

# **Appendix A**

## **Appendix A**

### **Cardiology: Summary of Breakout Discussion**

The Cardiology Work Group focused on these two areas of need in constructing frameworks for the study of drugs for newborns—inotrope usage in VLBW neonates and postoperative neonatal cardiac patients.

#### **Inotropes in VLBW Neonates**

The group began with three study proposals for premature, low birth weight babies: a randomized clinical trial comparing a new agent to a “gold standard”; a dose-ranging study; and a goal-directed study, in which infants would be randomized to receive an inotrope targeting a high or low normal blood pressure for 28 days. It was initially believed that a placebo-controlled study would not be well accepted.

During the breakout discussion, the work group engaged in considerable debate about a range of general and specific issues related to the study design. Highlights of key points made during the discussion about various issues follow.

#### **General Study Design**

During the initial general discussion, work group members made the following points:

- The presence of a shunt in a baby makes it hard to measure blood pressure.
- SVC flow may be a good measure of cardiac output, but it has not yet been validated in neonates.
- Just raising blood pressure may do nothing for brain, kidneys, and other organs.
- Some evidence in the literature suggests that DOB is better than DA at improving cerebral blood flow in the first 48 hours after birth. However, blood pressure is not necessarily a good marker of cerebral blood flow.
- A key question is whether there is a difference between going to the lower limit of blood pressure or keeping the baby in the midrange.
- Neonates and preterm babies face many other health problems besides low blood pressure, including hydration and temperature control. These babies are born with normal blood pressure (above 10 percent), and within an hour, their blood pressure falls. The etiology of this drop is unknown.
- A placebo-controlled study should be conducted only if randomization involving two blood pressure ranges is dropped.

- The proposed study could have three arms: 10th percentile, 90th percentile, and “wild type,” or unscripted practice, in which physicians would be allowed to treat using their own judgment.
- There was much negative response to the idea of a prevention trial, rather than a treatment trial.
- Hypotension is not associated with poor neurological outcome, but wavering blood pressure *is* associated with poor neurological outcome.
- About 63 percent of neonates survive in the group weighing 500–750 grams, and about 90 percent survive in the group weighing more than 750 grams.
- The incidence of IVH is 20 percent in the group of neonates weighing 500–750 grams, and 10 percent among the larger babies.
- PVL is a good predictor of outcome; IVH is not.

Additional discussion addressed the issues of whether to use epinephrine in a study, either as a treatment drug or as a rescue drug; to withhold treatment of neonates until they are symptomatic; and to compare two different drugs or to run a placebo-controlled study.

### **Study Objectives**

It was suggested that the study objectives should be to assess pharmacokinetics and pharmacodynamics, assess the efficacy and safety of the inotrope, and validate hemodynamic norms (blood pressure and SVC flow). The discussion centered on whether nurses and clinicians would agree to double the dosage of the study drug. It was agreed that the study would have to be designed to ensure buy-in from these two essential groups.

### **Stratification**

The age groups to be studied would include premature infants who were less than 28 weeks of age and weighed less than 1,000 grams. These babies would have normal cardiac anatomy and weigh 400 to 750 grams. (The original study design comprised two groups of babies stratified by weight: 500–750 grams and 751–1,000 grams.) The work group consensus was to extend the study to babies weighing as little as 400 grams and to include fewer babies because it would not be practical to enroll 800 babies in the study.

### **Standardization of Therapy**

Issues surrounding standardization of therapy include intravascular volume management, sequential therapy, a possible rescue therapy protocol, handling of recurrence, and the treatment of the randomization blood pressure target. The following areas were discussed regarding standardization of therapy:

- Rescue therapy and what neonatologists would agree to as rescue therapy
- Various possibilities for endpoints
- Intact survival as the endpoint (A surrogate outcome could be composite, using IVH, NEC, PVL, sepsis, and other conditions, which would be weighted. If a child goes home with a low composite score, the child had done well.)
- The possibility of extending the study to 2 years of age

### **Entry Criteria**

It was proposed that infants be enrolled prenatally, targeting high-risk pregnancies with expected delivery at 28 weeks. The plan was to randomize to a preventive design with two arms: “high normal” or “low normal” blood pressure (derived from published norms) or to randomize to a preventive versus symptomatic design with two arms: blood pressure of 25th to 50th percentile or placebo with rescue.

### **Exclusion Criteria**

The following exclusion criteria were proposed:

- Severe congenital anomaly incompatible with long-term survival
- Congenital heart disease with exception of PDA
- SGA or IUGR
- Clinically significant PDA after 5 days of life

### **Assessment Parameters**

The following efficacy and safety parameters were proposed:

- Primary endpoints: combined endpoint of survival to 28 days and IVH/PVL
- Secondary endpoints: NEC, ROP, perfusion and acidosis, organ damage, health care utilization (duration of ventilator), support, time in NICU, measures of need for resuscitation, duration of pressor support, total number of drugs needed to achieve targeted blood pressure, adverse events
- Long-term outcomes: chronic lung disease, neurodevelopment at 18 and 24 months, ROP
- PK/PD: drug levels, hemodynamic parameters (blood pressure, CO, SVC flow), metabolic parameters (lactate, BNP), tissue perfusion (gastric pH, brain infrared spectroscopy)

- Concern about a hemodynamic endpoint because if only that is used, the study will find what you want to find. First, optimum blood pressure ranges are needed.
- A weighted composite outcome using number of sepsis episodes, IVH/PVL, NEC, retinopathy, etc. If a baby goes home with a low composite score, that would be a success.

Work group discussion of assessment parameters included the following points:

- It needs to be determined when and how often assessments should be conducted.
- The measure-of-perfusion index would be interesting to use but is not well defined.
- Near infrared spectroscopy should be looked at as a measure in some centers, but only if MRIs become standard.
- The percentage of lower weight babies who persistently have blood pressure at or below the 10th percentile in the first week could affect the rescue design. If all babies were to eventually exit the study in the first 7 days, a placebo-controlled study could not be done.

### **Long-Term Followup**

The work group modified the original suggestion that the study should follow babies for 2 years. After much discussion, the consensus was that a much shorter study of less than 28 days (probably 7 days) was better and would eliminate some of the confounders.

### **Study Design Issues**

Discussion about study design focused on two key issues: a concern about a two-factorial design for DA and DOB with blood pressure targeting and drug sequencing, and the question of whether cuff blood pressure measurements can be used if UACs or arterial blood pressure is not available. Discussion of the study design included the following key points:

- The study could be set up to disprove the null hypothesis.
- Some work group members disagreed with the use of steroids in neonates or would greatly restrict the use of steroids.
- The milrinone study showed that clinicians could use whatever therapy they thought was best for the child after they had bailed out of the study. The same practice could be followed in the blood pressure study, with data being collected on the rescue therapy chosen by the clinicians.
- Bailout should not be based on blood pressure alone but also on end-organ compromise.
- There is value in doing a stimulation test and collecting data on the results of the test.

- There is a need to build in other clinical measures to detect LCOS because blood pressure is only one clue to LCOS.
- Ways to control for PDA as a confounder need to be explored although some institutions do not think the presence of PDA is important.

### **Ethical Issues**

The work group considered the following ethical issues:

- Obtaining informed consent in an ill population
- Use of placebo in a seriously ill population
- Performing studies in the setting of widely accepted (although unproven) treatments

The discussion of ethical issues included the following points:

- The study would get consent from the mother when she is in preterm labor. Reconsent would be needed after the birth.
- Neither preterm nor postnatal consent is a valid consent. An ongoing consent dialog is needed, but consent obtained during labor is enough to start the study.
- According to NIH regulations, the consent of both parents is needed for this type of study.

### **Clinical Trial Framework**

The Cardiology Group decided, after much discussion, that it was not ready to finalize a clinical trial framework before collecting data from neonatologists about issues discussed over the course of the breakout session. 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. The most important study question was thought to be whether treatment in the neonate is protective or harmful.

The work group agreed on the following hypotheses for the study:

- Hypotension in neonates is associated with increased risk of adverse outcomes.
- Preventing hypotension is protective.

The work group agreed on the following characteristics of the study:

- Pilot studies are necessary before a large trial.
- Target population is a 400- to 1,000-gram premature infant.

- Enroll prenatally.
- Use an arterial line.
- Exclude severe congenital anomaly, CHD (except PDA), SGA, or IUGR.
- Outcomes to be measured:
  - Primary outcomes: combined endpoint of mortality, IVH day 7, PVL day 28, or discharge
  - Secondary outcomes: NEC, ROP, BPD, long-term neurodevelopment, adverse events (arrhythmia, HTN, seizures)
  - Additional outcomes: SVC flow, cerebral oxygenation, MRI, pulse ox perfusion index, PK/PD

The work group agreed to present the following questions to neonatologists:

- What drug do you use first line—epinephrine, dopamine, or dobutamine?
- Do you use hydrocortisone to treat refractory hypotension?
- Would you perform a placebo-controlled trial in this setting if rescue occurred with a blood pressure < 20 mm Hg (400–750 grams)?
- Would you conduct a trial that used clinical signs only (e.g., poor cap refill, oliguria, acidosis) with no use of an arterial line/blood pressure measurement?

### **Critical Gaps in Knowledge**

The critical gaps in this study design are the optimal ranges for blood pressure in neonates and the fact that blood pressure may not accurately reflect cardiac output and end organ perfusion. The major unanswered questions follow:

- When do we treat blood pressure level?
- At what blood pressure level do we treat?
- Should we do a study to define what is appropriate blood pressure?

### **Vasoactive Agents in Postoperative Neonates**

The cardiology work group considered the initial study design for trials of vasoactive agents in postoperative cardiac neonates and discussed a range of related issues. Highlights of key points made during the discussion about various issues follow.

## **General Study Design**

The work group discussed whether it would be worthwhile looking at a preoperative versus postoperative group but decided that the greater heterogeneity of the preoperative group would make it more difficult to get information. Discussion of the general study design included the following points:

- Because 100 percent of neonates are on an inotropic agent coming out of the operating room, a placebo-controlled study probably could not be done.
- However, a placebo-controlled study could be done by adding a drug to the regimen being administered to babies when they come out of the operating room.
- The study would be a superiority trial.
- A low-cardiac output scoring system is needed for the drugs being studied.
- The study would need to be conducted as close to the time of bypass as possible.
- The less regimented the study (e.g., fewer rules about when to wean infants off inotropes), the more acceptable the protocol will be to clinicians.
- When the study extends beyond a few days after the operation, other factors that might affect the length of hospital stay come into play. Consequently, a shorter trial would be better.
- Complications that affect the length of hospital stay might be related to the inotrope.
- Looking at inflammatory mediators might be beneficial.
- Looking at mechanical therapy might be beneficial.
- It might be valuable to consider whether it is presumptuous to try to prevent LCOS instead of treating the condition as it appears.
- A prevention trial has a greater chance of success on a practical level because the clinician will want to take whatever steps are necessary to improve the baby's condition as soon as he or she starts doing poorly.

## **Study Objectives**

The work group considered the following proposed study objectives:

- Assess efficacy and safety of inotropic regimens in achieving target goals.
- Compare efficacy and safety of different combination regimens.

- Validate hemodynamic norms.
- Assess PK/PD issues—confirm titration scheme.

The discussion of study objectives addressed the following points:

- Whether the study should overshoot the optimal outcome (Is overshooting the 90th percentile of blood pressure optimal?)
- How often the study drug should be increased
- Whether SVC flow is a valid endpoint to be used in this trial (It would be difficult to achieve uniformity in the measurement of SVC.)
- Whether the study results are affected by variation in the SVC flow because the babies are on a ventilator

### **Age Groups and Stratification**

The work group discussed the following stratification categories for the study:

- Maturity of child: <34 weeks and >34 weeks
- Definitive repair versus palliation
- Other stratifications:
  - Center/surgeon
  - Underlying cardiac diagnosis
  - Presence of congenital lesions
  - Chronological age at surgery

Work group members made the following points about stratification:

- After much discussion, the consensus was that there was not a lot of interest in looking at babies born at less than 35 weeks.
- There would be a gap for babies weighing between 1,000 grams and 1,800 grams because the inotrope study would be looking at babies weighing from 400 grams to 1,000 grams. There was discussion about including babies weighing 1,001 grams to 1,800 grams as a third level of stratification, but the work group decided that a third level was too much stratification.
- There is a need to define subgroups within the definitive repair group.
- There is a need to stratify for other congenital lesions and other cardiac anomalies and to exclude as few babies as possible. Because babies with anomalies would be evenly

distributed throughout the study arms, they could be included. Cardiac anomalies would constitute neither an exclusion nor a stratification.

- There would be a need to stratify by center (i.e., surgeon). Each center would randomize by itself.
- The group favored being more inclusive about babies with trisomy 21 or 22q11. Babies with SGA and IUGR would be excluded.
- There would be a need to standardize for confounders such as hypercalcemia in DeGeorge patients and the effects of mechanical ventilation.
- Confounders could include comorbid conditions (e.g., infection or inflammatory disease), preoperative status (e.g., AVV regurgitation), hypocalcemia, residual structural lesions, and other therapies such as mechanical ventilation.

### **Standardization of Therapy**

The work group considered standardization of the following aspects of therapy:

- Intravascular volume management
- Rescue therapy protocol
- Mechanical ventilation management
- Intra-operative support protocol
- Blood loss and hematocrit management
- Electrolyte replacement strategy (Ca<sup>++</sup>)

### **Entry Criteria**

The work group considered the following entry criteria for preoperative enrollment:

- Preterm and term neonates with CHD (group A—definitive repair with CPB; group B—palliative surgery with CPB)
- Planned use of vasoactive agents postoperatively
- Written informed consent

The discussion about entry criteria included the following points:

- If babies are enrolled before they go to the operating room and the surgeon has the intent to treat with randomization, about 20 percent of the babies might never get the study drug. A discussion about how to handle intent to treat included a suggestion to randomize after the surgeon agrees that the baby is ready for surgery; alternatively, this issue could be handled in the analysis of the study.
- Babies who present with shock and multiorgan dysfunction would be allowed to recover and then have repair or palliation.
- Babies who are doing badly and need urgent surgery should be excluded from the study.
- Surgeon buy-in is critical to enrolling babies who meet the entry criteria.

### **Exclusion Criteria**

The work group discussed the following exclusion criteria:

- Known infection or inflammatory condition
- Major chromosomal anomaly except trisomy 21 or 22q11
- Severe congenital anomaly incompatible with short-term survival
- SGA or IUGR

### **Primary Outcomes**

The work group considered the following primary outcome measures for efficacy and safety:

- Infants undergoing palliative surgery: combined endpoint of hospital mortality or need for ECMO plus selected adverse events
- Infants undergoing reparative surgery: composite endpoint of hospital mortality or need for ECMO plus selected adverse events

Discussion of outcomes included the points that mortality and the need for ECMO constitute endpoints and that renal failure might be another endpoint.

### **Potential Secondary Endpoints**

Possible secondary endpoints considered by the work group included the following:

- Health care utilization (e.g., duration of ventilator support, time in NICU, time to sternal closure)

- Measures of need for resuscitation
- Duration and extent of pressor support (“inotrope score”)
- Creatinine clearance early after surgery
- Measures of end-organ injury (e.g., seizures, elevated liver function tests)
- PK/PD measurements (drug levels)
- Other hemodynamic measures (e.g., SVC flow)
- Serum lactate levels
- Tissue perfusion (e.g., gastric pH, cerebral oxygen [O<sub>2</sub>] content by NIRS)
- Long-term outcomes (e.g., neurodevelopment at 12, 18, or 24 months)

### **Long-Term Followup**

The work group considered the following parameters for long-term followup:

- Survival beyond 1 year
- Neurodevelopment at 12, 18, and 24 months
- Functional outcome assessment in childhood

### **Ethical Issues**

The work group’s discussion about ethical issues addressed the following issues:

- Whether there is consensus on a level of cortisol to be used and when replacement should be used
- Variation in baseline levels of hydrocortisone that make it hard to tell whether a baby is stressed (Stimulation tests are better measures of the baby’s stress.)
- How often equipoise should be reassessed
- When to review the data (The issue is complex and determined by statistical considerations as well as ethical considerations. The smaller the sample, the higher the needed confidence level. Changes in equipoise result in drops in enrollment over time.)

- Issues associated with the known use of hydrocortisone and the control of its usage (Do the issues surrounding hydrocortisone usage comprise a research question? Should the study look at hydrocortisone use as if it's a nested study?)
- How to decide which drugs to study
- The fact that intubating too late causes problems in results for inotropes
- Use of epinephrine to maintain blood pressure at the 50th percentile
- Concern about babies who would not normally be treated who now are going to be exposed to potentially harmful drugs

# **Appendix B**

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### **Neurology: Summary of Breakout Discussion**

The Neurology Work Group discussed frameworks for studying two key conditions in newborns—seizures and hypoxic ischemic encephalopathy.

#### **Electrographic Neonatal Seizures**

The work group discussed this initial study design and explored in more detail the study framework elements summarized below.

#### **Overall Design**

The proposed study would be a multicenter, randomized, delayed-treatment, placebo-controlled study done with blinding of clinical treatment staff and electroencephalographers.

High-risk neonates for whom informed consent had been received from parents would be subject to continuous video-EEG monitoring to establish the presence and number of seizures. Occurrence of at least two ENSs within a 3-hour period would be the criterion for randomization to PB or placebo. The goal would be to prevent more seizures.

After randomization, the occurrence of a third ENS, or the end of a 3-hour seizure-free period, whichever came first, would signal the endpoint of the study. Clinicians then would be informed of assignment of the study arm (PB or placebo) and start open-label treatment. A specific design for open-label treatment should be decided on to avoid scatter in the results.

Escape criteria would include (1) clinical seizures, which must be specifically defined as focal clonic, focal tonic, or sustained eye deviation, and verified by EEG; and (2) electroencephalographic status epilepticus.

Breakout session participants made the following comments about the overall study framework:

- Determining the presence of a seizure by EEG is more objective than determining by clinical endpoints, which are elusive. Furthermore, it is believed that seizures determined by EEG actually represent harm to the body, whereas seizures determined simply by body movements do not. However, electroencephalographers disagree about what constitutes an ENS. Therefore, tapes of ENSs would be provided in advance to investigators for training purposes, and interobserver disagreements could be settled later.
- The group did not agree about the procedure after the second seizure is noted. Some believed that randomization to PB or placebo should be done as soon as possible after the second seizure. Dr. Clancy believed that if the second seizure occurs before the end of the 3-hour window, then the 3 hours should pass before randomization.

- The group did not clarify how long continuous visual-EEG monitoring would continue in the event the infant did not reach the randomization criterion of having two ENSs during a 3-hour period. After randomization, continuous visual-EEG monitoring would continue for at least 6 hours.
- The traditional endpoint in epilepsy studies is a 50-percent reduction in the number of seizures in 50 percent of the participants. This endpoint is inappropriate for this study, whose aim is to prevent any additional seizures.
- The definition of status epilepticus lacks formality. The group did not discuss providing a definition.
- The timing for an actual observer examining the continuous video-EEG monitoring, such as minute-by-minute, was not made clear.
- If the study yielded results one way or the other as to the efficacy and safety of PB in neonates at high risk for seizures, an ethical question remains regarding additional testing in other populations, such as premature infants. It is unlikely that study results would be applicable to term infants who did not have an acute medical stressor but had unprovoked seizures caused by conditions such as tuberous sclerosis.
- An alternative to study in humans is to study the damage caused by seizures, PB, or both in a neonatal animal model. However, this approach is impractical. For example, it is difficult to monitor an EEG in a baby rabbit.

## **Study Population**

Participants would be term ( $\geq 37$  weeks' chronological age) neonates at high risk for ENS. Risks for seizures include surgery for coronary heart disease, HIE, and receipt of ECMO. Exclusion criteria include previous observation of seizures or receipt of antiepileptic drugs, premature birth, and low birth weight.

Discussion of the study population included the following points:

- Dr. Clancy observed patterns of ENSs lasting at least 10 seconds in 183 neonates for 48 hours after surgery for coronary heart disease. The total number of ENSs in all the neonates gradually increased. ENSs started no earlier than 10 hours after surgery. Many were subclinical. However, the number and occurrence times of ENSs in individual neonates varied widely. Therefore, preliminary data on patterns of subclinical ENS in other high-risk neonates, such as those with HIE or who had received ECMO, would need to be obtained in preparation for the study.
- Premature neonates are a heterogeneous group because prematurity has different causes and premature infants vary in their medication histories. The reasons for seizures occurring in premature neonates are much less understood than those for seizures occurring in term neonates. Premature neonates probably would have too few ENSs to make it practical to

enroll them. Theoretically and paradoxically, the administration of GABAergic drugs would depolarize neurons and lower seizure threshold in very young premature neonates, although this effect is not consistent with typical clinical observations.

- Selection criteria for birth weight need to be determined.

### **Selection of Active Drug**

As mentioned, PB is the most commonly used treatment for neonatal seizures and is the best studied. Selection of dose for this study has been established by published safety data. Because of variability in the amount of PB needed to reach the goal of a free (“unbound”) concentration of about 25 mg/L, in vitro binding studies would be done to determine dose. This concentration corresponds to a loading dose of about 35 to 45 mg/kg.

Participants made the following comments about the proposed active drug:

- The proposed loading dose of 35 to 45 mg/kg exceeds the often cited clinical convention of 20 mg/kg. Participating investigators might need to be persuaded to use the higher loading dose.
- Efficacy results for PB in this study will immediately apply to efficacy of phenytoin, another commonly used drug for neonatal seizures. In a study comparing PB and phenytoin, which did not include a placebo group, the two drugs were shown to be equally efficacious in preventing ENSs in neonates who had had ENS.
- Benzodiazepines and other drugs have not been adequately studied for consideration of use instead of PB in this study.

### **Enrollment Goal**

The number of infants to be enrolled in the study needs to be calculated. However, participants made the following comments on the enrollment goal:

- Of the 183 neonates Dr. Clancy observed for ENSs after surgery for coronary heart disease, 21 had at least one ENS. Of these, 12 had at least 10 ENSs during a 3-hour period. This number of ENSs was the enrollment criterion that Dr. Clancy had set arbitrarily for this study design. To reach a randomization goal of 46 participants in a two-armed trial, 702 high-risk neonates would have to be enrolled to reach the criterion of 10 ENSs. Fewer infants would be needed if enrollment criteria were made less stringent. Dr. Clancy asked the group to consider less stringent criteria. Dr. Nelson noted that an ethical issue involves the potential injury that might occur from delay in treatment or use of placebo.
- The group reduced the number of seizures to two within a 3-hour period. This number represents a balance of a concern about the extent of withholding treatment with the clinical practice that high-risk neonates are not monitored by EEG. Seizures detected by EEG can be

subclinical. By the time that seizures are noted clinically and treatment is started, the patients might have had many subclinical ENSs.

## **Followup**

Careful, long-term followup is needed. The group proposed followup to age 8 years. By this age, the participants are in school and more subtle adverse effects, such as deficits in vision, motor ability, attention span, and behavior, can become evident.

The group retained the belief that seizures are harmful, but also retained its concern about the safety of PB. The group wondered if the study could address the concern about PB effects on CNS growth and development. The conclusion was that it would probably be impossible to use the followup results of this study to distinguish the adverse effects from PB treatment from the adverse effects of the many other interventions in the participants' medical histories.

## **Other Variables**

Other variables might affect the outcome and should be noted on enrollment. These variables include gender, ethnicity, genetic polymorphisms, coagulation profile, presence of inflammation, and free radical buffering capacity. Collecting DNA samples and cells to develop cell lines may be considered but is subject to ethical concerns.

## **Rejected Study Designs**

The group considered and rejected the following alternative study designs:

- **ENS Prevention Trial.** Neonates at high risk for ENS would be subject to continuous video-EEG monitoring. They would be randomized to receive PB or placebo before the observation of a seizure. This design raises the scientific concern that it does not distinguish between prevention of seizures from treatment of seizures. The design also raises the ethical concern that many neonates at high risk for seizure would be exposed to PB, a potentially harmful drug, even though many of them would not go on to have seizures.
- **ENS Treatment Trial With PB/Pyridoxine Crossover.** The design is the same as the placebo-controlled PB treatment study, except that randomization would be to pyridoxine or PB. After a period, participants would be crossed over to receive the other. This design more closely resembles clinical practice in that a drug (i.e., pyridoxine) would be used instead of a placebo. The purpose of this approach is to maintain the sense that active treatment is being offered instead of placebo. Although pyridoxine has been used to treat neonatal seizures, it is inactive for this use, so its therapeutic value in this instance is merely illusory. An investigational review board that is progressive in its thinking might agree to this design if the board accepted the concept that PB is truly an unproven treatment for neonatal seizures, that the study is being done to find out whether PB is a safe and efficacious treatment for neonatal seizures, and that the risk of untreated seizures is minimized. The acceptance of this approach currently is unlikely, given the entrenched use of PB.

- **ENS Treatment Trial With PB/Placebo Crossover.** The design is the same as described for the PB/pyridoxine crossover design, except that placebo would be used instead of pyridoxine. This design was rejected as being too complicated.

## **Hypoxic Ischemic Encephalopathy**

During the breakout discussion, the work group attempted to answer key questions and to identify ethical issues, gaps in knowledge, and an appropriate study design.

### **Pathways That Contribute to Brain Injury**

The work group examined the biochemical pathways that contribute to injury in hypoxia-ischemia. For example, the switch from aerobic glycolysis to anaerobic glycolysis leads to the start of multiple pathways leading to free-radical production. The increase in intracellular calcium is central to these pathways, leading to necrosis. The damage in mitochondria leads to energy failure and necrosis, and DNA fragmentation and apoptosis.

After resuscitation, cerebral oxygenation and reperfusion and the ATP concentration return to baseline during this initial recovery phase. However, the process of cerebral energy failure recurs from 6 to 48 hours later in a delayed, second phase of injury, reperfusion injury, despite stable cardiorespiratory status. The mechanisms of secondary energy failure, which leads to apoptosis, are likely to be secondary reactions to the primary insults, such as calcium influx and free-radical generation. Recent evidence suggests that circulatory and inflammatory mediators also contribute to the ongoing injury.

### **Mechanisms That Contribute to Fetal Resistance to Hypoxia-Ischemia**

Although interference in placental blood flow and, consequently, gas exchange is fairly common, residual neurological sequelae are infrequent. They are more likely to occur when the asphyxial event is severe. Thus, despite having suffered a severe insult *in utero*, most neonates do well. The explanation of the mechanism contributing to fetal resistance to hypoxia-ischemia is that the fetus immediately adapts to an asphyxial event to preserve cerebral blood flow and oxygen delivery. This adaptation includes both circulatory and other responses. Circulatory responses to the onset of asphyxia include, for example, a redistribution of increase in cerebral blood until cardiac output decreases. At this critical threshold, however, cerebral blood flow decreases. Other responses include, for example, slower depletion of high-energy compounds and use of alternative energy substrates.

### **Early Identification of Neonates at Highest Risk for Brain Injury**

Currently, specific markers to identify early the term neonate at risk for asphyxia are made during labor, in the delivery room, and during the initial neonatal period. During labor, sentinel events include fetal heart rate abnormalities, meconium-stained amniotic fluid, and acute events such as abruption or cord prolapse. Early detection—within the first hour of life—of neonates at highest risk for having seizures secondary to perinatal asphyxia requires a combination of factors, including a combination of markers that would identify an intrapartum event and

postnatal evidence of moderate to severe encephalopathy. These factors form the basis for identifying neonates to enroll in neuroprotective studies.

### **Appropriate Animal Models**

The work group explored the general question of what animal models would be appropriate for study by addressing the following more specific questions:

- What is the appropriate animal: rodent, sheep, piglet, monkey?
- What is the appropriate lesion: carotid occlusion with a focal lesion or a global insult?
- What is the appropriate outcome in animal studies: biochemical; short-term or long-term; pathologic or functional?

Although the work group discussed examples of research using animal models, it did not specifically answer these questions. It remains up to investigators to decide on an appropriate animal model for their study.

### **Neuroprotective Strategies**

The clinical issues in devising neuroprotective strategies encompass the following key questions:

- **Who and when?** Infants at highest risk should be treated, as discussed. Results from a study in fetal sheep showed that the sooner that treatment with hypothermia was started after experimentally induced cerebral ischemia, the better the outcome. This result supports the view that the therapeutic window is short—the sooner treatment begins after birth, the better the outcome.
- **How long?** Treatment duration remains unclear and is debated. Evolving HIE peaks at 48 hours and then appears to subside. However, reperfusion might continue. For this reason, 72 hours of treatment is currently recommended, but this might need to be extended, based on severity and other presentation factors.
- **With what?** The question of what to use for treatment remains a complex issue subject to longstanding debate. The work group's discussion included the following considerations:
  - **Oxygen or room air for resuscitation**—The issue of whether the affected neonate should be resuscitated in the delivery room using room air or 100-percent oxygen is highly relevant, given the importance of free radicals in the development of ongoing injury. Studies showed that resuscitation with room air is comparable with or even better than resuscitation with 100-percent oxygen.
  - **Standard of care**—The current standard care for encephalopathy is basically supportive. Management beyond the delivery room entails taking general measures for maintaining ventilation and proper fluid and glucose status, and for managing oliguria, hypotension, seizures, and cerebral edema.

- **Drugs**—An ideal drug is targeted to the brain, readily crosses the blood-brain barrier, results in minimal or no adverse events, and has a fairly long half-life. It remains to be determined whether the drug(s) should be administered continuously or intermittently. The emerging understanding of the biochemical basis of perfusion injury illuminates how some existing drugs work and suggests the development of new ones. Many drugs might be useful for treating neonatal encephalopathy, leading to the idea of treating with a mix of them. Such a use would be unprecedented and a source of concern.
- **Hypothermia**—From the biochemical outline of potential strategies for preventing reperfusion injury, hypothermia is the most attractive treatment modality. This procedure might act at all the levels in the different pathways to reduce deleterious effects, although it also may have several potential adverse events. It remains unclear whether selective head cooling or systemic cooling is the better method of hypothermia. The temperature to which the brain should be cooled and the duration of the cooling also remain unclear. Pilot feasibility studies showed that mild hypothermia is safe. Recent studies of neonates with moderate or severe encephalopathy indicate that a statistically significant greater number of babies who were treated with hypothermia had a normal outcome at 18 months compared with babies in the untreated control group. However, treatment with hypothermia currently is a labor-intensive and time-consuming procedure that will need to be refined. Investigators also will need to consider what should be added to the treatment and the effect of lower temperature on drug action.

## **Ethical Issues**

The fact that surviving term neonates who have had severe perinatal HIE have brain damage leads to the ethical issue of whether to treat them. The group had considerable discussion during the breakout session about whether to save the life of a neonate who will be brain damaged.

Starting hypothermia sooner might be more beneficial but raises the ethical issue of obtaining informed consent in a timely way. In a conventional process of obtaining informed consent to enroll a child, parents would be taken through a complete consent form, consent would be granted, and the child would be enrolled. Following this process could take some time.

Dr. Robert Nelson, representative of the Ethics Work Group, suggested substituting a communication process in which parents are continually advised about what is being done and have the opportunity to withdraw at any time. It would take a regulatory exception to permit an ongoing communication process to substitute for a traditional process of obtaining informed consent. Dr. Nelson preferred that the investigators' beliefs about the most appropriate time to intervene, rather than the need to obtain informed consent, determine the timing of the therapeutic window. Because no pediatric trial to date has used an exception to informed consent, Dr. Nelson's suggestion to obtain an exception to use a different type of informed consent process is doubly innovative.

# **Appendix C**

## **Appendix C**

### **Pain Control: Summary of Breakout Discussion**

The Pain Control Work Group addressed three basic types of pain: pain during invasive procedures, pain in the perioperative period, and pain related to mechanical ventilation. Clinical trial issues addressed by the group included how to prioritize the clinical problem, selection of pain control agents, study subjects, study designs, outcome variable, and sample size.

#### **Procedural Pain in Neonates**

##### **Potential Study Designs**

Dr. K.S. Anand presented an overview of potential study designs for procedural pain. The gold standard is a blinded RCT. Other possibilities for prospective studies include an open-label RCT, a blinded RCT with open-label rescue, or a nonrandomized case-control study with matched and nonmatched controls. Retrospective studies also could be done.

Novel study designs that do not get used or published often but are applicable to the study of neonatal analgesia include the crossover study design, factorial trial design, equivalence trial, randomized withdrawal of treatment, dose-ranging study, single-patient trial, flexible randomization trial, and play-the-winner trial design.

Neonatal procedures include heel lancing, venipuncture, venous or arterial cannulation, chest tube placement, tracheal intubation or suctioning, lumbar puncture, circumcision, and subcutaneous or intramuscular injections.

Two study designs for procedural pain were presented; the group discussion focused primarily on the heelstick study. A third study comparing the safety and efficacy of lidocaine for intercostal nerve block versus local infiltration for chest tube placement was not reviewed.

##### *Study 1—Tracheal Intubation*

The objective of the study would be to compare the efficacy and safety of remifentanil versus midazolam for tracheal intubation in infants. The drug names are used simply as examples; other drugs also could be tested. Interventions would be tracheal intubation (nasal or oral), preoxygenation, and atropine. Randomization could be done for remifentanil and midazolam in various doses or placebo versus remifentanil or midazolam. Number of patients, entry criteria, exclusion criteria, concealment, and assessment parameters were reviewed. The important outcome that must be part of any study is how often a respiratory disaster occurs when the patient is sedated. A related question is how many children have to be studied for the one child who suffers a respiratory disaster. The study must be powered high enough to get the right answers.

## *Study 2—Heelsticks*

Work group discussion focused primarily on a study of procedural pain from heelsticks. The group addressed the following elements of the study framework:

### Objectives

The primary objective of the study would be to compare the efficacy of 12 percent sucrose versus 12 percent sucrose with S-caine (a mixture of tetracaine and lidocaine) for preterm infants undergoing heelsticks. The secondary objectives would be to evaluate the PK of tetracaine and lidocaine in preterm infants and to evaluate the long-term hypersensitivity in the heels of ex-preterm children at 18 and 24 months of age.

### Interventions That Need To Be Standardized

The work group recommended standardizing the following interventions:

- The preparation and positioning of the baby, cleaning with an antiseptic, whether to give a systemic analgesia, duration of squeezing, amount of blood, and postsampling care
- The site of the heel for heelsticks. If there are multiple sticks, one heel might be more traumatized than the other, so sensitivity of the data would differ. There also is a need to standardize the lance to be used and when the stick will be done.

### Study Design

The study would be a randomized crossover trial in which each baby is studied twice with one intervention versus the other on two consecutive heelsticks. The two groups will get 12 percent sucrose with or without S-caine; the group getting only 12 percent sucrose will get a placebo patch in place of S-caine. A 2 x 2 factorial design also could be used, whereby one group would get nothing, one group would get only the S-caine, another group would get sucrose only, and a fourth group would get both treatments.

Work group discussion on the study design included the following points:

- The group discussed whether placebos should be used for babies who get no treatment for pain even if no treatment is the SOC. It is unreasonable to design a study where a child is undergoing an invasive procedure, including heel lance, without getting sucrose. If investigators could justify that the SOC in younger preterm babies was not providing any treatment, then it would be valid to randomize these babies to a placebo group, a sucrose group, and an S-caine group.
- The group discussed one-time heelsticks versus repetitive heelsticks. Specific consideration of the latter may be important because repetitive heelsticks involve accumulated effects, and the repetitive administration of painful procedures changes the responsiveness to pain.

- Two populations would receive different interventions. The full-term population would get a single stick, using sucrose as the control, with sucrose plus S-caine as the experimental group; in the preterm group, a separate intervention would be needed with a placebo and S-caine.
- It is not clear why 12-percent sucrose was chosen because there is a range of dosage between 12 and 25 percent. It might be preferable to use 24-percent sucrose because most studies have used that dosage. No good evidence exists to suggest having a placebo or a no-treatment group.
- Because it is not known whether 12-percent sucrose is valid in 23- to 28-week GA babies, a placebo could be used for the controls in this age group.
- Comparing placebo groups from historical trials with S-caine plus sucrose would not be a good idea because the use of historical controls poses many problems.
- For legal purposes, using a placebo is not a SOC unless it is used by 50 percent of the physicians in a given medical specialty. However, 50-percent usage by physicians may be a problem for IRBs. A concern is how to justify using sucrose.
- Some journals will not accept a placebo for heel lance in infants because of the strength of the data on sucrose at a dosage of 24 percent or higher.
- The group proposed that sucrose should be the control group for any study in a term baby or older. Because data are lacking for babies less than 27 weeks GA, the correct sucrose dose was a concern.
- The group discussed several randomization possibilities by gestational age. It is important to include babies less than 27 weeks because they undergo the most heelsticks. Rather than exclude these babies because data are not available, they should be included with a different stratum of randomization. The efficacy of S-caine can be tested with or without sucrose for heelstick in term neonates 40 to 44 weeks GA; these babies would be randomized to sucrose or sucrose plus S-caine. Babies 27 to 32 weeks GA would be randomized similarly. However, the younger preterm babies would be randomized to placebo versus S-caine. Babies 32 to 40 weeks GA could be put in the group receiving sucrose versus sucrose plus S-caine plus a decreased number of heelsticks.
- There is a need to determine what constitutes an important minimum pain response in babies. Preliminary results from a study found a 15- to 20-percent change is significant. When data are not available for a particular class of drugs, the sample size can be calculated from other classes of drugs. In regard to sample size and the treatment effect, a small effect may be meaningful.
- The minimal clinically important difference for the individual is not the same as for the population. To power for the population adds a burden to the study. Another approach

would be a meaningful difference in populations reaching that minimally important difference.

- The study design should include a way to determine whether the study influences the number of heelsticks. A historical control is needed to look at change.

#### Entry Criteria

Proposed entry criteria included babies' GA between 23 to 28 weeks, occurrence of the heelstick in the NICU, age less than 2 weeks, the presence of an experienced operator, and written consent. The age criteria subsequently were changed to 23 to 30 weeks gestational age.

#### Exclusion Criteria

Proposed exclusion criteria included severe IVH or PVL, birth asphyxia, congenital anomalies of the lower extremity or the spinal cord, or receiving infusions for preemptive analgesia. Exclusion criteria also would need to address the chance that the very early preemie would be receiving an opioid concurrent with another drug.

#### Concealment

Concealment techniques would include using a similar patch for the placebo, blinded neonatal assessments and data analysis, and centralized randomization for multicenter RCTs. Randomization would be balanced in blocks, randomization tables would be generated for each stratum, and pharmacy and clinical staff would be separated.

#### Assessment Parameters: Efficacy

Efficacy parameters would include pain scores, changes in vital signs, time to recover, total procedure time, the need for additional analgesia, stress parameters, palmar sweating and transdermal conductance, and skin blood flow.

- The work group's discussion of efficacy parameters included the following points:
- For the PIPP score, a clinically important difference is about 2 points. All parameters can be statistically reduced to get a summary score. It is up to the group to decide what is a clinically meaningful difference. The efficacy parameters are three types: behavior, biomarkers, and success of procedure.
- The group discussed the merit of a composite score versus separate scores. A composite score can be misleading. Data show that even when people are calm behaviorally when sedated for procedural purposes, physiological reactivity to tissue damage still occurs; therefore, behavioral indicators should be kept distinct from physiological indicators. However, in a composite score, it is possible to single out the subscores. The issue of different kinds of indicators not being correlated needs to be studied across the age of the infant.

- An undisturbed baseline should be included at the very beginning of the study. The transition to mechanical ventilation also has to be considered. Anterior fontanel pressure and changes in intercranial pressure could be used as a biomarker to assess efficacy. The response to next handling also should be looked at when considering the time to recover. Markers of stress response such as cortisol could be simplified by using glucose, which is easy to study.
- Whereas most term babies get one or two heel lances, preterm babies undergo repeated lancing. Although efficacy of pain control could be shown for one lance, it is more important to know whether the intervention is effective across a long time period.

#### Assessment Parameters: Long-Term

Longer term pain scores would not apply. For long-term outcome, it may be necessary to randomize one group to get 12-percent sucrose and the other to get 12-percent sucrose and S-caine and not have a crossover trial. Whether the design is a crossover or a long-term study, efficacy must first be demonstrated for one event, and then long-term effectiveness must be examined.

#### Assessment Parameters: PK

Work group discussion of PK parameters included the following points:

- It will not be possible to get the PK data unless patients have an indwelling catheter. However, babies who have a catheter are not eligible for heelsticks. PK data for S-caine can be examined if enough blood can be drawn with the heelstick itself.
- In regard to plasma levels of lidocaine, it is known that epileptogenic activities come from the metabolite of lidocaine, MEG. Investigators could examine the formation of the metabolite and collect urine to look for metabolites to get an approximate idea of the plasma level of lidocaine.

#### Assessment Parameters: Safety and Adverse Events

Suggested safety/adverse event parameters included local reactions, lidocaine toxicity, prolonged hypoxemia and excessive bleeding from the heel site, tachycardia for more than 5 minutes, and allergic reactions. Little is known about using sucrose in infants 23 to 27 weeks; data also are lacking on how to assess pain in these babies. It would be safer to look at an age group for which validated measures exist.

Work group discussion on parameters included the following points:

- Reliable and valid indicators are lacking for assessing safety/adverse effects in younger preterm babies receiving S-caine versus placebo. The measurement problem is an issue that must be considered.

- In the population of term infants, in which each baby will get one or two heelsticks, serious long-term effects are unlikely. In preterm infants, who will receive repeated heel lancing, long-term adverse outcomes are possible.
- Powering the study for safety exponentially increases the number of patients needed because of the infrequent occurrence of side effects. Such a study would not be feasible. Postmarketing surveillance could be used but is unreliable. An approach to improving the safety outcome without having to overpower a study is to use open label extensions, which are easier to manage and follow routine care.
- Open label extensions are important, but once the skin has been pierced, investigators will need to monitor absorption of local anesthetics, which will change as the skin is broken repeatedly.

#### FDA Comments\*

FDA participants made the following comments:

- In regard to the selection of test arms, FDA has not approved dextrose for the use proposed, even though multiple randomized trials have shown that sucrose works for heelsticks. In writing a conclusion and indication for the study, it would be necessary to prove that dextrose alone is not harmful. The indication would be written to say that S-caine with dextrose is effective.
- FDA needs good data to be convinced. It could be convinced by a series of arguments with data supporting the rationale for the treatment arms and subsequent studies. It is difficult to make conclusions based on the published literature alone because the data often are not included in their entirety and may not be clearly reported. The regulatory route provides an extra level of scrutiny.
- Many clinical trials have been presented to FDA as successful, but upon closer scrutiny, FDA is not convinced of their efficacy. It is advisable to select outcome measures that are reliable and to correlate different outcome measures to see what makes them reliable over time among different centers and in different conditions. It is extremely powerful to incorporate outcome measures from other trials regardless of new instruments or ideas.

#### Reactor Comments

Selected comments from the reactor, Dr. Bonnie Stevens, included the following:

- Painful neonatal procedures can be categorized as caregiving, diagnostic, therapeutic, and surgical. The most common procedures in infants are suctioning, insertion of tubes, heel

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lancing, and circumcision. Heel lancing is the most frequent in terms of acute painful procedures in NICUs. Priorities for study are suctioning, heel lancing, or any skin puncture; for circumcision, there already are trials with sufficient information.

- Almost all studies of drugs involve a single administration, and continuous administration of drugs needs to be studied. Efficacy and safety studies on repeated use of drugs are lacking.
- Out of 47 RCTs on sucrose, only 17 were able to be included in the Cochrane Review and only 3 in a meta-analysis. Sucrose is an intervention that has been studied, but researchers and clinicians still do not have answers to some important questions.
- Many scales measuring pain exist, but the desire to have one scale that can be used to measure pain in all circumstances is comparable to saying one treatment would be used for all babies across all gestational ages. Such a universal scale or treatment is not possible.
- Gaps in knowledge or issues that need further research include the ideal pharmacologic approach (i.e., the gold standard for pain management); single use versus repeated use of drugs studies; determination of intermediate and long-term safety indicators; and the combination of pharmacological, behavioral, physiological, and cognitive interventions. There is a need to look at whether the RCT is the ideal design and whether the placebo control is ethical.

### *Changes to the Study Design*

The work group decided to change the following elements of the proposed study design:

- The dosage of sucrose was changed from 12 percent to 24 percent.
- Entry criteria were changed to 23 to 30 weeks GA.
- There will be two phases to the study—an initial pilot study and a subsequent RCT.
- Exclusion criteria were changed to include babies between 30 and 37 weeks GA because they are less sick and less likely to receive a large number of heelsticks.
- In the pilot study, all babies older than 27 weeks GA will get sucrose with S-caine because it is unethical to use a placebo in this age group.
- Treatment will be provided for every heelstick in younger preterm babies for the first 14 days after birth up to a maximum of three heelsticks a day. It is unethical to use more than three heelsticks per day for blood sampling.

### **Perioperative Pain in Neonates**

The basic issues in study designs for perioperative pain in neonates include what constitutes an efficacy measure and whether that efficacy should be a primary outcome measure in a neonatal

and young infant population. Determining appropriate efficacy or benefit measures is a common problem for the design of all studies on the control of perioperative pain. A corollary is whether a baby must experience significant or severe pain to study the benefit of a drug.

The classic paradigm of perioperative pain for adults is third-molar extraction. All patients get local anesthetic. When the local anesthetic wears off, pain intensity goes up and the patient is treated with either an anti-inflammatory drug in tablet form or a placebo. However, such a study would not be approved for an infant population. A paradigm used in older children is a randomized, placebo-controlled design with two groups—half of the patients receive a nonsteroidal drug, and the other half receive a placebo. In many studies, all patients receive a PCA pump with morphine. These studies examine pain scores and cumulative morphine use and measure the opioid-sparing effect.

### **Potential Study Designs**

Dr. Berde reviewed three postoperative study designs and a general anesthesia study design. A fifth design, general versus regional anesthesia, was not discussed.

#### *Study 1—Postoperative: NSAID or COX-2 Inhibitor*

##### **Objective**

The objective of the study would be to evaluate the efficacy, safety, and PK of an NSAID or COX-2 inhibitor for systemic administration for postoperative pain. The study design is placebo controlled, single or multiple dose, with nurse-administered opioid for rescue analgesia. Patients may experience moderate pain, but there is immediate rescue. The ethical argument is that because opioids have adverse effects, the patient is exposed to less harm with a very small intermittent bolus NCA paradigm if there is an opioid-sparing effect and the amount of opioid a patient gets can be minimized. The study design could be used for a range of surgeries in babies for whom extubation is planned.

##### **Entry Criteria**

Proposed entry criteria include neonates and infants less than 3 months of age undergoing major or minor surgery.

##### **Exclusion Criteria**

Babies with bleeding, nephropathy, gastropathy, IVH, and NEC would be excluded from the study.

##### **Concealment**

Concealment techniques would include straightforward use of a placebo. It was noted that blinding with IV saline for IV dosing is easy.

## Assessment Parameters

For PK assessment, blood sampling can be done from indwelling lines. Postoperative populations would have to be studied over a range of ages and diseases. The effects of pharmacogenetics, other drugs, and the role of DNA sampling would have to be considered. Investigators would examine observational pain scores, the reduction of supplemental opioid use, and physiologic parameters to assess efficacy. One question is whether examining the reduction of wound hyperalgesia by flexion withdrawal reflexes could serve as a surrogate marker of an antihyperalgesic effect.

Adverse effect parameters include bleeding, renal and hepatic dysfunction, gastropathy, and NEC as well as the role of surrogate markers of risk. Neonates are not given NSAIDs for surgery because of the lack of safety data. An adequate measure of short-term risk is crucial.

Long-term assessment parameters include postoperative complications, time course to recovery, changes in pain response, and behavioral consequences.

## Study Design Issue

A problem with the NSAID or COX-2 inhibitor study design is how to adjust for differences in formulations among study centers because some centers use tablets and others use a liquid form of these drugs. Pediatric formulations for many of these drugs are needed. IV COX-2s currently are under review. Bioavailability must be part of any process for oral or rectal dosing.

### *Study 2—Postoperative: Epidural/Peripheral/Perineural Drug (Single Dose or Infusion)*

#### Objective

The objective of this study would be to evaluate the efficacy, safety, and PK of the regional administration of a new drug for postoperative analgesia. The study would be a blinded RCT. Patients would be randomized to an epidural drug or control in a single-dose (caudal) or continuous infusion design. Both patient groups would receive NCA for breakthrough pain.

#### Entry Criteria

Neonates and infants less than 3 months old who are undergoing thoracic, abdominal, inguinal, or pelvic surgery would be entered in the study.

#### Exclusion Criteria

Exclusion criteria would include neonates who have a critical illness; contraindications to epidural anesthesia (e.g., uncorrectable coagulopathy, spinal anomalies, sepsis, and bacteremia); and surgeries in the head, neck, or upper extremities.

## Concealment

Concealment in this study would pose an issue because using an epidural catheter cannot be justified without administering an active drug. For an infusion study, an epidural catheter would be taped to the skin, and a black-box infusion pump would be used to obscure whether the infusion was running. For single-dose studies, a Band-aid is applied over the caudal skin entry site to conceal whether a needle was placed intraoperatively.

## Assessment Parameters

For PK assessment of local anesthetics, blood concentrations relate poorly to effect-site concentrations. Blood concentrations are needed to predict limits on maximum safe dosing to avoid risks of seizures, arrhythmias, and cardiac depression. Local anesthetics need to be studied in relation to disease states, age, and pharmacogenetics. The role of DNA sampling is a question.

Efficacy parameters include observational pain scores, sparing of supplemental opioid use, physiologic parameters, and reduction of wound hyperalgesia.

For safety and other outcome measures, respiratory function, cardiovascular parameters, recovery of gastrointestinal function, local neurotoxicity, and clinical outcome measures would be assessed.

Long-term assessment parameters include time course to recovery, neurodevelopmental injury to nerve roots, outcomes, opioid tolerance, and injury to nerve roots.

### *Study 3—Postoperative: Ultra-Low-Dose Opioid Antagonists*

#### Objective

The objective of the study would be to evaluate the efficacy, safety, and PK of an opioid antagonist to reduce opioid side effects in the treatment of postoperative pain. The study would be a blinded, randomized, placebo-controlled add-on trial. Half of the patients would get a very low-dose infusion of an opioid antagonist, and the other half would receive a placebo. All patients would receive NCA opioid for analgesia.

#### Entry Criteria

The study's entry criteria would be similar to the criteria for study 1.

#### Exclusion Criteria

Babies who have had significant amounts of opioids preoperatively would be excluded from the study.

## Assessment Parameters

For PK assessment, blood sampling for an antagonist in clinical settings might be an issue because of the low infusion rates.

Efficacy assessment parameters would include observational pain scores, NCA opioid dosing, and respiratory, cardiovascular, and GI functions.

Clinical outcome measures would be the time course to recovery and reduced complications. Conceivably a patient could become hypertensive, develop pulmonary edema, have convulsions, or experience opioid withdrawal. There might be long-term changes in pain responses and the development of tolerance, but such changes would be difficult to measure.

## *Study 4—General Anesthesia*

### Objective

The objective of the general anesthesia study would be to evaluate the efficacy, safety, and PK of a new inhalational or intravenous anesthetic for intraoperative management. Placebo anesthetic trials are no longer done. General anesthetics can be studied in comparison group trials in which two general anesthetic regimens are compared or regional anesthesia is compared to general anesthesia. The study design could be blinded to some observers and would be a randomized, active controlled trial in which patients are randomized between a new versus old anesthetic agent.

### Entry Criteria

The study would use the same entry criteria as study 1.

### Exclusion Criteria

The study would exclude babies with severe hemodynamic instability and genetic disorders that contraindicate use of volatile anesthetics.

### Concealment

It is unethical to use a true placebo. The anesthesiologist cannot be blinded.

### Assessment Parameters

Efficacy measures include intraoperative hemodynamics, the need for additional analgesics intraoperatively and during initial postoperative dosing, and time to extubation.

Adverse effect parameters include hypotension and hemodynamic instability, respiratory depression, delayed emergence, and impaired organ perfusion. Many anesthetic regimens cause

marked hypotension and are direct myocardial depressants in the neonate, so a useful intervention is something that can provide all components of anesthesia without hypotension.

For PK measures for volatile anesthetics, MAC determinations and variance of MAC determinations are standardized. Other PK measures include intravenous agents and the effects of maturation, renal and hepatic dysfunction, and respiratory and cardiac disease.

A question for long-term assessment is whether general anesthesia in an infant has long-term beneficial or harmful effects on neuronal maturation and survival.

### Basic Study Issues

Basic issues about the study of perioperative pain include whether surrogate measures of efficacy (e.g., opioid sparing) are sufficient, and whether one can control for the interactions of the supplemental opioid with the other agent under study. It is clear that the only way to get large enough numbers of the stratified populations is by conducting multicenter trials. The long-term effects of opioids and general anesthetics are important but difficult to study.

### Comments on the Designs Overall

Work group members made the following points about the proposed study designs for perioperative pain:

- The inclusion criteria of 0 to 3 months in the study designs could be used in other neonatal pain studies, not just postoperative pain. Because a significant amount of surgery is performed on neonates from 3 weeks to 3 months of age, 0 to 3 months must be included for surgical outcome studies.
- A drug-by-drug justification should be done based on mechanism of action and clearance routes.
- IRBs like NCA because it provides immediate rescue, and the infant gets a drug only when needed. It is harder to get IRB approval for a design that has a placebo group without immediate rescue. An issue is whether NCA based on an observational pain score criterion has validity. A preferred approach is to have the bedside nurse give the PCA bolus based on a PIPP or other pain score criterion.
- Interoperative management and all intraoperative procedures need to be standardized so that all patients being evaluated postoperatively in any of the trials are managed similarly for similar procedures.
- The measure used to calculate sample size will be a clinically meaningful difference in cumulative rescue opioid use. The measure cannot be a pain score.
- Total accumulative opioid dose will provide a much different exposure based on the age of the infant. An infant that is 1 week old will have much higher opioid levels than a

3-month-old infant on the same dose of opioid. Consequently, the enrollment will need to be stratified by age, depending on the type of opioid used and the type of operation the infant has undergone.

- A change from baseline could be looked at rather than absolute pain score from an assessment scale. The baseline need not be pain scores as the baby is emerging from anesthesia; it could be a preoperative value. However, it might not be meaningful to look at a change from a preoperative resting PIPP score. Because the intervention is intended to treat the postoperative pain resulting from the surgery, the preoperative baseline is not a true baseline.
- Sensitivity to change is an important issue because overall normalized values are not of much interest, especially when looking at the side effects of morphine. Although PIPP is used in premature children, it has never been validated in postoperative children. However, other measures that have been validated in postoperative children and validation of PIPP postoperatively are in press. A suggestion was made to look at multiple measures of pain and come up with the best one for the study population.
- In regard to outcome measures, it is important not to overlook response to pain in infants at the lower end of the age spectrum. Even if there is a concordance between biologic and behavioral measures, there could be an important finding at the lower age limit where discordance could be the norm.
- When accounting for all the patients eligible for a study, investigators need to include patients who are eligible but not approached.

#### FDA Comments\*

FDA participants made the following comments about the perioperative study designs:

- The use of an unlabeled comparator in a study of a new drug involves several considerations. A general anesthetic drug that provides profound hypnosis does not need a comparator. For other drugs, the need for a comparator depends on what would be accomplished with the comparator group. The best possible design is to establish superiority of the new drug and then determine the effect size of the comparator.
- In special circumstances, published data from other trials of the unlabeled comparator would be acceptable. If there is no alternative, historical data can be used to anticipate the effect size. It is necessary to translate that effect size into the population, setting, and diseases being studied.

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- With a neonatal population, chances are good of qualifying for the IND process because of the risk factor and safety issues.
- An IND on an approved product does not require approval of the company; it requires an interaction with the FDA. For an unapproved product under study, it is necessary to have the cooperation of the sponsor. For an approved product, it is problematic to get additional proprietary information that was not included on the NDA application.

#### Reactor Comments

The reactor, Dr. Dick Tibboel, made the following selected points about perioperative pain studies:

- Gaps in knowledge exist about pain perception and the morphological substrate, the relationship between neurophysiological parameters and pain assessment, sensitization following repeated painful stimuli, and the lack of correlation between pain assessment instruments and plasma levels of analgesics.
- Validation of a pain assessment scale against a number of parameters for surgical patients is important. Assessment of validated pain scores is essential for comparison of analgesia regimens. There will not be one general pain assessment scale for all circumstances.
- Sensitization is an important issue. A major tissue insult to infants in the newborn period has been shown to change the neuroanatomy of the spinal cord and higher areas of the brain. An important issue is whether there are validated techniques for measuring sensitization to neuroanatomical changes.
- An ideal protocol for evaluating drugs would include validated pain assessment instruments for the particular circumstance and age group, stress markers, DNA sampling, drug metabolism and measurement of excretion products, and neurophysiological measurements.
- In comparing morphine with acetaminophen, for example, insufficient painful events will make it difficult to prove that one therapy is better than another. However, if intermittent morphine is used so that infants will have painful moments, there will be difficulties with ethical review committees.
- Adherence to the study protocol is equally important after a study has ended. It is especially helpful to have an algorithm for the protocol. Long-term followup of patient cohorts with neonatal pain experiences is warranted.
- In reporting on trials, the difference between eligible patients and the number enrolled deserves attention. There is a need to be aware of children whose parents did not consent to their child's participation.
- DNA sampling should be done routinely in every study patient who has the need for analgesia. DNA analysis is urgently needed in all future pain trials.

## **Pain During Mechanical Ventilation in Neonates**

### **Potential Study Design**

Dr. Jacob V. Aranda presented a design for a randomized double-blind placebo-controlled trial of an IV NSAID for pain control in mechanically ventilated preterm newborns. The design would use an IV NSAID versus an opiate. The NSAID was not specified. Currently, three IV NSAIDs are on the market: intravenous indomethacin, Toradol, and ibuprofen (in Europe only).

#### *Study Design—IV NSAID for Pain Control in Mechanically Ventilated Preterm Newborns*

##### Objectives

The objectives of the study would be to determine the efficacy and safety of IV NSAIDs in the management of pain and stress during mechanical ventilation in preterm babies and to determine the population PK of IV NSAIDs in preterm newborns. The rationale for using IV NSAIDs is that they are potentially a good IV analgesia in newborns, they have an opioid-sparing effect and obviate the potential for addiction, they have been used extensively in newborns for PDA closure and IVH prevention, there are defined PK/PD profiles, and they have anti-inflammatory effects.

##### Hypothesis

The proposed hypothesis was that daily intravenous NSAID decreases pain experience and opioid need in mechanically ventilated newborns. The work group decided to change the hypothesis to “Does daily intravenous NSAID with or without midazolam decrease pain experience in opiate need in mechanically ventilated preterm newborns?”

##### Population Group

The proposed population group would be premature newborn infants, 25 to 30 weeks GA with birth weights of 500 to 1,250 grams and who were less than 7 days postnatal life (preferably at birth). Stratification according to birth weight would be 500–700 grams, 751–1,000 grams, and 1,001–1,250 grams.

##### Sample Size and Study Population

Based on the primary outcome, which will be N-PASS, the study population would consist of 448 babies, with 224 babies in each group. The mean difference would be 1.2, or 25 percent, with a standard deviation of 3. The confidence interval would be 99 percent. The study would be overpowered so that a meaningful analysis on secondary outcomes could be conducted.

##### Outcome Measure

The primary outcome measure would be N-PASS. A secondary or alternate primary outcome would be pain scores and a composite outcome (IVH, PVL, death). The work group considered

whether an infant must die or have IVH to determine whether the IV NSAID relieved pain and whether pain in itself justified the giving of analgesia or sedation in newborn babies. If a composite measure were used, a smaller population would be needed.

It was noted that the classical way of determining minimally important clinical outcomes has been to ask adults the degree to which an agent makes pain better. With infants, there is a need to develop methodologies to determine this outcome, rather than extrapolate from adults. It is important to have a standardized outcome that is clinically important.

#### Intervention

The intervention would be a placebo or IV NSAID (5 mg per kg per day for 7 days).

#### Entry Criteria

Entry criteria would include preterm newborns with birth weights of 500 to 1,250 grams with a need for mechanical ventilation longer than 24 hours.

#### Exclusion Criteria

Infants with severe congenital malformations and severe IVH grades 3 and 4 would be excluded from the study. The work group specified few exclusions because the intent of the study is to be very inclusive so that it can be applicable to all babies who are intubated.

The work group noted that a way needs to be found to include babies with grades 3 and 4 IVH and asphyxia or at high risk for neurological impairment in the study designs. A possibility is to include these infants in a stratification group or design a parallel study that includes babies with these problems. Although these babies' responses pain to are dampened, they still respond.

#### Assessment Parameters

The primary outcome measure would be N-PASS, a chronic neonatal pain score. A problem with this score is that one of its domains is facial expression, which is difficult to observe when the baby's face is taped.

For secondary outcomes, measures would be a composite of severe IVH (grade 3 to 4) and/or death, pain scores (PIPP) during acute pain stimulus (intratracheal suctioning), and the need for fentanyl or morphine and/or midazolam or any other analgesia or sedative. Investigators should try to make rescue in the trial uniform with the same drug, so that a meaningful analysis will be possible.

The work group discussion on assessment parameters included the following points:

- The group agreed that it is not known whether midazolam is efficacious for the neonate. The drug does sedate, but it has serious side effects. Although a meta-analysis of midazolam was based on three studies, only a small number of babies were in those trials.

- Using midazolam for prolonged periods might pose problems regarding apoptosis neurotoxicity.
- Data are scarce on renal toxicity in small babies given NSAIDs for a week. If a potentially toxic agent were going to be used, it would be better to use a more clinically effective agent rather than NSAIDs, which are used for mild to moderate pain. Fentanyl versus a placebo could be used instead of midazolam versus a placebo. The designs would be similar, but the sample size would change.

### Safety Outcomes

Nonsteroidals are known to cause bleeding from any site and to cause problems with renal and hepatic function, serum bilirubin, and platelet count. Arterial blood pressure also will need to be monitored. Other morbidity factors are associated with how sick the babies are. Outcomes known to change in previous trials using IV NSAIDs include days to full oral feeding, length of stay in hospital, and lung function.

The work group discussion on safety outcomes included the following points:

- Using a drug for pain control that is being used simultaneously for a PDA ligation poses a difficulty. For example, using ibuprofen or indomethacin for two indications (i.e., for pain control and ligation of a duct) could cause problems because the dosage would be increased with potentially increased side effects. In such a case, the patient would be taken out of the study and appropriate treatment would be done for PDA.
- An alternative would be not to study a drug that could be useful in mechanically ventilated preterm babies who are experiencing mild to moderate pain in addition to acute physiological pain from invasive procedures. Given the constraints, the effects of NSAIDs with or without fentanyl versus placebo is the best possible study design. One way to resolve the PDA question would be to blind clinical staff. If PDA is diagnosed, the pharmacy staff would be asked to give PDA treatment.

### Exploratory Outcomes

Exploratory outcomes would include cytokines (proinflammatory and anti-inflammatory), PGF1a, plasma cortisol, and plasma adrenalin/noradrenalin.

### Long-Term Followup

At 18 months, neurodevelopmental outcomes would be assessed using scoring systems, such as the Bayley scales and neurological examination.

## FDA Comments\*

FDA participants made the following comments about the study design:

- The FDA would need greater clarity on the indication being sought for pain-indication labeling. An indication would be a discrete clinical entity associated with a well-identified set of clinical trials, populations in clinical settings, and clinical outcomes. To make a risk-benefit assessment and decide whether to grant an indication, the FDA must understand the benefit. If the work group says a change in distress score in itself is a meaningful clinical benefit, the FDA needs to know how much change in a distress measure is a meaningful benefit.
- The FDA would need appropriate safety information for the use in neonates of parenteral NSAIDs that are not currently used in adults. Safety information would need to be submitted with the protocol. If a population is at risk for multiple complications and bad outcomes, adequate preexisting information would be needed. European clinical toxicology data are acceptable. A clinical protocol submitted as a research study does not need FDA approval if it is not done under an IND. Because the study could technically—although not clinically—represent a new route of administration, additional information would be requested if it were submitted for an IND.
- In analgesic trials, the FDA looks for duration and time to onset. If those parameters can be assessed in the study population, they are important features for describing dosing interval. The kind of outcome measures associated with a dental pain model for single-dose studies can be very informative for planning multiple-dose studies.

## Reactor Comments

Selected comments from Dr. Arne Ohlsson included the following points:

- Fifty-six percent of infants with birth weights of 1,500 grams or less are intubated in the resuscitation room, and 70 percent of these infants are ventilated during their hospital stay. Data show that 94 percent of babies less than 28 weeks GA are ventilated for a mean of 25 days. Consequently, the starting point for trials should be in the resuscitation room.
- Infants are known to perceive pain and distress while on mechanical ventilation. Intubations and reintubations, as well as different types of ventilations, should be part of the study module.
- Although fentanyl and morphine appear to reduce the behavioral/physiological measures of pain and stress associated with mechanically ventilated neonates without serious adverse effects, the evidence for these effects is rather weak.

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\* 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.

- Intravenous midazolam should not be used because some studies suggest that it is associated with adverse effects.
- Indomethacin has been used for PDA, but it has many well-documented side effects and should not be used in the proposed study. In PDA trials in France, ibuprofen caused persistent hypertension in three patients.
- To avoid confusion about terms, it would be best to use define low birth weight as less than 2,500 grams, very low birth weight as less than 1,500 grams, and extremely low birth weight as less than 1,000 grams. Both gestational age and birth weight should not be used in the criteria; one or the other should be used.
- Research questions regarding preterm/low birth weight infants requiring mechanical ventilation include whether adverse long-term outcomes are reduced by effective analgesia compared to no analgesia, whether adverse long-term outcomes are reduced by effective sedation compared to no sedation, whether adverse long-term outcomes are reduced by effective analgesia compared to effective sedation, or whether a combination of them reduces adverse long-term outcomes.
- Assessment of adequate sedation/analgesia for mechanical ventilation during other invasive procedures may not be appropriate. Consensus is needed on what constitutes a clinically important reduction in a pain score or increase in sedation score.

### *Changes to the Study Design*

Dr. Aranda redesigned the IV NSAID trial to a randomized planned placebo trial of IV NSAID with or without midazolam. Midazolam was added to the hypothesis. The sample size was doubled. The highest birth weight that qualifies as an entry criterion was changed from 1,250 grams to 1,500 grams. The agreed-on treatment arms were placebo, NSAID, solvent-free midazolam, and NSAID plus midazolam. Rescue criteria for PDA were added, and fentanyl was chosen to be used for pain rescue.

## **Ethical Issues in Research on the Treatment of Neonatal Pain**

Dr. John Lantos made a presentation to the work group on ethical issues and commented on different clinical scenarios. He noted that the concern for RCTs is with what sort of studies can be done ethically. No standard therapy exists, and variation in clinical practice is widespread for the treatment of procedural and mechanical ventilation pain in neonates. Postoperative pain may be an exception. For these types of pain, the traditional research ethics paradigms fall apart. There are uncertainties about which drugs might be used, in what doses and in which patients they should be administered, with what outcomes they are associated, how they should be measured, and what relevance preceding events have for the treatments of pain. There is no clear SOC or widely used and agreed-on treatment for neonatal pain control.

The lack of clear SOC raises special problems in trials because equipoise (i.e., a genuine state of uncertainty between two treatments, the precondition of a RCT) is not possible. It is unclear

what the default care ought to be for infants whose parents do not agree to participate in the trial. Even when SOC exists, studies still are designed in the same way as when there is a paradigm. For example, the sucrose versus S-caine study is designed to look like a standard versus experimental study design, but there is no standard and every drug use is “off label.”

Specific ethical challenges include the need to explain why the research is appropriate and why the risks of analgesia are acceptable. The simple answer to that is pain is bad, and analgesia may be able to control it; therefore, a study is reasonable and ethical. An important ethical question is why a control group is acceptable if pain is bad and analgesia is good; why not just use analgesia? It is uncertain whether any treatment really has any benefits, particularly where SOC exists. The short-term measures of benefit are ambiguous, and there is disagreement regarding which measure is most relevant for the short term or as surrogate measures for long-term outcomes. Uncertainty also exists about the short-term and long-term risks of treatment. Another ethical challenge is to avoid simple and wrong conclusions.

A realistic goal would be to develop a specific trial design with defined risks, benefits, and outcomes and then come up with the ethical justification for the study in language suitable for an IRB or the FDA. Developing boilerplate informed consent language also is advisable. The fundamental paradox of pediatric research is that whereas it is acceptable to use unapproved and unstudied drugs, it is not acceptable to study them in a trial. In the latter case, investigators face many regulatory roadblocks.

#### Comments

The work group made the following points about ethical concerns:

- Boilerplate informed consent has been tried and does not work well because each IRB has its own opinion. Consent language also needs to be appealing to the parent. Bilingualism also needs to be addressed.
- It would be hard for a mother to refuse consent for anesthesia for her baby during surgery, but it would be easier for her to refuse pain control for a heelstick. A mother might want to refuse pain control because of side effects or unknown complications.
- Drawing blood in neonatal studies is an important. A study design would be problematic if it is predicated on the need for the treatment of heelsticks because pain is bad yet involves doing heelsticks on infants. The study should start with current SOCs, then add PK onto clinical care. Methods exist for getting extra volume when taking blood, but an extra heelstick would be hard to justify.

## **Gaps in Knowledge**

The work group identified the following research needs:

- Empiric foundations for composite measures in the youngest neonates (23 to 26 weeks GA)
- Understanding of autonomic responses and how they change in the youngest neonates
- Development of noninvasive pain measurement
- Development of assessment scales for ongoing pain/chronic pain (e.g., At what point does acute pain become chronic?)
- PK and PD data of all analgesic drugs
- Development of a gold standard for pain measurement
- Determination of whether one agent is better than another for a given patient population
- Incorporation of models that show patterns of response
- Explanations for biological variation

## **Recommendations for Future Directions**

The work group discussed future directions and made the following recommendations:

- Collect DNA on all patients in trials to look at genotype and phenotype issues.
- Study mechanisms of tolerance and withdrawal.
- Conduct neuroimaging studies on pain in term and preterm infants using FMRI/EEG monitoring/ERP/near-infrared spectrophotometry.
- Select appropriate long-term measures. What are the measures? What is the timeframe?
- Look at developmentally crucial or sensitive periods (18 to 24 months) of development, including attention and emotional regulation.
- Look at measures of executive function and attention to determine where things go wrong.
- Investigate publication options, including the possibility of publishing the three clinical trials issues as a supplement to *Pediatrics*. The papers also could be published as separate review articles.

# **Appendix D**

## **Appendix D**

### **Pulmonary: Summary of Breakout Discussion**

The Pulmonary Work Group broke into two separate breakout sessions to discuss apnea of prematurity (AOP) and bronchopulmonary dysplasia.

#### **Apnea of Prematurity**

The literature on AOP shows a number of basic issues and questions yet to be resolved. The pulmonary subgroup discussing apnea agreed that the NDDI presents an important opportunity to better frame and possibly answer these basic questions, and to create a context for effective pharmacological treatment. Depending on the results, a large, multicenter RCT (blinded, with placebo) could fundamentally alter the way AOP is perceived and treated. Four sets of issues were identified: definition (of apnea itself and of outcomes that could drive the field), GERD issues, study methodology, and pharmacology issues.

#### **Definition**

To impose the necessary rigor for a large multicenter clinical trial, a uniform definition of AOP is needed; a standard must be imposed to decide how long a pause in breathing will qualify as an apnea event, as well as how large/old a baby must be to be no longer considered “premature.” Apnea needs to be defined in a way that not only mirrors clinical reality but also is consistent with a standard used in other large neonatal development trials, both past and future. Any large multicenter trial must fit within the de facto practices and SOC already in place at a particular NICU and permit the PI the prerogatives of his/her institution. The buy-in and support of nurses will be critical to implement an effective clinical trial.

The standard definition recommended by the work group is equivalent or close to the SOC found in most NICUs. Any occurrence lasting longer than 20 seconds is an AOP event per se. The duration should be reduced to 10 seconds when the heart beats per minute simultaneously dip below 80—and/or when the O<sub>2</sub> saturation falls below 80 percent. Most NICUs currently establish an algorithm based on specific combinations of these three readings to trigger an automatic alarm on the monitor. Even if a local standard varies slightly (e.g., O<sub>2</sub> less than 85 percent), the equipment setup lends itself to a precise collection of defined events. While certain significant cases of AOP will be missed, the recommended parameters represent the best compromise with the practicalities of running a large trial.

The work group also believed that any study of AOP should focus on idiopathic clinical apnea by excluding obstructive apnea. Airway monitoring is a complex undertaking, perhaps not feasible in the entire study population; at least a subset should be monitored and a methodology adopted to assure that nasal airflow is also absent.

Other issues that the work group considered include the following:

- **Does the etiology of apnea affect the response to therapy?** Because apnea is so universal in premature babies, scientific rigor requires considering the possibility that apnea could be just a symptom, rather than a primary disease. While GERD is the most noticeable co-morbidity, many others (e.g., sepsis, temperature dysregulation, IVH) also could be implicated. All these conditions must be ruled out as the primary disorder before the safety and efficacy of a pharmacologic intervention for AOP can be proven. The theory holds that using adenosine inhibitors to disinhibit and, therefore, encourage respiratory mechanisms might be addressing the apnea symptoms without affecting some underlying disease.
- **What is the most effective way to intervene?** Even though the methylxanthines (primarily caffeine and theophylline) are in widespread use, mechanical ventilators and CPAP are also routinely used to treat AOP. Some clinicians argue that ventilation is safer and more effective; thus any global efficacy claims for a drug must be regarded in that context, absent studies that compare modes of treatment.
- **Does neonatal apnea affect long-term neurodevelopmental outcome, or is it merely a marker of other complications of prematurity?** The work group believed that the answer to this question is the linchpin of its recommendations. If the answer is demonstrated to be “no,” then much of the urgency felt about AOP might dissipate eventually. Conversely, if AOP can be shown to cause any specific long-term deficits, scientific attention and resources will be redirected to more and better treatments. Consequently, appropriate outcome measures for the apnea study are crucial. Recognizing that intelligence, often used as a proxy for neurodevelopment, is easier to assess after language has developed, the work group recommended that study outcome should be neurodevelopment, measured at 18 to 24 months. The studies should be powered so that the measures chosen for neurodevelopment can pick up fairly small though tangible effects in both cognitive and psychomotor assessment within that time frame. The proposed trial(s) also should include assessments of short-term outcomes (e.g., effect of a pharmacologic or mechanical intervention on the frequency/severity/duration of apnea episodes in the succeeding 8–24 hours) and a set of intermediate term variables, with measurements taken 2 days after birth and weekly until discharge. These shorter term measures could also become candidates as surrogate markers for the long-term effects of AOP.

### **Gastroesophageal Reflux Disease Issues**

GERD and apnea are found so frequently in the same patients that nurses and doctors often conclude that one or the other has occurred even without unequivocal clinical evidence. No phase 3 study has found evidence supporting the general perception that a relationship exists between the two conditions. The work group examined the following GERD issues that could have an effect on study design:

- **Does esophageal reflux cause AOP and, if so, are pharmacologic treatments effective for the reflux and/or the AOP?** The work group believed that no pharmacologic treatment for AOP could be studied or administered until some scientific clarity is developed on this basic

question. In the context of the NDDI, the work group believed that it is reasonable to ask whether GERD might potentiate AOP or play some pathophysiological role, especially in infants whose AOP does not resolve. GERD is known to exacerbate BPD, so treating it even in its subclinical state could have an impact on BPD morbidity and mortality, if not on AOP. The work group suggested that if trials proposed under the NDDI were to study antireflux drugs (e.g., prokinetic agents and acid blockers) for their effect on apnea as a primary outcome, any results showing no positive effect would help to dispel the myth underlying their continuing use for the treatment of apnea. The work group also saw a need to foster better communication and coordination of care in the clinic between the neonatologists/other NICU caregivers and the gastrointestinal community.

- **What is the effect of the xanthines (theophylline, caffeine) on GERD?** In the context of studying AOP, researchers do not *necessarily* need to include a measure of reflux; to do so could divert the focus of the study from the search for effective drug treatments for AOP. Nonetheless, the issue is further tangled by the belief—again without corroborative data—that the xanthines commonly used to treat AOP actually *cause* gastric distress. Trying to conduct a trial on this question would be further complicated because caregivers must respond to apnea events, if not with xanthines then with other interventions that could potentially confound such a study.

## Study Methodology

Even in the context of a very large multicenter trial with placebo, it remains important to consider carefully which babies could potentially confound the study or compromise generalizable results. The work group considered the following two questions related to the issue of how to define the parameters of the study population:

- **What is the appropriate threshold to treat?** Potential problems for a sound study lie at both ends of the spectrum. With babies less than 26 weeks GA, it may be too early for xanthines. Such young neonates react very strongly to them, dosing is more problematic, and using this class of drugs in that group is believed by some to postpone GI motility and the initiation of feedings. With babies at least 28 weeks GA, these problems are minimal or absent. The other basic defining parameter requires drawing a (somewhat arbitrary) line between AOP and infant apnea. Because neuronal immaturity in the brainstem is believed to be a primary cause of AOP, many clinicians use the GA or CA standard to define the population. However, the work group believed that a sharper criterion is mass/weight, which correlates very highly with AOP. Babies larger than 1,500 grams have less problematic AOP and are less likely to require xanthines or assisted ventilation once they leave the hospital. As a result, their families are less likely to keep them in the study after they are released from the hospital.
- **Which is the better measure to gauge the response to a drug and the risk associated with using it—GA or weight?** Although several early functions are due to specific unfolding stages of development, AOP itself and a number of patient management issues seem to be more clearly related to a baby's mass/weight. Acknowledging that this may be a controversial decision, the work group recommended that groups be stratified by weight.

The work group identified and discussed other issues related to study design, including the following:

- **Relationship of a baby’s position on AOP**—While position in the crib has been shown to have an impact on oxygenation, it is generally not significant in the absence of other lung disease and would have only a very small effect on AOP. Possibly it should be controlled for, but this is a low priority. On the other hand, it is not trivial to consider the role of O<sub>2</sub> on AOP.
- **Effect of baseline oxygenation on the incidence and severity of AOP**—Although this issue is more important to the BPD trial(s), it has often been poorly defined and inconsistently controlled in most AOP studies to date. Data should at least be gathered.
- **Confounders**—In addition to GERD, a suite of neonatal morbidities (e.g., ROP, respiratory distress syndrome, PVL, NEC, IVH, and BPD) are seen in this population that are suspected either to cause or independently have an impact on AOP. The work group did not regard these conditions as exclusionary but thought that the trial design must control for any disorder or pathology thus implicated. By enrolling children very early after birth, in a large enough study, some of these morbidities will accumulate but may assume little or no statistical significance due to the randomization process. Conversely, if patients are recruited later in their GA, researchers may be able to stratify study arms according to different specific complications already present.
- **Entry criteria**—The basic challenge is to balance logistical and practical issues against the ability to provide an unambiguous answer to the research question. Any trial to test caffeine in the NICU faces inherent challenges because the drug is often used for other reasons in preterm babies. Study designers should anticipate that babies in the smallest/youngest group may require caffeine for clinical reasons beyond the scope of the study and design a way to stratify them without compromising the study’s power. This is precisely the subpopulation where prophylactic use of caffeine is already common and may be the most efficacious.
- **Exclusion criteria**—Some conditions rise to the level of exclusions. In some cases, AOP can be traced to an event such as sepsis and some cases of IVH. Many congenital anomalies may be implicated in pulmonary complications and also should be excluded from the recommended studies. In many of these clinical circumstances, premature babies will have already received xanthines for reasons not related to the study.
- **Power and reliability**—Depending on which measure is selected to evaluate long-term neurodevelopment, the trial may require from 500 (e.g., to discern a 5-point difference in Bayley score) to 3,000 (e.g., to discern a 5-percent difference in incidence of some disorder) subjects. Power requirements are (in part) a function of the variance in the measure, but whichever measures are used, the study should be designed to pick up meaningful effects. A study designed to determine a physiologic outcome on a smaller group and then conduct a long-term followup would not provide the broad, solid scientific findings of efficacy that are possible under the NDDI. Long-term followup should be added onto a study when feasible, but until apnea is proven to be—and widely recognized as—a significant threat to

neurodevelopment, such studies probably will need to be supported in special contexts such as the NDDI and the BPCA.

## **Pharmacology Issues**

The current therapies for AOP include the methylxanthines, such as caffeine and theophylline, and the central stimulant doxapram. The methylxanthines have a beneficial effect in reducing apnea episodes, but their exact mechanism is uncertain, and long-term effects are unknown. Known short-term adverse effects include a doubling or tripling of cerebral metabolism and increases in cerebral blood flow, cardiac output, and blood sugar levels. Current FDA labeling for caffeine permits short-term use only within a limited GA population.

Drug trials need to be designed within the context of the many unanswered questions about AOP, including its uncertain etiology and the belief that prescribing drugs for GERD constitutes effective off-label treatment of AOP. Because using off-label drugs to treat apnea and reflux is so common, it may be unrealistic to think that even a new drug will be confined to only those uses specified on the label. GERD appears to be a multifactorial disorder, and no single drug treatment exists that is comparable to the impact xanthines have on AOP. Oxygen (O<sub>2</sub>) clearly has an enormous role in this context but cannot be licensed or controlled as a drug, and there is no financial incentive for industry to test it.

Other pharmacology issues addressed by the work group included the following questions:

- **Is xanthine (and other future drug therapies for AOP) associated with improved outcome (short- and long-term)?** This question highlights the work group's major recommendation to conduct a study that is rigorously controlled and structured to test for long-term impact on cognitive and psychomotor development. Such a trial would address shortcomings of the literature to date, which suffers from no uniform definition of AOP across studies, few of which are long term, and none of which are large enough to be adequately powered.
- **Are other agents effective and safe in treating AOP? Is xanthine use outside the hospital setting for postneonatal infants safe and effective?** Because of its efficacy in addressing apnea events, the xanthines are routinely used when premature babies go home, although dosing can be problematic. Conservative doctrine suggests that babies must be monitored very closely under such circumstances. It has been suggested that other adenosine inhibitors (for example, progestins) might be safer and just as effective in treating AOP.
- **Can xanthines be legitimately used for other apnea disorders than just AOP?** The work group concluded that the answer to this question was yes. These drugs are used for older babies with respiratory control problems. They may be used when treating apnea with prostaglandins or postanesthesia, or in the wake of acute life-threatening events, the definition of which changes as the baby grows into other clinical categories. Xanthines are commonly used after a baby has a hernia repaired.

- **What is the appropriate dosing regimen for pharmacologic agents commonly used to treat AOP (caffeine in particular, but also theophylline and doxapram)?** Guidelines vary, as does common usage across different NICUs; there is no real consensus. While caffeine may have a higher therapeutic index, decisions on when to use how much of which drug are often ad hoc.
- **Is prophylactic use of xanthines for AOP safe and effective?** One consequence of the near universal occurrence of AOP is the use of xanthines as a prophylaxis. A wide spectrum of beliefs is played out in NICUs everyday—some clinicians dose all VLBW babies (500–800 grams) with xanthines throughout their hospital stay until discharge, whether AOP occurs or not. It also is common practice to use xanthines to move a baby off a ventilator. Others believe the drug should never be used except in the event of clear and severe clinical apnea; they will often treat even those babies with mechanical ventilation.

After deliberating these pharmacology issues, the work group prioritized the following drugs for study:

- **Caffeine.** This is the top priority, in order to expand its use beyond the limitations of the current label. Pharmacokinetics will vary depending on whether the drug is caffeine or caffeine citrate. Since theophylline can partially metabolize to caffeine, dose-ranging studies are important.
- **GERD agents.** Such as promotility agents and protein pump inhibitors, histamine blockers, and acid blockers. The work group would expect such trials to show no efficacy, but such a finding is still valuable in that it might bring more coherence to the de facto and off-label use of such drugs for AOP, and encourage NICU clinicians to rely on more proven pharmacology.
- **Additional adenosine receptor subtype agonists.** The goal would be to find agents with better specificity than that found in the xanthines, doxapram, and progesterone.

The work group noted that given the time involved in funding, setting up, and conducting a 2-year trial of this magnitude, it is certainly possible that other drugs—even other classes of drugs—may come to light and overtake the drugs recommended here. It also is important to consider the study’s impact on the label and how quickly the drug under study could be fully approved. Long-term followup may well produce additional insights but should not forestall near-term approval for specific uses.

## **Ethical Issues**

The work group considered the following ethics questions related to the study of AOP:

- **If AOP has been exaggerated as a problem, do we need to evaluate the ethical premise that treating it aggressively could be causing other systemic health problems?** This question derives from the view held by some that AOP is *not* a serious problem with long-term consequences and that it is currently treatable. This view throws a new light on another

important question, namely, what is the effect on other organ systems of treating AOP? The work group believed that a pause in breathing is not a situation that clinicians can ignore. Thus, it is reasonable to ask what are the side or adverse effects of the intervention used (e.g., pharmacology, ventilation, other physical interventions). The difficulty in providing a certain answer to such questions comes from the fact that so many events and responses occur together in the neonatal premature population, especially VLBW babies who are routinely administered xanthines for AOP.

- **Is it ethical to perform RCTs with placebos in preterm infants?** The work group explored the underlying ethics of doing a large AOP trial in three distinct areas: trials for AOP as an outcome, for reflux, and for both. Members addressed the level of risk, the SOC, and treatment of the control arm/placebo group. The work group concluded that it is ethical to perform RCTs with placebo in preterm infants in all three models: looking for AOP alone, for GERD alone, and for both together. The justification for studying both conditions in a single trial derives from the fact that they occur together so often in the clinic and drugs approved for GERD are being used off-label to manage AOP. The FDA is interested in what this situation signifies about clinical practice and what might be done to improve it. Thus it is ethical to look at reflux outcomes, even in an AOP treatment study. However, the work group did not consider this trial design a higher priority than those designs targeted directly at AOP. The group thought that a study on both GERD and AOP, with AOP as an outcome, was the top priority.

### **Critical Gaps in Knowledge**

While AOP is treatable, there remain major gaps in the definition and treatment of apnea that hinder optimal clinical care. Most of these have been discussed in earlier sections. A partial list includes the following:

- **Genetics.** While it is probably not within the scope of this project to begin to identify genes implicated in AOP, study designers should think about banking tissue/blood samples in anticipation of future studies that might spin off of these.
- **Technology.** Notwithstanding advances in neonatal monitoring, a consensus needs to be developed around criteria that would clearly isolate crucial factors and define events more consistently from clinic to clinic.
- **Conflation.** Because bradycardia and desaturation are inevitably part of an apnea episode, and most often GERD is also present, the value of disentangling these symptoms and conditions into distinct phenomena would be a great aid to clinical caregivers.

### **Bronchopulmonary Dysplasia**

The pulmonary subgroup focused on BPD in neonates discussed a general approach to drug development and testing in this population, developed a scheme for studying the drugs in trials, and addressed problematic issues with studying therapies in neonates.

## Definition of BPD

The work group noted that there are two ways to define BPD in newborns—clinically and physiologically.

### *Clinical Definition of BPD*

The work group defined three types of BPD for newborns less than 32 weeks or  $\geq$  to 32 weeks of gestation.

Definition of BPD at  $<$  32 weeks gestation:

- Mild: O<sub>2</sub> needed at 28 days, but breathing room air at 36 weeks gestation
- Moderate: O<sub>2</sub> saturation  $<$  30 percent at 36 weeks gestation
- Severe: O<sub>2</sub> saturation  $>$  30 percent, CPAP or ventilation at 36 weeks gestation

*Source: NIH Consensus Conference, 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.]

Definition of BPD at  $\geq$  32 weeks gestation (all receiving O<sub>2</sub> for at least 28 days):

- Mild: O<sub>2</sub> for 28 days but not at 56 days or at discharge, whichever is first
- Moderate: O<sub>2</sub>  $<$  30 percent at 56 days or at discharge, whichever is first
- Severe: O<sub>2</sub>  $>$  30 percent, CPAP or ventilation at 56 days or at discharge, whichever is first

*Source: NIH Consensus Conference, 2001.*

The work group discussed whether it should address the treatment of mild BPD or focus on the treatment of moderate and severe BPD. The group also discussed whether the trials should be designed specifically for the type of BPD (i.e., mild, moderate, or severe) presented by a neonate.

It was noted that following and treating the mild cases of BPD could provide important data—and a wealth of data—because nearly all premature newborns have *at least* mild BPD. Data on long-term exposure to the treatments also could be collected from this subgroup of patients.

### *Physiologic Definition of BPD*

Mild and moderate BPD may be better defined by the physiologic definition. The work group noted that health care providers should identify why newborns are on oxygen—because the need for oxygen may not be related to BPD.

To physiologically diagnose a newborn with BPD, the newborn must undergo the following test. Challenge newborns with birth weights less than 1,250 grams with saturation at < 30 percent O<sub>2</sub>. The effective FiO<sub>2</sub> is calculated. Then, the newborns are weaned in increments to room air so long as their O<sub>2</sub> saturation stays at > 90 percent. The newborns who fail the oxygen reduction test are defined, physiologically, as having BPD.

### *Discussion*

The work group compared the clinical and physiologic definitions of BPD and found that each definition of BPD significantly changed the number of “defined” cases of BPD for a selected population. It was discovered that these definitions do not help to identify patients at high risk for BPD who might qualify for prevention or early intervention.

The work group discussed the difficulties in collecting standardized data for oxygen need and/or consumption by BPD populations. The work group wanted to know whether it is possible to measure accurately the amount of oxygen consumed in newborns with nasal blockages and physiological abnormalities and in centers at high altitudes. The work group also noted that it knew of no standard flow measurement for oxygen.

The work group determined that trying to test newborns by lowering oxygen was unethical. However, eliminating this measurement drastically affects the potential numbers in the trials. Each institution’s unique definition of “ethical” also affects study numbers. The group reiterated the challenge of collecting standardized data and finding a large group of study subjects for BPD clinical trials.

### **Trial Design Basics**

The BPD work group recommended the following three study designs for BPD future clinical trials:

- 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

The work group also identified subgroup populations within each BPD phase:

- Newborns with extreme risk of mortality
- Newborn subgroups for targeted therapy with the following conditions:
  - Reactive airway
  - Fluid retention
  - Oxygenation defect
- Newborns with genetic susceptibility

The three study phases will look at the following classes of drugs:

- Inhaled corticosteroids
- Anti-inflammatories
- Diuretics
- Inhaled bronchodilators
- Vitamin A, early protein, trace metals, and lipid therapy

### **Sample Trial Design: Prevention of BPD**

The work group identified the following common study design issues that need to be addressed before conducting a BPD clinical trial:

- Assessment of long-term outcomes
- Parallel group trials with placebo controls
- Maternal protective and risk factors
- Neonatal risk factors

#### *Type of Study*

A placebo RCT was recommended by the work group for all three types of BPD clinical trials. Using this type of study does not indicate that patients are not receiving treatment—they are often getting standard care. The work group also indicated that there should be an opt-out option written into the study design.

### *Objectives*

Prevention of BPD as defined by the **NIH consensus conference criteria** supplemented by a physiologic definition.

BPD at 36 weeks must be the primary endpoint of the study (mortality), and secondary endpoints should be at 18 months or 2 years for neurodevelopment and pulmonary development outcomes.

### *Age Group (Stratification)*

- Infants born at < 32 weeks GA with persistent mechanical ventilation and supplemental oxygen at 2 weeks CA

The work group suggested an upper limit of 28 weeks GA for prevention trials. The work group discussed the need for prevention studies to be more inclusive and stratified to include a larger part of the premature newborn population.

The work group identified three possible GA strata:

- Less than 26 weeks
- 26 to 28 weeks
- 28 weeks or older

There is a large population of newborns on persistent mechanical ventilation, so one can stratify by GA (and possibly birth weight), as well as possibly randomize in blocks.

### *Number of Patients*

The work group did not identify the number of patients that would be needed for the studies.

### *Entry Criteria*

The work group identified high-risk premature newborns for entry to the studies, but the specific criteria are open to discussion, with the following possibilities:

- ? < 1,250 grams
- ? <= 28 weeks
- ? <= 30 weeks
- ? <= 32 weeks

### *Exclusion Criteria*

The work group posed the question, “Are there any contraindications for this study?”

The work group agreed that moribund newborns should be excluded from the trials. Newborns with major anomalies—including pulmonary (excluding PDA), airway, genetic, and lethal anomalies—also should be excluded. Sepsis (the type of sepsis needs to be identified) and the inability to provide followup also constitute exclusion criteria.

The work group discussed maternal exclusion criteria such as smoking, illness, infections, and the ability to provide followup information. A final decision was not made regarding maternal exclusion criteria.

### *Assessment Parameters: Efficacy*

To provide efficacy parameters, the work group identified the following questions that must be answered:

- What short- and long-term outcomes should be measured?
- Are there any surrogate biomarkers?
- How should growth be measured, by incremental growth versus caloric intake?

### *Assessment Parameters: PK*

There are no PK data for any of the indications the BPD work group is examining, other than diuretics. Preclinical studies have not been conducted for the drugs that are widely used to prevent BPD.

The work group recommended using postnatal and GA data and encouraged PK data collection.

The FDA prohibits the study of well children for PK; therefore, data collection must be done with patients enrolled in the trials. PK assessments can be done simultaneously with phase 2 and phase 3. The PK measurement can be added into a large outcome study. To get PK parameters with the least amount of “noise,” large stratified groups must be used.

### *Assessment Parameters: Safety*

Parameters for safety need to be determined for the following agents:

- Corticosteroids—monitor for abnormal growth, hypertension, infection, perforation, and neurodevelopment.
- Diuretics—monitor for bone and long-term renal complications.

The work group emphasized that researchers need to include all clinically and statistically significant outcomes in adverse events reporting. The group acknowledged that sometimes it is difficult to report all adverse events because the newborns are so sick. The work group would like to remind health care professionals that it is best to report everything on the case report forms and that the study monitors will take care of filtering out the relevant information.

The work group noted that hyperbilirubin levels are not to be reported as an adverse event.

### *Long-Term Followup*

The work group decided on the following types of long-term followup:

- 1 year and beyond: respiratory morbidity and health care utilization
- 2 years and beyond: neurodevelopmental outcomes

The work group emphasized that the study design needs to take long-term outcomes into account. The group questioned whether long-term followup should be figured into the initial study design.

The work group suggested an MRI as a possible method for measuring long-term outcomes. It also is important to note that long-term data collection can be affected by the after-care that the child receives. The person collecting the long-term data should be aware that the subject might have received anti-inflammatories and/or steroids since being discharged from the hospital for BPD.

A concern of the work group was how to power a study that has the potential of many treatment failures. An extreme number of treatment failures would contaminate all short- and long-term outcome studies.

### **Sample Trial Design: Specifics for Evolving and Established BPD**

The trial designs for evolving and established BPD are similar to the design suggested for the prevention of BPD design. Differences and considerations in the designs are identified below. Both evolving and established BPD trial designs will be randomized, placebo-controlled trials. The established BPD trial design should include open-label rescue dose.

### *Type of Study*

The BPD work group addressed the design and ethical issue: How does one test unproven, yet widely used, treatments? For example, is it possible to study the use of diuretics using a placebo control group? Conducting a placebo-controlled study with diuretics is difficult because the effects of diuretics are very obvious.

This question may be answered with one study, but the work group noted that short- and long-term outcomes are very important. Dose variation should be built into these studies. The work

group suggested one low-dose, one high-dose, and one placebo group for a study design. Exit criteria, or rescue dose criteria, must be identified for a diuretic study design.

Getting colleagues to participate in these studies may prove to be a huge obstacle. For example, the use of diuretics is widely practiced for the treatment of newborn BPD. It would be difficult to convince health care providers that a study needs to be done to determine their effectiveness.

Endpoints suggested by the work group include reduced need for ventilator support at 36 weeks, need for less ventilator support, decrease in health care utilization, and diminished use of late steroids. The work group also considered moving from a “moderate” BPD diagnosis to a “mild” BPD diagnosis as a possible endpoint.

The work group recommended building in the long-term outcomes into the initial study design because obtaining funding to conduct long-term studies is often difficult.

### *Objectives*

Treatment of BPD as defined by the **NIH consensus conference** criteria supplemented by physiologic definition.

### *Entry Criteria*

The required entry criteria for evolving or established BPD are newborns requiring oxygen and/or positive pressure at 28 days.

The work group discussed entry criteria for the evolving BPD trial designs. Evolving BPD entry criteria were suggested for newborns 7 to 10 days of age. Or, the age could vary depending on the therapy. For example, hydrocortisone therapy may be ideal 7 days of age, but 10 days of age may be more appropriate for diuretics.

It was suggested that the evolving BPD group could be recategorized as “early prevention” and “late prevention” groups as well as “early therapy” and “late therapy” groups. Other suggested age stratifications are

- Antenatal prevention
- Postnatal prevention
- Evolving BPD treatment at 7+ days of age (prevention may overlap here)

The work group then discussed how to collect antenatal data for the trials. One suggestion was to use the placenta. Using the placenta is a more feasible way to collect and analyze placental histology, specifically cytokines, than to collect biomarkers, amnion fluid, and tracheal aspirations. But the specific cytokines to be analyzed still need to be identified.

The work group also discussed the entry criteria for established BPD clinical trials. Participants considered whether 28 days of age was too late for entry. Newborns have varying pulmonary issues, tracheal inflammation, and need for oxygen. All newborn pulmonary issues need to be addressed when designing the studies. The question of whether to use GA rather than birth age was left unanswered.

*Assessment Parameters: Efficacy*

The work group agreed on the following efficacy measures:

- BPD at 36 weeks
- Health resource utilization in first year

The work group also discussed the following possible efficacy measure categories:

- Nutritional status
- Growth (including brain growth)
- Language delay
- Cognitive impairment
- Motor function (cerebral palsy)
- Neurotransmitter dysfunction
- Attention, behavior
- Academic performance
- Hearing deficit

*Assessment Parameters: PK*

The work group noted that this assessment parameter varies by drug class, dose, and interval of dosing.

*Assessment Parameters: Safety*

This assessment parameter also varies by drug class. For studies using steroids, growth and long-term neurodevelopment will be examined. For studies with diuretics, renal function and osteopenia most likely will be examined.

### *Short-Term Outcomes*

The work group identified the following short-term outcomes that should be measured in clinical trials:

- Reduced BPD at 36 weeks
- Improved short-term surrogate markers, i.e., FiO<sub>2</sub>, respiratory rate, and respiratory exacerbations

### *Long-Term Outcomes*

The work group identified neurodevelopment, pulmonary health, and overall health as long-term outcomes that should be measured in clinical trials. The group identified the following long-term followup measurements:

- NICU discharge: Use neuroimaging or volumetric analysis to measure treatment outcome.
- 1.5 to 2 years of age: Start looking for major disabilities. At this age, socioeconomic status does not yet have an effect on development. Also look at language skills and evaluate motor skills.
- 3 to 5 years: Start looking at attention and behavior and range of cognitive abilities.
- Continue screening for developmental status throughout adolescence and adulthood.

### Surrogate Biomarkers for Long-Term Neurodevelopmental Outcomes

The work group did not identify biomarkers that could serve as a surrogate for identifying BPD before 34 weeks. Measuring CO<sub>2</sub> is not a usable biomarker.

The work group identified respirator-free days as a possible outcome measure. Oxygen use and oxygen need as outcome measures are difficult to monitor and measure in a standardized way. The work group suggested that perhaps the duration of oxygen need could be used as an outcome measure.

### **Ethical Issues**

The work group identified a significant problem with the current study designs. The neonatology field needs to go back to the basics by further defining the disease with animal models and identifying the necessary outcome measures.

Mortality is not an ethical endpoint because the effects of the treatment could be severe (i.e., disabling neurological damage).

A baseline must be identified before studies with these drugs can begin. The work group suggested identifying and working with a population that has very young newborns with a high rate of BPD. This approach will increase the chances of having comparable studies and data.

### **Critical Gaps in Knowledge**

The work group identified basic science gaps as a lack of knowledge in the following areas:

- Normal and abnormal lung development
- Basic biology of BPD
  - Biomarkers
  - Critical window for intervention
  - Genetic susceptibility
- Preclinical science—juvenile animal models
- Refined tools for outcome measures
- Longitudinal studies

The pharmacology gaps include a lack of knowledge in the following areas:

- Population PK
- Data by postnatal age and postmenstrual age
- Impact of renal and hepatic insufficiency
- Pharmacodynamics
- Pharmacogenomics and proteomics (currently unexplored)
- Drug-drug interactions
- Corticosteroids—need to determine if health care providers are willing to randomize to a placebo
- Diffusion of technology/innovation
- Methods of administering vitamin A

## **Drug Cases To Be Evaluated**

### *Antenatal Corticosteroids*

It is accepted that the admission of corticosteroids constitutes a standard care. But the meta-analysis of corticosteroids for BPD does not show a decrease, but an increase of BPD. The work group concluded that the issue of multiple dosing of corticosteroids requires more study. The current studies have addressed only gestations of 24 weeks or more. The use of corticosteroids at less than 24 weeks also requires study. The work group posed the question: Are repetitive studies not appropriate until corticosteroids are studied in greater detail?

### *Early Use of Postnatal Corticosteroids*

According to the work group, the early use of postnatal corticosteroids is an area of major concern and may be a therapy that the field should no longer use. Studies need to be done to determine whether the window opens again for administering corticosteroids—or the use of different types of steroids at a later age. Twenty to 25 percent of newborns under 1,250 grams are given steroids. Currently, there is no clinically proven guide to determine which steroid to use, what dose should be administered, how long the drug should be administered, and for which type of BDP steroids should be used. Corticosteroids have long half-lives, so repetitive dosing is not a good idea. There are ethical issues preventing the randomization to a placebo (which would require a mortality endpoint). Few work group members thought that health care providers would be willing to randomize to true placebo.

The work group also considered the following issues for postnatal corticosteroid studies:

- The appropriate animal model needs to be identified for the neonatal population.
- The issue of the huge monetary expense for laboratories willing to undergo this type of experiment needs to be addressed.
- The issue of whether death or BPD should be used as an outcome needs to be decided.
- The effect of these oxygen desaturations on the brain needs to be explicated.

### *Antioxidant Therapies*

Antioxidant therapies will be difficult to study because 50 percent of babies on antioxidant therapy for BPD were treated with a rescue dose of steroids.

### *Anti-Inflammatory Medications*

The data available for anti-inflammatories are perplexing. Whereas some data have shown increases in the development of BPD, others have shown no decrease in BPD. The work group suggested looking at fluid retention with anti-inflammatories. Nitric oxide also is considered an

anti-inflammatory medication. Instead of using cytokines in general as a sign of inflammation, investigators should consider working more selectively with cytokine identification and treatment.

### *Drug Cocktails*

The work group suggested looking at cocktails of the above-listed drugs for BPD treatment. The work group also felt that a lot could be learned from studies with adults and steroids, antioxidants, and anti-inflammatories.

### *New Drugs to Study for BPD*

The work group suggested studying the following new drugs for treatment of BPD:

- SOD
- IL-10
- Proteinase inhibitors
- TNF-alpha antagonists
- New surfactant components, surfactant boost at 10 to 14 days
- Novel anti-inflammatory agents
- INO
- CC 10
- Bombesin blocking antibody
- Vitamin A, noninjectable

### **Overarching Issues**

The work group identified the following overarching issues that need to be addressed when designing studies of BPD in neonates:

- Identify funding sources for preclinical studies as well as phase 1 clinical trials for BPD.
- Identify better tools for assessing structure and function of the newborn brain and lung.
- Address resistance of neonatologists to participating in trials of existing and widely used therapies (e.g., diuretics).

- Address the perception among families that clinical research is experimentation.
- Address the need for research infrastructure to include biopharmacologists, toxicologists, and statisticians.
- Address the need for multidisciplinary research teams that include neonatology, pulmonary, and neurodevelopmental specialists.
- Determine methods and funding for tracking families for long-term assessments.

# **Appendix E**

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# **Appendix F**

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### **Abbreviations and Acronyms**

AOP	apnea of prematurity
ATP	adenosine triphosphate
AVV	abnormal visibility of transcerebral veins
BNP	brain natriuretic peptide
BPCA	Best Pharmaceuticals for Children Act
BPD	bronchopulmonary dysplasia
CA	chronological age
CHD	coronary heart disease
CLD	chronic lung disease
CO	cardiac output
COX	cyclooxygenase
CPAP	continuous positive airway pressure
CPB	cardiopulmonary bypass
CPR	cardiopulmonary resuscitation
DA	dopamine
DNA	deoxyribonucleic acid
DOB	dobutamine
ECMO	extracorporeal membrane oxygenation
EEG	electroencephalogram
ENSs	electroencephalographic neonatal seizures
ERP	event-related potential
FDA	U.S. Food and Drug Administration
FMRI	functional magnetic resonance imaging
GA	gestational age
GABA	gamma-aminobutyric acid
GERD	gastroesophageal reflux disease
GI	gastrointestinal
HIE	hypoxic-ischemic encephalopathy
HTN	hypertension
IND	investigational new drug
IOM	Institute of Medicine
IRBs	institutional review boards
IUGR	intrauterine growth retardation
IV	intravenous
IVH	intraventricular hemorrhage

LCOS	low-cardiac output syndrome
MAC	minimal alveolar concentration
MEG	magnetoencephalography
MRI	magnetic resonance imaging
NCA	nurse-controlled analgesia
NDDI	Newborn Drug Development Initiative
NEC	necrotizing enterocolitis
NICHD	National Institute of Child Health and Human Development
NICUs	neonatal intensive care units
NIH	National Institutes of Health
NIRS	near-infrared spectroscopy
N-PASS	Neonatal Pain Agitation Sedation Score
NSAIDs	nonsteroidal anti-inflammatory drugs
PB	phenobarbital
PCA	patient-controlled analgesic
PD	pharmacodynamic
PDA	patent ductus arteriosus
PGF1a	prostaglandin F1 alpha
PI	principal investigator
PICC	peripherally inserted central catheter
PIPP	Premature Infant Pain Profile
PK	pharmacokinetic
PVL	periventricular leucomalacia
RCT	randomized controlled trial
RFPs	Requests for Proposals
ROP	retinopathy of prematurity
SGA	small for gestational age
SOC	standard of care
SOD	superoxide dismutase
SVC	superior vena cava
UAC	umbilical arterial catheter
VLBW	very low birth weight