responses, rather than merely responses in isolation.

The work group identified the following future areas of investigation that would benefit pain control research in neonates:

- DNA for pharmacogenomic analyses
- Mechanisms of tolerance and withdrawal in early life
- Neuroimaging studies for pain in preterm and term infants
- Selection of appropriate long-term outcome measures and time frames, particularly focused on crucial or sensitive developmental periods

Plenary Discussion

During the plenary session discussion, Pain Control Work Group members and other workshop participants made the following points about pain control in neonates:

- Very limited data are available on the potential neurodevelopmental effects on children from drugs ingested by the mother during pregnancy. A few studies have examined the development of infants born to mothers who have abused drugs such as heroin, cocaine, and crack. However, there is a social overlay to the effects of such drugs. An ongoing study of maternal lifestyles is examining the issue more systematically. Emerging data indicate a relationship between a baby's exposure to the mother's cocaine abuse during pregnancy and long-term effects on neurological function, such as abnormal neurotransmitter synthesis correlated to behavioral abnormalities at 7 to 8 years.

- It is difficult, but not impossible, to distinguish the effects of multiple factors that cause prematurity and the incident factors associated with immaturity from the effect of repetitive pain. Requirements include a well-designed study with detailed data collection, along with elegant statistical techniques such as principal components analyses or structural equation modeling. Exploratory analyses could look at which factors have significant load onto subsequent developmental outcomes. Exploratory structural equations could precisely define the impact of all the different factors.
- After much debate, the work group decided that the inclusion of a placebo in the youngest study group was essential, given the lack of data regarding the efficacy of sucrose in very small babies as well as the lack of validated pain scales for use in this group. However, once a validation of the PIPP scale is available for the sickest and smallest babies, this tool could be used to observe sucrose efficacy in the youngest study group.
- The three GA groups included in the framework represent the ages at which the largest number of heelsticks occurs. This stratification is intended to require the least number of patients while still being able to answer the study questions.
- The work group considered the issue of intermittent versus continuous infusion therapy. Studies by Tible and others indicate no difference between the two when using morphine as the drug under investigation. However, the design of the therapeutic regimen will be based on better PK data about which drugs have the longest lasting effects.
- Another important issue that needs to be addressed is withdrawal, tolerance, and the discontinuance of therapy. The framework includes criteria to discontinue therapy after 14 days. If an opioid drug is used, the protocol will include a schedule for gradually reducing the drug dosage.
- State **[[Sleep state??]]** or sleep development is a physiologic marker that might be used in future studies. Particularly in the immature brain, sleep is a biologic or surrogate marker for brain organization and maturation. Alteration of sleep could have an effect on developmental neuroplasticity and perhaps on developmental outcome. Infants' monitoring could include physiologic measures to look at **[[sleep??]]** state. The effects of different methods of analgesia on the progression of sleep state also present an appropriate subject for postoperative studies in neonates.

Pulmonary

The Pulmonary Work Group identified two conditions that were unique to the newborn: apnea of prematurity and bronchopulmonary dysplasia.

Apnea of Prematurity

Presented by Rosemary Higgins, M.D., John Kattwinkel, M.D., and Richard J. Martin, M.D.

Background

Apnea of prematurity (AOP) is the most common and frequently recurring problem in VLBW infants. AOP is found in more than 50 percent of premature babies and is almost universal in babies smaller than 1,000 grams. The literature defines clinically significant apnea in infants as breathing pauses lasting more than 20 seconds, or more than 10 seconds if associated with bradycardia (e.g., less than 80 beats per minute or oxygen desaturation [e.g., O₂ saturation of less than 80 to 85 percent]). This definition may vary depending on geographic location or the baby's symptomatology. Moreover, there is no consensus about the duration of apnea that is considered pathological, and there is no agreement regarding the degree of change in oxygen saturation or severity of bradycardia that constitutes a true apnea event.

Although scientists cannot yet say whether AOP causes a clinically certain outcome and is harmful, providing no treatment when a baby stops breathing in the NICU is not an option. The immediate and irresistible urge to respond to apnea is based partly on the uncertainty about exactly what causes the apneic episode and whether the unknown causative factor might also harm the brain or other systems and produce a long-term effect on neurodevelopment. Although caregivers are able to respond successfully to apnea events with drugs (as well as physical and mechanical interventions) in the NICU, it remains unproven whether such interventions have any other long-term effects, good or bad. Moreover, most premature babies also suffer from gastroesophageal reflux disease (GERD), and many clinicians use off-label drugs approved for GERD in the belief that such treatments also have an impact on AOP, although this link has never been demonstrated. One of the most effective drugs, caffeine citrate, is currently labeled for short-term use only, within a limited GA population.

Treatment Issues

Before the workshop, the Pulmonary Work Group identified the following key issues concerning the treatment of AOP:

- The diagnosis and treatment of the condition have not been standardized.
- The benefit of intervention, apart from a reduction in apnea itself, remains largely unproven.
- Most studies of apnea have not collected real-time data documenting the actual event and the preceding baseline, including physiologic parameters such as oxygen saturation.
- Few studies have evaluated sustained treatment improvement at 7 days or later after the initiation of therapy, and the improvements noted at 1 to 3 days after therapy usually are not sustained at 1 week.
- Most studies are small in number and thus are not stratified by birth weight, gestation, postconceptional age, or disease or disease processes that have occurred in individual babies.

- Previous studies have not addressed confounding conditions such as hypoxemia, the requirement for oxygen therapy, pharmacologic sedation, glucocorticoid therapy, acute or chronic lung disease, PDA, IVH, or other treatments such as DA.
- No good evidence exists to support the view that apnea and reflux are temporarily or causally related and that the use of antireflux medications (e.g., cisapride, metaclopramide) decreases apneas.
- The most important issue is the role of apnea in determining infants' long-term neurodevelopmental outcomes.

Study Design Issues

The Pulmonary Work Group summarized study design issues that it identified in four basic categories.

Important Questions About Neonatal Apnea

The work group agreed that the following key questions need to be addressed as a priority:

- Does neonatal apnea affect long-term neurodevelopmental outcome, or is it merely a marker of other complications of prematurity?
- Is xanthine, the primary drug currently used to treat apnea, and other future drug therapy for AOP associated with improved outcome, both short-term and long-term?
- Does esophageal reflux cause apnea, and, if so, are pharmacologic therapies effective, both for the reflux and the apnea?

Other secondary questions about apnea include the following:

- What is the effect of xanthines on GERD (e.g., potentiation)?
- What is the most effective way to intervene for apnea (i.e., pharmacologic versus mechanical intervention)?
- Does the etiology of apnea affect response to therapy?
- What are the response and the associated risk as a function of GA and weight?
- What is the appropriate threshold for treatment?
- Is xanthine use outside the hospital setting for postneonatal infants safe and effective?

- Are other agents (e.g., other adenosine inhibitors, progestins) effective and safe in treating AOP?
- What is the effect of baseline oxygenation on the incidence and severity of apnea?
- Are there legitimate uses of xanthines for apnea disorders other than AOP (e.g., to counteract apnea associated with prostaglandin administration, for apparent life-threatening event, for postanesthesia apnea)?
- What is the relationship of body position to apnea?
- What is the appropriate dosing regimen for pharmacologic agents commonly used to treat AOP (e.g., caffeine, doxapram)?
- Is prophylactic use of xanthines for AOP safe and effective?

Methodology Requirements for Study

The Pulmonary Work Group identified the following important methodological requirements for studies:

- Studies should include simultaneous assessment of multiple relevant variables, with minimal inclusions being chest wall movement, heart rate, and oximetry.
- A portion of monitoring should include an assessment of nasal airflow to distinguish between central and obstructive apnea.
- AOP must be uniformly defined (e.g., apnea duration of 20 seconds, or 10 to 20 seconds if accompanied by bradycardia [< 80 beats per minute] or desaturation [$SpO_2 < 80\%$]). The work group was unable to resolve a concern about failing to account for apnea events of less than 10 seconds' duration that are associated with significant bradycardia/desaturation.
- Studies should examine treatment duration over the long term (e.g., several weeks) and over a wider range of GAs. The work group noted that current caffeine labeling is for short-term use and 28 to 32 weeks GA.
- Studies must control for conditions believed both to cause apnea and to independently influence outcome (e.g., IVH, PVL, respiratory distress syndrome, BPD, reflux).
- Studies must be randomized and blinded.
- It is appropriate to conduct studies examining reflux treatment and its effect on apnea without necessarily including measurement of reflux. The work group acknowledged that no good evidence is available to support the relationship; nevertheless, clinicians continue to use it. Although apnea and GERD occur in nearly all premature babies, they may be unrelated. The work group agreed that it was important to bridge the investigation of this issue between the

gastrointestinal community and neonatologists because both groups are examining it independently.

Appropriate Outcome Measures

The Pulmonary Work Group agreed that studies need to include and be powered for short-term, intermediate-term, and long-term outcomes. (See proposed clinical trial framework below for more details.)

Ethical Considerations for Future Studies

The Pulmonary Work Group made the following determinations about ethical considerations:

- It is ethical to perform randomized placebo-controlled trials for apnea in preterm infants. The work group recognized that placebo does not mean there is no treatment for apnea. The availability of other treatments such as mechanical ventilation makes a placebo-controlled trial ethical. Moreover, the risk/benefit analysis is acceptable according to the criteria proposed by the Drug Prioritization Work Group.
- It is ethical to perform randomized placebo-controlled trials for reflux (not involving apnea) in preterm infants.
- It is ethical to perform randomized placebo-controlled trials for reflux and apnea, with apnea being the outcome, in preterm infants.

Proposed Clinical Trial Framework

The Pulmonary Work Group proposed a sample framework for the study of apnea in neonates. The design included the characteristics listed in the text box below.

FRAMEWORK FOR A STUDY OF APNEA IN NEONATES

- **Hypothesis**—There is no difference in outcome between patients managed with drug X for apnea versus placebo. Subhypotheses would include the following:
 - There is no difference in apnea (frequency and severity) at predetermined times sequentially measured between drug X and placebo.
 - There is no correlation between apnea (frequency and severity) and neurodevelopmental outcome.
- **Drug priorities**—The following drugs should be used in studies of apnea (in order of priority):
 - Caffeine (Dose-ranging studies with development will need to be performed.)
 - GERD agents for treatment of apnea
 - Drugs for future consideration include specific adenosine receptor subtype antagonists, doxapram, and progesterone
- **Primary Outcome**—The study should be powered for neurodevelopmental outcome at 18 months.
- **Secondary outcomes**—Proposed secondary outcomes include the following:
 - Length of hospitalization
 - Number of days hospitalized for apnea only
 - Frequency and severity of apnea events (measured 2 days after initiation of therapy and weekly until discharge)
 - Duration of assisted ventilation/continuous positive airway pressure (CPAP)
- **Type of study**—The study should be a randomized, blinded, multicenter, placebo-controlled trial.
- **Stratification**—Neonatal groups would be stratified by the following criteria:
 - < 800 grams
 - 800 to 1,200 grams
 - 1,200 to 1,500 grams
- **Sample size**—The work group proposed a range of sample sizes based on a first-pass power analysis, given neurodevelopmental outcome versus control (80 percent power):
 - 3,000 patients to discern a 5-percent difference in incidence of some disorder, (e.g., 30 percent vs. 25 percent)
 - 500 patients to discern a 5-point difference in the Bayley score (SD15)
- **Entry criteria**—Entry criteria would require consideration of the following issues:
 - Use of periextubation caffeine
 - Use of prophylaxis, particularly for very immature infants
 - Use of a nonprophylaxis strategy that might require defining frequency and duration

- **Exclusion criteria**—Infants with the following characteristics would be excluded from the study:
 - Apnea judged to be primarily caused by an alternative etiology (not AOP; e.g., IVH, sepsis)
 - Congenital anomalies
 - Prior study drug exposure
- **Assessment parameters**—The work group identified the following assessment parameters for efficacy, safety, and PK:
 - Short-term parameters include the following:
 - ◇ Frequency, severity, and duration of apnea episodes at periodic time points throughout hospitalization
 - ◇ PK information for various GAs and CAs
 - Intermediate parameters include the following:
 - ◇ Various assessments of duration (e.g., duration of hospitalization, intermittent positive pressure ventilation, O₂)
 - ◇ Morbidities (NEC, IVH, PVL, BPD, ROP)
 - Long-term parameters include cognitive and psychomotor assessment.

Future Research Needs

The Pulmonary Work Group identified the following future research needs:

- A large prospective study is needed to distinguish the role of apnea from the many confounding conditions and other predictors of neurodevelopmental outcome, including GA, neuroanatomic abnormalities, exposure to mechanical ventilation, sepsis, and occurrence of BPD.
- Studies and their analyses should include rigorous control of potentially confounding variables.
- Randomized trials ideally should have a primary hypothesis or co-primary hypotheses powered to assess long-term followup.

Plenary Discussion

During the plenary session, Pulmonary Work Group members and other workshop participants made the following points about the study of apnea in neonates:

- The issue of confounding therapies and morbidities when examining long-term outcomes is an important one that will need to be addressed, perhaps with statistical techniques. The work group considered excluding the smallest babies, who were likely to have comorbidities, but group members believed that the smallest babies were the ones most in need of intervention for apnea and were receiving prophylactic therapy. Multiple variables should fall out if the RCT is large enough.

- Although maturation is more relevant than size to respiratory drive, the work group chose to categorize infants by birth weight because it is more precise than GA.
- The work group may need to consult available PK data to address the issue of whether to adjust drug doses to maintain the same serum levels as the baby grows.
- Many monitoring systems that record retrievable data on heart rate, respiratory rate, and oxygen saturation offer opportunities for documenting apnea events. Nurse observations clearly have been shown to be unreliable in documenting apnea episodes.
- The work group's proposed study is exploring questions that are different from the xanthine study being conducted by Dr. Barbara Schmidt's research group, which is not specifically addressing apnea. Although the work group's study would build on any results from Dr. Schmidt's study, it would explore new territory by asking whether an association exists between AOP and impaired neurodevelopmental outcome and, if so, whether the association is causal. Answering the second question would require an intervention to reduce apnea.
- The work group did not discuss the issue of the potential confounding effect of xanthine, which might affect growth and, thus, long-term outcome. A suggested approach to addressing the issue was to record birth rate velocity.
- The framework will address differentiation between central and obstructive apnea by having a subset of the study measure nasal airflow. This assessment would not be conducted for the entire study because it is impractical to measure airflow on a continuing basis.
- The work group considered the issue of nonapnea desaturation and was unable to resolve concerns about defining AOP in a way that would miss apnea events of less than 10-second duration. The final design of the study will need to address whether to include all events, including two to three second apneas.

Bronchopulmonary Dysplasia

Presented by Michele Walsh, M.D., M.S.

Background

The incidence of chronic lung disease (CLD) varies according to birth weight, with CLD increasing as birth weight decreases. Infants who weigh less than 1,250 grams constitute 97 percent of babies with this condition. The development of CLD is a multifactorial process, with the impact of injury and repair on immature lungs and any imbalance in the processes leading to the CLD called bronchopulmonary dysplasia, which may have lifelong consequences for the infant.

Although neonatal care has improved substantially over the past three decades, BPD continues to occur in about 30 percent of newborns with birth weights below 1,000 grams and contributes to significant morbidity in this population. Because of the gaps in knowledge about the treatment

of BPD in newborns, children treated in NICUs have developed unintended short- and long-term sequelae. For example, preterm newborns with BPD are more likely to develop language delay, cerebral palsy, minor neuromotor dysfunction, and cognitive impairments than are preterm newborns who did not develop BPD.

Study Design Issues

Prior to the workshop, the Pulmonary Work Group identified the following four key issues related to BPD clinical trials in neonates:

Definition of BPD

The work group agreed to use the definition developed by the NICHD Workshop on BPD in 2001. [Note to reviewers: The BPD presentation listed the “NIH Consensus Conference, 2001” as the source of this BPD definition. However, no such conference is listed at the NIH Consensus Development Web site, and the BPD clinical trial issues paper cites the “NICHD BPD workshop summary (2001)” as its source for the definition.] The NICHD definition is stratified by GA, with different endpoints for infants born at less than 32 weeks and those born at 32 or more weeks. The following endpoints are for infants born at less than 32 weeks:

- Mild BPD: Oxygen requirement for the first 28 days but in room air at 36 weeks
- Moderate BPD: Oxygen less than 30 percent at 36 weeks corrected age
- Severe BPD: Oxygen more than 30 percent, CPAP or mechanical ventilation at 36 weeks of gestation

The definition for infants born at more than 32 weeks is adjusted for the time endpoint of 56 days of life. The work group agreed that this definition should be supplemented with the following physiologic definition of BPD:

- Challenged selected infants < 1,250 grams at birth, still in less than 30 percent oxygen at 36 weeks corrected age at 16 research centers
- Calculated the effective FiO₂
- Weaned in stepwise increments to room air so long as saturation stayed at more than 90 percent

The work group felt that these two definitions worked well together to provide information on the severity of disease at 36 weeks as a short-term endpoint.

Subgroups Within BPD

The Pulmonary Work Group identified opportunities to study the following subgroups within the general definition of BPD:

- Infants with extreme risk of mortality
- Subgroups with different components of BPD for targeted therapy:
 - Reactive airway
 - Fluid retention
 - Oxygenation defect
- Genetic susceptibility

Three Phases of BPD

Because BPD is an evolving process of lung injury, the Pulmonary Work Group found it useful to conceptualize BPD in three phases. The work group fine-tuned the periods for intervention in the phases to the following time points:

- **Phase 1**—Prevention of BPD
 - Perinatal: before birth and up to 4 days of age
 - Early postnatal: up to first 7 days
- **Phase 2**—Treatment of Evolving BPD
 - Beginning at 7 to 14 days of age
- **Phase 3**—Treatment of Established BPD
 - Beginning at 28 ± 7 days of age

Use of Corticosteroids

The use of corticosteroids to treat BPD presents the following challenges:

- The majority of RCTs and open-label studies have been performed with dexamethasone and raise the question of whether researchers should be studying another steroid.
- The correct dose and optimal timing are unknown.
- Inhaled steroid deposition to small airways is unknown. This knowledge gap presents a major challenge for treatment with both steroids and aerosolized bronchodilators.
- Existing studies with severe side effect profiles may limit the ability to mount additional trials of similar agents in neonates without going back to preliminary studies and dose-finding activities.

In addition, other drug classes used to treat BPD are largely unstudied. Those studies that have been conducted focus on short-term surrogates. Moreover, long-term studies of efficacy and PK studies are lacking, and toxicities are largely undefined.

Gaps in Knowledge

The Pulmonary Work Group identified two areas in which gaps in current knowledge hamper investigators' ability to conduct effective BPD clinical trials—basic science and pharmacologic knowledge.

Basic Science. Knowledge is limited in the following areas of basic science:

- Normal and abnormal lung development in the smallest infants and how those are perturbed by introduction too soon into the air environment
- Basic biology of BPD, including the following:
 - Biomarkers validated for with the short-term outcome of oxygen requirement at 36 weeks
 - Critical windows for intervention for targeted therapy
 - Genetic susceptibility
- Preclinical science studies, particularly using juvenile animal models

Pharmacologic Knowledge. Current gaps in pharmacologic knowledge are extensive. For example:

- Similarities in pathophysiology to asthma and extensive preclinical work on the role of inflammation in BPD suggest that anti-inflammatory strategies may be beneficial. However, these strategies remain largely unstudied, and major drug classes have not been explored for use in this patient population.
- Evaluation of the possible role of drugs other than corticosteroids is largely unstudied, despite opportunities.
- The use of inhaled bronchodilators and chronic diuretics is widespread, but evidence for efficacy and safety are lacking.

In addition, pharmacologic information is needed in the following areas:

- PK and PD studies for all drugs in this area (PK population studies may be the most workable arrangement.)
- Data analyzed by both postnatal age and postmenstrual age
- Impact of renal and hepatic insufficiency on PK
- Pharmacodynamics
- Pharmacogenomics/proteomics
- Drug-drug interactions (i.e., issue of polypharmacy)

The work group recommended to regulatory bodies that for all drugs considered in neonates, assumptions about excipients—whether preservatives or vehicles for the actual drug—must be taken into account, with an underlying assumption that these are potentially active ingredients unless proven otherwise.

Drug Priorities

The Pulmonary Work Group developed the following list of drugs to be studied in BPD trials:

- Antenatal corticosteroids
- Early use of postnatal corticosteroids
- Bronchodilators
- Diuretics
- Antioxidant therapies
- Anti-inflammatory medications

The work group also suggested studying nutritional agents such as vitamin A.

Other Study Design Issues

The work group identified the following additional study design issues:

- Need to assess long-term outcomes, including language
- Need for parallel group trials with placebo for all drugs
- Need to address issues of open-label drugs and competing drug-drug interactions
- Need to recognize maternal protective and risk factors (e.g., antenatal steroids, tobacco, asthma, chorioamnionitis)
- Need to address neonatal risk factors

Proposed Clinical Trial Framework

Components of the Pulmonary Work Group's proposed BPD clinical trial framework would vary according to the different phases of the disease. However, the overall design would include the characteristics listed in the text box below.

FRAMEWORK FOR A STUDY OF THE TREATMENT OF BPD IN NEWBORNS

- **Type of study**—Placebo-controlled RCT, with no crossover trials so that long-term outcomes can be assessed
- **Entry criteria**—The entry criteria would differ according to the phase of disease studied. Generally, entry criteria would focus on infants of less than 32 weeks GA. In addition to disease, entry criteria would focus on severity and potentially would have stricter criteria for drugs such as glucocorticoids that have a higher potential for harm.
- **Exclusion criteria**—Exclusion criteria would include the following:
 - Newborns with major anomalies, including pulmonary (excluding PDA), airway, genetic, and lethal anomalies
 - Sepsis (type of sepsis needs to be identified)
 - Inability to provide followup
 - Moribund newborns (The work group came to no consensus about the criteria for deciding whether an infant was moribund, except the expectation that the baby would die within 72 hours of the enrollment window.)
- **Exit criteria**—The work group supported stringent predefined criteria for failure to minimize and discourage the use of open-label drugs.
- **Duration of outcome assessment**—The work group supported the following parameters for outcome assessment:
 - Longitudinal evaluations (ideally 8 to 10 years of age), particularly if the studied involve steroids
 - Minimum 2 years of age for assessment
 - Duration dependent on drug class studied (e.g., shorter for diuretics than corticosteroids)

Overarching Issues

The Pulmonary Work Group discussed issues that applied not only to studies on BPD but probably also to the other therapeutic areas addressed in the workshop. These overarching issues included the following:

- More funding is needed for preclinical studies as well as phase 1 clinical trials.
- Better tools are needed for assessing the structure and function of the lung and brain.
- The participation of neonatologists is needed in trials of unproven but existing and widely used therapies (e.g. diuretics).
- Investigators are increasingly encountering the perception among families that clinical research is experimentation on their children.

- The research infrastructure for conducting neonatal trials needs to include a biopharmacologist, a toxicologist, and a statistician. The participation of an ethicist was helpful to the work group.
- Multidisciplinary research teams need to be assembled and need to include specialists in neonatology, pulmonology, and neurodevelopment.
- Methods and funding are needed to track families for long-term assessments.

Future Directions

The Pulmonary Work Group ended its discussion by looking to the future of BPD studies in neonates. The group identified the following new drugs that have some potential for future study:

- Superoxide dismutase (SOD)
- IL-10
- Proteinase inhibitors
- TNF-alpha antagonists
- New surfactant components (e.g., SP-B), surfactant boost at 10 to 14 days
- Novel anti-inflammatory agents
- iNO
- CC 10
- Bombesin blocking antibody
- Vitamin A (noninjectable)

Other areas for future research include the following:

- New and less expensive alternatives (e.g., phone/journal contact) to the current standard long-term followup programs
- Role of MRIs at term
- Growth outcomes
- Functional outcome measures that include more widespread measures of health

Plenary Discussion

During the plenary session discussion, Pulmonary Work Group members and other workshop participants made the following points about the study of BPD in neonates:

- The work group discussed the possibility that different agents or strategies would be more effective at different phases of BPD. The group agreed in general that an anti-inflammatory approach including steroids might be more effective in the prevention and early treatment phases of the disease. The role of these agents was uncertain in the later phases of disease, when treatment targeted to specific problems (e.g., fluid retention or continued oxygenation defect) would be more appropriate. Treatment also would vary according to GA because mechanisms may be different in the three stratified age groups.
- Educating the public, parents, and other groups about neonatal research is an important issue that applies to all NDDI work groups. Although considerable publicity surrounds the dangers of conducting research in this population, little information is disseminated about the danger of *not* performing the right studies in neonates and the uncontrolled experiments that are conducted daily with off-label use of drugs in infants. The scientific community needs to educate the public about neonatal research, rather than let the media and less educated persons take charge of the issue, with potentially detrimental effects.
- Regarding health and growth outcomes for BPD studies, the work group discussed pulmonary and respiratory disease outcomes. Some standardized tools have been validated in pulmonary populations (e.g., infants with cystic fibrosis). The work group discussed infant pulmonary testing, but thought that although tests exist for different ages, they may not be widespread in their applicability. The work group agreed that pulmonologists could play an important role in trial design and assessment.

Crosscutting Issues

Ethics

Presented by Robert Nelson, M.D., Ph.D.

Members of the Ethics Work Group were assigned to the various work groups focused on therapeutic areas. Although issues and proposed study designs varied among the different work groups, the overall impression of the work group members was that the ethical issues involved in designing studies that seek to validate current or emerging medical practice are solvable in one way or another. The Ethics Work Group identified five major themes emerging from the discussions of the other work groups.

Scientific Necessity

The first question that needs to be answered when designing a clinical trial study is whether it is scientifically necessary to conduct the research in neonates. If the answer is no, the study should not be performed. However, the answer often is yes because no appropriate juvenile animal models exist or data cannot be extrapolated from other populations.

It is important to set studies in the context of rational drug development, which is an incremental process of building evidence to support drug labeling. However, many of the drugs discussed by the work groups have been used in practice for years without undergoing rational drug development. Moreover, most academic researchers usually do not conduct rational drug development and may need to learn new skills in designing studies and gathering evidence with drug labeling as the endpoint.

Balancing Risks and Potential Benefits

Three major issues emerged related to balancing risks and potential benefits in neonate clinical trials:

- **Component Analysis of Risks**—A recent report by the Institute of Medicine (IOM), *Ethical Conduct of Clinical Research Involving Children*, recommended that institutional review boards (IRBs) should assess the potential harms and benefits of each intervention or procedure in a pediatric protocol. IOM further stated that when some procedures present the prospect of direct benefits and others do not, the potential benefits from one component of the research should not be held to offset or justify the risks presented by another component. Thus, researchers need to look separately at interventions that offer benefit and those that do not. Interventions or procedures with no prospect of direct benefit need to limit risks to either minimal risk or no more than a minor increase over minimal risk. The justification of risk needs to be different for interventions that offer the prospect of direct benefit. For these types of studies, the anticipated benefit to the subjects must justify the risk, and the relation of the anticipated benefit to the risk must be at least as favorable to the subjects as that presented by alternative approaches available both within the trial and outside of the trial.

- **Equipoise and the Choice of Control Group**—The Canadian Tri-Council Policy Statement of August 1998 defines clinical research equipoise as “a genuine uncertainty on the part of the expert medical community about the comparative therapeutic merits of each arm of a clinical trial. The tenet of clinical equipoise provides a clear moral foundation to the requirements that the health care of subjects not be disadvantaged by research participation.” Uncertainty on the part of the expert medical community does not necessarily mean that each individual in that community is uncertain; equipoise could exist if half of the community was passionately in favor of one alternative, and half was passionately in favor of another alternative. Studies that withhold “standard” treatment must meet one of two criteria: (1) achieving equipoise, or balance, between the alternatives; or (2) structuring the withholding of standard treatment to restrict the risk to “no more than a minor increase over minimal risk.” Additional challenges include achieving clinical or personal equipoise among the investigators and participating clinicians and balancing research equipoise with clinical acceptability.
- **Ethics of “Off-Label” Practice**—The difficulty of achieving equipoise is exacerbated by the fact that, because the FDA does not regulate the practice of medicine, physicians administer medications without regard to what is written on drug labels. In addition, physicians often believe the myth that they “know what is best” for a patient in the absence of information on drug safety or efficacy. The difficulty is further compounded by the societal attitude that intervention is best (if a drug is available, use it) combined with the assumption that physicians would not engage in “off-label” drug use if it had not been proven safe and effective.

Process of Parental Permission

Off-label drug use makes it harder to convince parents that they should enroll their infant in the study of a drug that has been in clinical practice for years. Because issues concerning recruitment and consent processes will vary across protocols, there is no one solution for the approaches discussed by the work groups. Issues that need to be addressed include the timing of recruitment; the therapeutic misconception concerning research versus the “standard of care”; and the timing of the intervention, or the “therapeutic window,” which may require obtaining parental permission within a narrow time frame or using an ongoing communication process rather than the orthodox informed-consent approach.

Efficiency and Effectiveness of IRB Review

Claims that a study design is “not approvable by an IRB” need to clarify whether the impediment involves ethical, design, or IRB issues. The variability in the quality of IRB reviews is well documented. However, the proposed shift to a centralized IRB process for the sake of efficiency could potentially lose the effectiveness of the review. A key aspect to enhancing IRB review is transparency (e.g., providing information about the issues reviewed by the IRB) and communication between IRBs. In addition, submitted protocol documents need to include more substantive discussion of ethical concerns. Another potential innovation is the development of IRB coordinating centers that would assist investigators in multicenter networks with the design and local implementation of studies.

Multicenter Collaboration

The performance of multicenter studies are undermined by firmly held biases in the absence of supporting data and by the current system of academic incentives that reward individual rather than group behavior. A lesson might be learned from oncologists, who have linked individual productivity to group research productivity. Such lessons are important because multicenter collaboration in defining a consistent standard of care is a necessary first step in the ethical design of research.

Plenary Discussion

During the plenary session discussion, Ethics Work Group members and other workshop participants made the following points about ethical considerations for neonate clinical trial design:

- The cost of IRB approvals in multiple centers is an important consideration in the proposed development of IRB coordinating centers. A study reported in the *Journal of the American Medical Association* estimated that an eight-center study incurred \$56,000 in additional research costs for the IRB approval process. It might be useful to concentrate pediatric expertise in an IRB coordinating center.
- Because the IRB system has been generally underfunded, the level of support needed for the process is not clear. However, the cost for IRB approval should be consistent with the quality of the product. Mechanisms exist for developing transparency that is cost-effective. See www.IRBNet.org for information on how one NIH-funded project is trying to develop a mechanism that would allow multi-institutional research that is cost-effective.
- The IOM report on pediatric research can provide additional guidance on the definition of minimal risk for balancing risks and potential benefits. Briefly, the IOM recommends that minimal risk be indexed to the healthy population rather than to the sick population. A minor increase over minimal risk should be indexed to the condition of the child. The IOM report and the National Human Research Protection Advisory Committee list procedures and provide guidance on what constitutes minimal risk. For example, heelsticks would be considered minimal risk. Dr. Nelson suggested that investigators discuss this component of analysis of risk in the section of their protocols dealing with IRB issues, rather than let the IRB make the determination. This approach would help to reduce variability in the quality of IRB reviews.
- Enrollment of the same participant in multiple studies is ethically acceptable if one study is simple and another is complex, and if outcome measures do not overlap so as to obscure an answer to a question. If these conditions are absent, then a coherent combination study could be designed. Such a study might be more complex, such as including four arms, but would enable investigators to combine two studies in one population.
- The ethical issue of enrollment in multiple trials has not been well studied. More empirical evidence is needed to determine the number of studies in which children could be

simultaneously involved. Scientific issues include the incompatibility of certain types of studies; for example, one investigational new drug (IND) study should not be combined with the study of another investigational drug or device. However, many of the interventions discussed at the workshop involve long established treatments. Consequently, it is preferable to have a patient's second intervention randomized rather than left to individual discretion, if that second intervention already is happening as a co-intervention because it is so commonly but variably used. Enrollment in multiple studies with specified interventions also would provide control over variables in clinical practice that might profoundly affect endpoints and scatter results.

- In studies of the same population with the same outcomes, it is important to assess the outcomes in the same manner. Conducting standardized testing at the same age would allow investigators to pool all samples and increase power to conduct multifactorial analysis.

Prioritization of Drugs To Study in the Newborn

Presented by Robert Ward, M.D.

The goal of the Drug Prioritization Work Group was to determine factors that identify which drugs are most important for study in neonates, especially when resources are limited. A secondary goal was to develop a list of criteria that would help to inform FDA review committees, which often lack pediatric and neonatal input regarding the evaluation of new drugs.

Factors Supporting Studies

The Drug Prioritization Work Group used five categories (i.e., disease/indication, evidence, drug, feasibility, ethics) to describe factors that it considered important for studying drugs in newborns. Within these categories, the work group identified the following 23 factors that favor studies in neonates (on a scale of 0 to 5, higher scores indicate a greater need for study):

Disease/Indication Factors

- **Potential for adverse outcomes (morbidity, mortality, long-term disability) associated with the disease based on studies in neonates**—If the risk for known morbidity or mortality was high or frequent, the drug warrants study for treatment of the disease. (Score = 5) If the risk had not been studied in neonates but a treatment was now available, the drug warrants study. (Score = 5)
- **Disease or indication unique to the neonatal population**—If the disease or indication occurs almost exclusively in neonates, the drug warrants study. (Score = 5)
- **Frequency in neonatal population(s) based on a valid database**—The increasing frequency of a disease or indication in neonates increases the need for study in that population. The highest priority for study is a disease or indication that is common in specific neonatal populations or moderately frequent in all neonatal populations (> 2,000 cases per year). (Score = 5)

- **Diversity of the severity or distribution/frequency of disease varying by gender, race, or ethnicity (genetic variation)**—If a disease is more common in a specific gender or racial group, it might warrant study. (Score = 2)
- **Diversity of the severity or distribution/frequency of disease varying by gestational age or postnatal age**—If the disease frequency or severity is much more common in specific GAs (e.g., 23 to 28 weeks) of term and preterm neonates, study is warranted. (Score = 5)

Evidence Factors

- **Evidence for treatment not established in neonates**—Study is recommended if no evidence is available to support efficacy in neonates, even though efficacy is established in older populations for a similar disorder. (Score = 5)
- **Efficacy of treatment established in alternate populations for the same disease or indication**—The interest in studying a drug is increased if efficacy is established in infants and children age 1 to 24 months but not in term or preterm neonates. (Score = 5)

Drug Factors

- **Duration of drug exposure**—Increasing duration of exposure increases the need for studying the drug, especially if the anticipated duration of exposure is more than 28 days with direct evidence that drug accumulation will occur. (Score = 5)
- **No appropriate formulation for neonatal populations**—Study is warranted if administration of the drug requires manipulation of existing formulation (e.g., dividing existing powder by weight, pulverizing a tablet to put it into solution or suspension, subdividing existing liquid dose into smaller aliquots, using parenteral formulations orally). (Score = 5)
- **Potential or known toxicity of the drug**—The need for study is increased if the risk for known morbidity or mortality is high or frequent or if toxicity in other populations is due to factors that are likely to be more frequent in neonates (e.g., reduced clearance, open blood-brain barrier). (Score = 5) [Note: Although this factor by itself may seem to be a reason not to study the drug, it is important to consider toxicity as part of an aggregate score that includes the other 22 factors.]
- **Known clinically relevant drug-disease interactions**—Known interactions between the drug and diseases that occur in neonates warrant study to determine the drug's safe and effective use in neonates. (Score = 3)
- **Known clinically relevant drug-drug interactions**—Known interactions between drugs that are used to treat neonates warrant study to determine drug safety and effectiveness in neonates. (Score = 3)

- **Drug disposition unknown or varying by gestational age, postnatal age, gender, race, or ethnicity (genetic variation)**—Study is warranted if drug disposition pathways are unknown or are known and vary with the maturation of renal, hepatic, gastrointestinal, or other organ function that changes significantly during the neonatal period. (Score = 5)
- **Frequency of off-label drug use**—Study is warranted if the dosing and indications for a drug are not labeled for any neonates, yet the drug is used frequently in some neonatal subpopulation. (Score = 5)
- **Preclinical evidence of toxicity**—A drug warrants study if there is preclinical evidence of reversible, non-life-threatening toxicity that is likely to occur in neonates. (Score = 5)
- **Availability of alternative, similar treatment**—Study should be prioritized if no alternate, similar drug has been studied and shown to be safe and effective for the proposed indication (Score = 5) or if the new drug has been shown in other pediatric populations to increase safety or efficacy over existing treatments. (Score = 5)

Feasibility Factors

- **Likely availability of adequate number of appropriate subjects**—Study is warranted if the indication occurs with a frequency that could result in an adequate and representative study population for a multicenter study of two to five sites. (Score = 5)
- **Assay available or can be readily developed**—Study is warranted if drug concentrations and safety laboratories can be studied within the blood volume limits set by the NIH guidelines per body weight. (Score = 5)
- **Clinically relevant endpoints that are identifiable and reliably measured in neonates**—Study is warranted if endpoints are directly relevant to the indication and can be measured easily in neonates (e.g., sterilizing blood stream infections, achieving a specific blood pressure). (Score = 5)
- **Disease can be studied in the neonatal population**—A drug is most highly recommended for study if the disease can be studied in all populations of neonates. (Score = 5)

Ethical Factors

- **Benefit or harm of drug exposure appropriate for the study population**—A drug is recommended for study if the risk is low (a frequency of 10 percent or less with minimal severity) and the benefit is high (more than 50 percent) from neonatal treatment. (Score = 5)
- **Benefit or harm of study methodology appropriate**—A drug is recommended for study if the study methodology represents a risk of 5-percent or less frequency with minimal severity over the usual risks from usual care for the study indication. (Score = 5)

- **Benefits of a new treatment relative to existing treatment**—A study is most highly recommended if the new drug is shown in other populations to significantly increase safety or efficacy over existing treatments. (Score = 5)

Additional Issues and Questions

The Drug Prioritization Work Group also raised the following issues and unanswered questions:

- Are the suggested criteria clear and unique?
- Do the suggested criteria discriminate among drugs?
- Do the large numbers of factors obscure differences between drugs? (The work group noted that it was important to outline all factors that would identify issues relevant to neonatal studies.)
- How should drugs for different disease categories be evaluated and prioritized (e.g., a drug for the cardiac system versus a drug for the respiratory system, a drug for analgesia versus a drug for infection)?
- Should the risk of treatment and the risk of the disease favor or discourage study?
- Are the weights of all the scores of 3 and 5 equivalent among the various factors?

Next Steps

The Drug Prioritization Work Group proposed testing the discriminatory value of these criteria for studying a drug against prioritization by a group of experienced neonatologists. These individuals would be asked to prioritize a group of 20 drugs for their need for study. The neonatologists would then be asked to apply the work group's proposed scoring system to the same 20 drugs. The work group will compare the two sets of rankings and use statistical analysis to identify factors that correlate with each other. The work group will then develop a shorter list of factors that can prioritize drugs effectively.

Plenary Discussion

During the plenary session, Drug Prioritization Work Group members and other workshop participants made the following points about drug prioritization:

- Another way to test the work group's scoring system is to ask members of each of the other work groups to prioritize the drugs within their respective therapeutic areas using the suggested criteria. Another factor that might be included is a drug's use across a variety of conditions (e.g., analgesic drugs).
- Concerns were expressed about the possibility that pharmaceutical companies might stop making certain drugs if they find they are not getting sufficient return on their investment.

Dr. Ward reported that the reasons for the cessation of the availability of drugs in the past 4 to 5 years usually are related to manufacturing issues that arise after an FDA inspection rather than because of a profit motive. The FDA has an office of drug shortages that may be able to answer some questions about shortages.

- In response to a question about how to stop the off-label use of drugs in neonates, Dr. Ward replied that the most effective way to reduce off-label treatment is to study the drugs in the neonatal population. The study of surfactants for respiratory distress syndrome provides an example of how RCTs can be conducted effectively in this population. The goal is for drug inserts to contain relevant information (e.g., genetics of the population, pathways of clearance) that will allow neonatologists to make informed assessments of the risk factors involved in using the drugs in their patients.
- One important issue is the problem of creating labels for widely used drugs that have no sponsor for clinical trials. Generic companies often make these drugs. Currently, only the owner of the label can change the label for such drugs, and legislation probably is needed to change how labeling can occur. A process does exist for changing labels in off-patent drugs without the consent of the label owner. If the owner turns down a Written Request by the FDA and a study of the drug shows a major difference in the label, then the FDA can insist that the owner change the label. If the owner does not change the label, a legislated advisory committee can review the issue. If the advisory committee finds in favor of the FDA, the owner must change the label or the drug will be considered misbranded. If the study has been sponsored by a Federal agency, the data collected during the study will be publicly accessible while the issue is being considered. Although this review process is a critical one, it is expensive and time-consuming. Therefore, its application probably is limited to only a few instances.

Future Directions for the NDDI

Workshop Chair Summation

Presented by Eduardo Bancalari, M.D.

Dr. Bancalari, M.D., reflected on the two days of intensive and productive discussion and predicted that the work done before and during the workshop would have a significant impact on the future practice of neonatology. He noted that the dissemination of information generated by the workshop should increase awareness of the lack of safety and efficacy evidence for the use of many medications in neonates. The field also will benefit from workshop discussions that have clearly delineated the considerable challenges in evaluating medications in babies younger than 28 weeks, including the many confounding factors that occur in these preterm infants, the gaps in knowledge concerning the mechanisms of diseases that affect neonates, ethical considerations, and the difficulty of achieving equipoise among clinicians participating in studies. In addition, the clinical trial frameworks developed by the work groups should help the pharmaceutical industry, the NIH and the FDA, and the clinical investigators who embark on answering some of the critical questions raised at the workshop.

Acknowledging the critical need for clinical research on the drugs currently used in neonates, Dr. Bancalari called attention to other areas needing study, including the development and testing of new pharmaceutical agents for the care of these infants, studies in other therapeutic areas such as infectious and gastrointestinal diseases, and studies of long-term effects in neonates.

Dr. Bancalari noted that it was important to ensure that the work invested during the past year was carried forward. He invited work group chairs to participate in a discussion of how to implement recommendations generated at the workshop.

Summary of Questionnaire Data

Presented by Susan McCune, M.D.

Before turning to the future, Susan McCune, M.D., who will join Dr. Giacoia as co-chair of the NDDI, presented a brief summary of preliminary data about the review process used by the NDDI during the past 14 months. The data were collected through a questionnaire completed by work group members about the benefit of the extended process of planning and discussion conducted by the groups. In addition, the questionnaire asked respondents to identify ways to improve future activities and processes for considering pediatric clinical trial issues.

Dr. McCune reported the following findings from a preliminary analysis of responses to the questionnaire:

- Most respondents said they understood the purpose of the NDDI, the work to be done, and the overall objectives and goals of the initiative. However, for some respondents, these elements were not clarified until the opening session of the workshop. In future efforts, many respondents would like to have the goals and objectives articulated at the beginning of the process.
- Workshop product utilization is a work in progress, and some respondents were somewhat confused about how the information from the workshop would ultimately be turned into drug labeling for pediatric patients. Another issue is how to publish the primary output of the workshop so that all colleagues will be informed about this important work.
- Respondents were fairly familiar with the conduct of pediatric trials in health centers, but the FDA could help people better understand the process of drug labeling in pediatrics.
- Everyone was fairly satisfied with the core composition of the work groups and very satisfied with the multidisciplinary composition of the groups.
- Most people felt that sufficient time was allowed for the work group discussion. Several people in the Pain Control Work Group would have liked more time.
- Opinions about the teleconferences varied among the work groups, with the Pain Control Work Group rating them as “very productive.”

- In general, members of smaller work groups found the workshop to be more productive than did some members of the larger Pain Control Work Group.
- Respondents thought that the reactors understood their roles. Comments indicated very positive reinforcement to having reactors participate in the workshop.
- Most people felt that they would like to have an ethicist involved from the beginning of the process.
- A large majority of respondents thought that the presence of a biostatistician on the work groups would have helped in the design of the clinical trial framework during preworkshop activities or at the workshop.
- Most people thought that NICHD and FDA facilitators were helpful and that the time allotted for preworkshop activities was appropriate.

Positive responses to yes/no questions varied among work groups, but Dr. McCune noted that the high percentage of positive responses indicating an interest in future NDDI work group participation was heartening.

Written comments by respondents indicated that people were very interested in continuing to develop clinical trial frameworks to look at study questions and methodologies and to develop finalized protocols into Written Requests, Requests for Proposals (RFPs), and, ultimately, labeling of drugs.

Planning Workshop Roundtable

Presented by George Giacoia, M.D.

As part of planning for future NDDI activities, Dr. Giacoia asked the work group chairs to envision their future involvement with the initiative. Chairs agreed that the efforts begun by the work groups were not completed and suggested undertaking future activities such as continued collaboration and refinement of work group documents and the possible development of a clinical trials network that could implement some of the work outlined during the workshop.

It was noted that the work groups have fulfilled the charge of examining existing data and drugs, identifying gaps in knowledge, and identifying drugs that should be studied. However, concern was raised about the work groups developing frameworks or protocols that others would study, if work group members would not be eligible to compete for contracts to conduct the studies they have designed. Dr. Giacoia clarified that the NICHD would write the RFPs, and no one would be excluded from applying. However, an important issue was to develop an appropriate design or framework that could be applied to a number of different drugs in certain therapeutic areas. The challenge was whether the NICHD could use information provided by the work groups to look at common elements among the proposed frameworks and to move forward to the next stage, rather than shifting to an examination of other drugs.

Dr. Giacoia reiterated that published workshop products would be part of an ongoing process that would use various methods to disseminate knowledge generated by the workshop. This dissemination is important to obtaining buy-in for future NDDI efforts, including the studies proposed at the workshop. Dr. Giacoia noted that the NDDI still needs to address issues such as ethical concerns about possible exceptions to the informed-consent process and the collection of samples for proteomic studies and long-term followup. Thus, Workshop I is only one step in a continuum of NDDI activities.

Dr. Nelson noted that the process of informed consent in the different proposed frameworks was variable. He thought that it would be possible to design a communication process that would meet ethical concerns about appropriate communication and perhaps be better than the IRB informed-consent process. However, such a process would require an exception from an IRB informed consent because researchers would be starting an intervention before they have parents' signatures on a form. As an example, Dr. Nelson described a process used at the Children's Hospital of Philadelphia for a proposed trial of hypothermia within 30 minutes of cardiac arrest in inpatients. A focus group found that parents agreed it was not feasible to obtain informed consent within a half-hour of their child being resuscitated for cardiac arrest. However, the parents wanted an ongoing communication process that would allow them to dissent as soon as possible. This model might be useful for the proposed hypothermia trials and studies involving the administration of PB at the time of birth.

Concluding Remarks

Presented by George Giacoia, M.D., and Donald Mattison, M.D.

Dr. Mattison provided additional insights on the NDDI process, which has been ongoing for the past 2 years. He explained that although the need for trials in newborns was recognized, controversies emerged about the design of appropriate clinical trials to study therapeutic strategies in this population. The need for the NICHD to obtain more partners and input for certain kinds of newborn clinical trials led to the first NDDI workshop. The NICHD intends to bring together all the material from the workshop into a single publication, possibly a journal supplement that would be available both in print and electronically.

Dr. Mattison acknowledged that the NICHD and the FDA will need to access practicing experts in other groups within the pediatric population for help with developing appropriate clinical trial strategies and ethical approaches. Both agencies hope to continue to engage workshop participants in NDDI activities as the NICHD and the FDA go forward in implementing the BPCA.

Dr. Mattison clarified the process by which the NIH works with the FDA to develop Written Requests to conduct pediatric trials and translate them into RFPs. The process for off-patent drugs includes the following steps:

- The NIH develops on a regular basis (at least annually) an updated list of off-patent therapies that “most urgently” require study in pediatric populations for label modifications.

- The NIH establishes a procedure to study off-patent drugs from a priority list in collaboration with the FDA and NIH Institutes. This procedure includes the following actions:
 - The NIH distributes funding for the BPCA among many Institutes, with approximately 25 percent of the funding going to the NICHD.
 - The NICHD organizes a study design team with the FDA and relevant NIH Institutes.
 - The NICHD has primary responsibility for organizing, contracting, and monitoring IND data for potential label modification as well as drafting as well as drafting label modifications for specific ages and indications.
- After the NIH develops a priority list of off-patent drugs, the FDA issues a Written Request to producers and distributors of a drug, who have 30 days to respond.
- If industry does not respond or declines to conduct studies on the drug, the referral comes back to the NIH.
- The NIH evaluates the declined written request and assigns it to NIH clinical scientists at the NICHD and another NIH Institute to develop into a description of what is considered the appropriate clinical trial.
- The more detailed description ultimately becomes a Statement of Work that the NIH would like a group of clinical investigators to perform.
- The Statement of Work becomes a Request for Proposals, which is published and competed.
- The NICHD's Contracts Management Branch manages the RFP.
- Responses to the RFP are sent to the NICHD's Division of Scientific Review and reviewed by a scientific review team led by a scientific officer.
- Contracts are awarded for preclinical and clinical studies.
- After a contract is awarded, the NICHD works with the principal investigator and the FDA to negotiate the IND.
- The clinical trial leads to development of data that are submitted to the FDA for modification of the drug label.
- This information is presented to the FDA's Pediatric Advisory Committee.
- The NICHD works with the FDA and the advisory committee to propose a label modification.
- If industry wants to oppose changes to the label, it can institute a complaint and review process that ultimately could engage the Secretary of Health and Human Services.
- FDA and NICHD involvement ends after the label is modified.

Dr. Mattison added that workshop participants have been engaged in an attempt to build a rational approach to developing neonatal clinical trials within the context of the BPCA. Participants have been invaluable to this process and will be needed as the NICHD and the FDA prepare workshop material for publication and develop clinical trials. Dr. Mattison expressed his hope that other networks (e.g., pediatric, neonatal, pharmacological) will become engaged in the continuing NDDI process.