Management of the Patent Ductus Arteriosus in Premature Infants Trial (PDA Trial)

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SECTION 1. ABSTRACT

Study Hypothesis/Question
Aim: Estimate the risks and benefits of active treatment versus expectant management of a symptomatic patent ductus arteriosus (sPDA) in premature infants.

Hypothesis: In premature infants with a sPDA, expectant management reduces the incidence proportion of death or BPD by 10% (from 50% to 40%) when compared to active treatment.

Study Design Type
This is a pragmatic randomized multicenter, effectiveness study comparing active treatment of a sPDA to expectant management

Sample Size
N=836 premature infants

Eligibility Criteria
Inclusion:
1. Postnatal age 48 hours to 21 days
2. Infant 22 0/7 to 28 6/7 weeks gestation at birth
3. sPDA (defined on pages 10-11)

Exclusion:
1. Cardiopulmonary compromise (at time of randomization)
2. Known congenital heart disease (besides atrial septal defect or ventricular septal defect)
3. Known pulmonary malformation (e.g. congenital lobar emphysema, congenital pulmonary adenomatous malformation)
4. Received prior treatment for sPDA
5. Any condition which, in the opinion of the investigator, would preclude enrollment

Study Intervention/Methods
sPDA and cardiopulmonary compromise will be defined by this protocol, requiring both clinical and echocardiographic evidence. Participants with a sPDA allocated to the active treatment arm will receive indomethacin, ibuprofen, or acetaminophen (depending on center preference). The decision for further treatment (e.g., ligation or cardiac catheterization) will be left to the clinical team.

Participants with a sPDA allocated to the expectant management arm will receive supportive care at the clinical team's discretion. Infants assigned to the expectant management arm will receive treatment per local site if cardiopulmonary compromise occurs; treatment may include indomethacin, ibuprofen, acetaminophen, ligation, or continued expected management.

Primary Outcome
The primary endpoint for the study will be death or BPD (as assessed by the physiologic definition) at 36 weeks postmenstrual age (PMA).

Secondary Outcome(s)
Secondary outcomes will be death and BPD (separately), severity of BPD, NEC, ROP, receipt of therapies designed to close the PDA, growth, and neurodevelopment at 22-26 months corrected age. Severity of BPD, NEC, ROP, receipt of therapies designed to close the PDA, and growth will also be evaluated at 36 weeks PMA.

SECTION 2. STATEMENT OF PROBLEM

2.1. PRIMARY HYPOTHESIS OR QUESTION

Aim: Estimate the risks and benefits of active treatment versus expectant management of a sPDA in preterm infants.

Hypothesis: In premature infants with a sPDA, expectant management reduces the incidence of death or BPD by 10% (50% to 40%) when compared to active treatment.

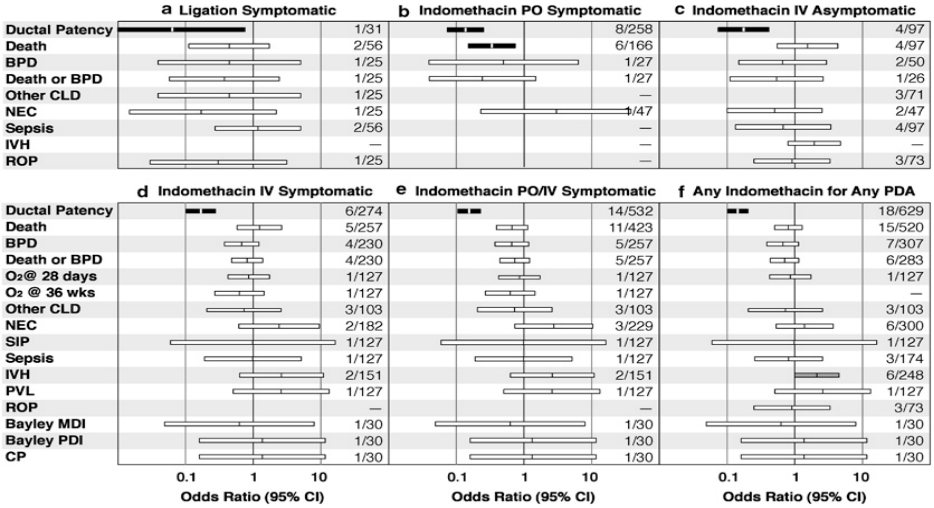
2.2. BACKGROUND AND RATIONALE

Patent ductus arteriosus (PDA) is common and treatment varies widely in premature infants. Evidence to provide guidance for treatment of the PDA is lacking. During fetal life, the ductus arteriosus (DA) connects the pulmonary artery to the aorta and provides a channel through which the majority of pulmonary arterial blood flow is shunted into the systemic circulation. In the majority of infants, the DA closes shortly after birth. In some infants, especially premature infants, there is a delayed closure of the DA [1], sometimes even as late as after discharge. [2] Approximately 65% of infants born < 28 weeks gestation will have a diagnosis of a PDA at some time during the early neonatal period.[3] [4]

In premature infants, PDA is associated with BPD. In a large, prospective, population-based study of 1460 infants in North Carolina, PDA was a risk factor for BPD in multivariable analysis, OR=1.9 (95% CI 1.2, 3.1) among infants ventilated at 48 hrs. [5] This is consistent with other cohort studies.

The risks and benefits of an active treatment or an expectant management approach need to be evaluated in a randomized, controlled trial (RCT). The Cochrane Database of Systematic Reviews currently includes two meta-analyses of the efficacy of indomethacin in the treatment of the PDA. The first review identified 19 trials designed to determine the benefits of prophylactic indomethacin. [6] The other examined enrolled infants with asymptomatic PDAs.[7] The authors conclude that indomethacin reduces the incidence of sPDAs, subsequent ligation, and the incidence of intraventricular hemorrhage. However, the incidences of BPD or other

Figure 1 Treatment for symptomatic or asymptomatic PDAs



morbidities were not reduced in treated infants. Other systematic reviews have been published and, taken together, report that the most consistent finding is that treatment of the PDA results in ductal closure with little, if any, effect on death, BPD, or other morbidities of prematurity (e.g. NEC, Figure 1). [8] [9]

There is wide practice variation for management of sPDA. Because of the uncertainty about which approach is optimal, there is wide practice variation. In 2014, 42% of infants <29 weeks gestational age in the NICHD Neonatal Research Network GDB who were diagnosed with a PDA were treated with indomethacin or ibuprofen (or acetaminophen[10]) and 18% had their PDA surgically ligated. The percentage of infants with a sPDA who were treated with a COX inhibitor ranged from 19-100% depending on the center; the percentage of infants receiving a PDA ligation ranged from 5-35%. These treatment differences are superimposed on the differences in identification of sPDA which ranged from 14-80% among the centers. Thus, the percent treated for sPDA ranged from 5-60%.

Four studies reveal widely disparate approaches in the management of the PDA:

1. **Vanhaesebrouck 2007:** A comparison of two relatively conservative approaches is reported by a single center in Belgium. [11101] In a before-after design, the authors examined the difference between an "active treatment" approach (1999-2004) to a "expectant management" approach (2005-2006). Both "active treatment" and "expectant management" approaches included an echocardiogram on postnatal day 2 or 3 and, if a PDA was found, fluid restriction and adjusting ventilation. There was no indomethacin or ibuprofen treatment in either era. In the "active treatment" approach, some infants received a PDA ligation. Outcomes, included death or BPD, were similar in both eras.

2. **Jhaveri 2010:** A comparison of two relatively active treatment approaches is reported by a single center in California: UCSF. [12112] In a before-after study design, the authors examined the differences between an "active treatment" approach (1999-2004) and an "expectant management" approach (2005-2008). All infants received indomethacin for prophylaxis. In both approaches, infants received an echocardiogram on postnatal day 2-3, and indomethacin if there was an open PDA. In the "active treatment" approach, 100% of PDAs that persisted after medical therapies were ligated; in the "expectant management" arm, 72% were ligated. The "expectant management" approach was associated with less NEC and similar rates of death or BPD.

3. **Kaempf 2012:** A comparison of two intermediate approaches is reported by a single center in Oregon. [13] In a before-after study design, the authors examined the difference between an "active treatment" approach (1999-2004) and an "expectant management" approach (2008-2009). The "active treatment" approach included indomethacin for all infants with a PDA and ligation if there was no closure. The "expectant management" approach included "watchful waiting", fluid restriction, limited use of indomethacin, and ligation only in infants who met cardiorespiratory distress criteria. The "expectant

management" approach was associated with fewer infants treated with indomethacin, fewer PDA ligations, and no difference in death or BPD, after adjustment.

4. **Sung 2016:** A comparison of a traditional "active treatment" approach to a very "expectant management" approach is reported by a single center in Korea. [14] In a before-after study design, the authors examined the difference between an "active treatment" approach (2009-2011) to a "expectant management" approach (2012-2014). The "active treatment" approach included indomethacin for infants with a PDA and ligation if the PDA remained open. The "expectant management" approach included diuretics and fluid restriction and no indomethacin or ligation. There was no difference in mortality or NEC, but they reported less BPD in the latter (expectant management approach) era.

Table 1. Summary of cohorts, year, management of PDA, and outcomes of 4 "before-after" cohort studies

	Vanhaesebrouck 2007		Jhaveri 2010		Kaempf 2012		Sung 2016	
years	99-04	05-06	99-04	05-08	05-07	08-09	09-11	12-14
N	31	30	216	180	139	72	81	97
GA, mean	*	26	26	26	27	27	25	25
BW, mean	*	994	830	827	973	945	728	718
Indomethacin, %	0	0	100[1]	100[1]	79	26	64	0
Ligation, %	6	0	24	17	45	33	82	0
BPD, %	8	7	32	28	32	42	46	35
Mortality, %	13	12	12	11	8	12	9	9

[1] 100% of infants in this study received prophylactic indomethacin; and 100% with a PDA received indomethacin (27% of cohort in "before" and 28% in "after")
* Not reported

All groups conclude that new controlled, randomized trials to reexamine the benefits and risks of different approaches to PDA treatment are warranted. The AAP Clinical Report on PDA in premature infants calls for "well-designed and meticulously executed intervention trials, for which the end points are clinically important long-term outcomes and not simply rates of ductal closure or measures of short-term physiologic changes." [15]

SECTION 3. METHODS

3.1. STUDY POPULATION

Premature infants with a sPDA

3.1.1. Inclusion Criteria

1. Postnatal age 48 hours -21 days
2. Infant 22 0/7 to 28 6/7 weeks gestation at birth
3. sPDA (defined below)

3.1.2. Exclusion Criteria

1. Cardiopulmonary compromise (at the time of randomization)
2. Known congenital heart disease (besides atrial septal defect or ventricular septal defect)
3. Known pulmonary malformation (e.g. congenital lobar emphysema, congenital pulmonary adenomatous malformation)
4. Received prior treatment for sPDA
5. Any condition which, in the opinion of the investigator, would preclude enrollment

Note: Prophylactic indomethacin is not an exclusion criterion.

3.2. DETAILED STUDY PROCEDURES

3.2.1. Screening

The presence of a sPDA and cardiopulmonary compromise will be defined using a modified McNamara Scale [16] using clinical and echocardiographic criteria (Table 2). Echocardiograms are performed at the discretion of the clinician and are not mandated by this study. Outborn infants will be included if they are admitted within 7 postnatal days.

Protocol Definitions

The definitions for no PDA, symptomatic PDA, and cardiopulmonary compromise will require both clinical and echocardiographic criteria within 3 days of each other, as follows:

No PDA

1) No PDA by echocardiogram, regardless of Clinical Criteria
2) Asymptomatic Clinical Criteria, regardless of PDA size on echocardiogram

Symptomatic PDA

1) Mild, Moderate, or Severe Clinical Criteria with Small or Medium size PDA on echocardiogram
2) Mild or Moderate Clinical Criteria with Large PDA on echocardiogram

Cardiopulmonary Compromise

1) Severe Clinical Criteria with Large PDA on echocardiogram

Only infants with symptomatic PDA will be eligible for this study (see Inclusion/Exclusion criteria). An echocardiogram is required to diagnosis sPDA (i.e., for inclusion criteria or for assessing subsequent courses of indomethacin/ibuprofen/acetaminophen in the active treatment arm).

Table 2. Modified McNamara Criteria for Pragmatic PDA Trial

CLINICAL		ECHOCARDIOGRAPHIC	
Asymptomatic	No positive airway pressure	None	No PDA
Mild	• FiO_2 <0.30 • Positive airway pressure	Small: 3 of 3	• 0.1-1.5 mm diameter • DA flow Vmax >2.5 m/s • LA:Ao ratio <1.5:1
Moderate	• FiO_2 0.30-0.50 • Positive airway pressure OR • Hypotension requiring a single vasopressor medication	Medium: 1 of 3 (supersedes Small)	• 1.5-3 mm diameter • DA flow Vmax 1.5-2.5 m/s • LA:Ao ratio 1.5 to 2:1
Severe	• FiO_2 >0.50 • Mechanical ventilation (conventional or high frequency) OR • Hypotension requiring > 1 vasopressor medication	Large: 1 of 4 (supersedes Medium)	• >3 mm diameter • DA flow V_{max} <1.5 m/s • LA:Ao ratio >2:1 • diastolic flow reversal in the abdominal aorta

Notes for CLINICAL:

- Positive airway pressure=NCPAP, NIPPV, MV, HFV, OR NC > 1 LPM
- Hypotension requiring a vasopressor medication is an automatic qualification for moderate (one vasopressor medication) or severe (>1 vasopressor medication), regardless of respiratory support. Vasopressor medications include dopamine, dobutamine, epinephrine, vasopressin, or phenylephrine.

Notes for ECHOCARDIOGRAPHIC:

- Infants with an atrial septal defect or ventricular septal defect might have altered LA:Ao ratios; in this case the size and flow will be used to assess PDA size.
- Flow is left to right; infants with right to left flow are not considered to have a sPDA.

Examples of ECHARDIOGRAPHIC:

1) PDA diameter 1.3 mm, V_{max} 2.6 m/s, LA/Ao 1.3:1 = Small
2) PDA diameter 1.3 mm, V_{max} 1.6 m/s, LA/Ao 1.5:1 = Medium
3) PDA diameter 1.3 mm, V_{max} 1.6 m/s, LA/Ao 2.5:1 = Large

3.2.2. Consent Procedures

Details of consent will be left to the individual center. A center might choose to consent all gestational age eligible participants prior to development of an sPDA, might choose to wait until an sPDA was diagnosed, or might choose an alternative method.

3.2.3. Randomization Procedures

The infant will be randomized to either active treatment or expectant management within 48 hours of identification of a sPDA. If the infant is not randomized within 48 hours of identification of a sPDA it will be considered a protocol deviation. An infant must meet all inclusion and none of exclusion criteria at the time of randomization. After meeting eligibility and obtaining consent, randomization to management arms will be 1:1 and stratified by center and GA (22-25 weeks and 26-28 weeks). Higher multiples enrolled in the study will be randomized individually.

3.2.4. Study Intervention and Comparison

Infants assigned to the active treatment group will receive indomethacin,ibuprofen, or acetaminophenper their local site usual care dosing, formulation (i.e., intravenous or enteral)and schedule if the infant has a sPDA (Table 2) within 48 hours of diagnosis of sPDA. The choice will be left to the center; however, infants may only receive one medication. If the infant receives more than one, it will be considered a protocol deviation. Infants assigned to the expectant management group will receive treatment per local site if cardiopulmonary compromise occurs; treatment may include indomethacin, ibuprofen, acetaminophen, cardiac catheterization, ligation, or continued expected management.

Table 3. FLOWCHART OF STUDY PROCEDURES

PROCEDURE	Baseline	36 weeks PMA	22-26 months corrected GA
Informed Consent/Privacy Acknowledgement	X		
Demographics	X		
Pertinent Medical History	X		
Medical Baseline Conditions	X		
Body Weight	X[a]	X	
Echocardiogram report	X	X[b]	
Pharmacologic and surgical treatments for sPDA		X	X
Assessment of death/BPD		X	
Neurodevelopmental Assessment			X

[a] Within 48 hours after enrollment
[b] if obtained per clinical care

Baseline Study Procedures

1. Obtained signed and dated informed consent
2. Record demographics, medical history and medical baseline conditions
3. Record results of echocardiogram within 48 hours before study entry

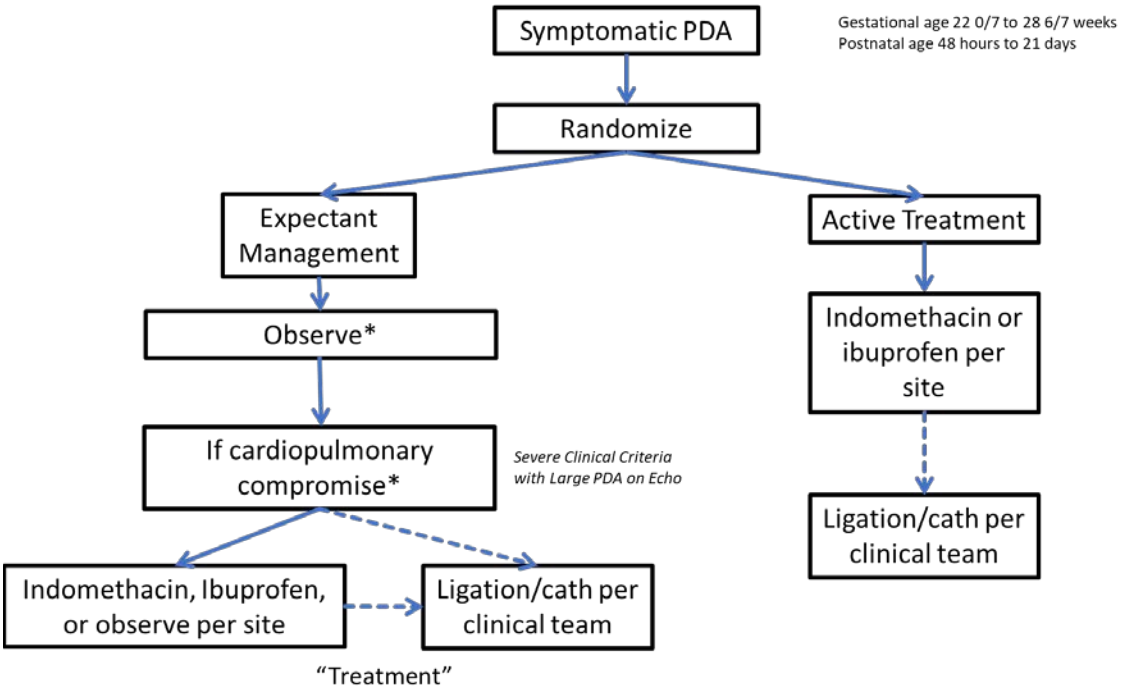
Study Procedures to 36 weeks PMA

The following will be recorded:

1. Record pharmacologic and surgical treatments for sPDA.
2. Stage of sPDA at time of treatment.
3. If the infant develops cardiopulmonary compromise in the expectant management arm, the PDA treatment will be that of the local site standard of care. The treatment(s) will be recorded.
4. Assess and record AEs believed to be related to study procedures (definite and probably related) and all SAEs.
5. Results of echocardiograms (details to be in the MOP).

This protocol will not mandate a PDA ligation at any time. The decision for ligation is up to the clinical team. In the expectant management arm, treatment with indomethacin,ibuprofen, acetaminophen, ligation, or cardiac catheterization prior to cardiopulmonary compromise will be considered a protocol violation.

Figure 2: Study Course; NOTE: dotted lines indicate clinical team's decision



*** Protocol violation if treatment prior to cardiopulmonary compromise**

3.2.5. Blinding/Masking

None

3.2.6. Control or Monitoring of Co-interventions

This study will not prescribe diuretics, fluid restriction, red blood cell transfusions, or other medications (besides indomethacin,ibuprofen, or acetaminophen) that might be used to treat a

sPDA because the evidence from RCTs is not sufficient to justify their use. However, these are common approaches used in many NICUs.

3.2.7. Primary Outcome

1. Primary endpoint: Death or BPD (physiologic definition, per NRN guidelines) at 36 weeks PMA

3.2.8. Secondary Outcomes

1. Mortality: assessed at 36 weeks PMA and before discharge
2. Bronchopulmonary dysplasia: physiologic test of oxygen therapy at 36 weeks PMA
3. Bronchopulmonary dysplasia: NIH consensus definition of moderate, or severe at 36 weeks PMA
4. Other standard NRN outcomes of infant morbidity collected as part of GDB at 36 weeks PMA and status (22-26 months corrected age), including:
   a) NEC (NRN definition: proven NEC, no surgery, Stages IIA, IIB, or IIIA AND proven, surgery, Stage IIIB)
   b) ROP (NRN definition: Stage 3 or worse in either eye AND as any intervention therapy—retinal ablation, scleral buckle/vitrectomy, avastin or other anti-VEGF drug)
5. Receipt of therapies designed to close the PDA (NRN definition: ligation or cardiac catheterization).
6. Growth at 36 weeks PMA and status (22-26 months corrected age): weight, height, and head circumference (if available)
7. Neurodevelopmental impairment at status (22-26 months corrected age): NRN definition of moderate NDI (Bayley IV cognitive 70-84, motor 70-84, GMFCS 2-3) or severe NDI (Bayley IV cognitive <70, motor <70, GMFCS 4-5, bilateral blind, bilateral hearing loss) or profound NDI (Bayley IV cognitive ≤54, motor ≤46, GMFCS 4-5, bilateral blind, bilateral hearing loss).

3.2.9. Compliance Monitoring

Data collection will continue and participants will remain in the assigned group regardless of treatment for data analysis (intention-to-treat analysis). Parents may request withdrawal of their infant from the study at any point in time. Study exit means that management of the infant is no longer defined by study guidelines.

3.2.10. Study Specimens

None.

3.2.11. Post-hospital follow-up

It is suggested that infants with PDAs near the time of discharge be referred to a pediatric cardiologist or other appropriate care provider for management.

3.2.12. Follow-up at 22-26 Months

1. Growth and neurodevelopmental outcomes (see section 4.2.8)

2. Surgeries or procedures designed to close a persistent PDA after discharge (e.g. cardiac catheterization or ligation)

3.2.13. Additional Follow-up Assessments

None.

3.3. POTENTIAL RISKS AND BENEFITS TO SUBJECTS

Since both of the management strategies are commonly and variably used by providers and sites in the NRN and across the US (and world), and encompass the middle of management strategies as noted in the background section, the main risk to participants is the loss of confidentiality of trial data. However, it is acknowledged that participants assigned to one management strategy or the other might have increased or decreased incidence of mortality, BPD, or other important morbidities of prematurity.

Integrating endpoints and risk

Upon completion of the trial we will integrate the inter-related endpoints of efficacy (death or BPD at 36 weeks postmenstrual age, the primary endpoint) and safety (e.g., necrotizing enterocolitis, other SAEs, and neurodevelopmental impairment) in order to provide results and suggestions for subsequent uptake of each approach.

NDI information is available, the suggestions for practice adoption will be based on the difference between mortality and NDI. Since death and NDI are competing outcomes, it is possible that the endpoints might be divergent. If there are safety concerns (e.g. increased risk of NEC or SAEs > 10%), then the suggestions will be modified. The suggestion for practice will depend on the risk difference of NDI and the risk difference of mortality.

Table 4: Suggested recommendation of expectant management treatment approach using neurodevelopmental impairment results and mortality or BPD outcomes

	Expectant management Mortality or BPD risk difference (RD)		
NDI RD	**Mortality/BPD RD -8 to -2%**	**Mortality/BPD RD -2 to 2%**	**Mortality/BPD RD 2 to 8%**
< -5%	Yes	Yes	No
-5 to 0%	Yes	Yes	No
0 to 5%	Yes	Tentative	No
> 5%	Yes	No	No

SECTION 4. ANALYTICAL PLAN

4.1. STATISTICAL ANALYSIS PLAN

Demographic and baseline characteristics such as age, gender, race, primary underlying disease, etc. will be summarized and compared between treatment groups. The full analysis set is defined as all randomized participants. All statistical tests will be two-sided with a type I error of 0.05, unless otherwise specified. Type I error for the primary outcome will be 0.044 to adjust for 3 planned interim analyses, as specified in 4.5.2.2. Analyses will be conducted on an intent-to-treat basis. All analyses by treatment group will use robust Poisson regression to produce adjusted relative risk estimates summarizing the treatment effect for binary outcomes (including the primary outcome), adjusting for stratification variables (gestational age and center). Statistically significant treatment effects for secondary outcomes will not be considered definitive and will require further studies to produce conclusive results. We will evaluate the treatment effect on outcomes by severity of clinical symptoms and by GA stratum. Analyses will be specified in a statistical analysis plan (SAP) finalized prior to enrollment.

4.2. SAMPLE SIZE AND POWER ESTIMATES

Table 5. Sample Size

Effective Sample Size	1	776*
Lost to follow up: 5%	0.05	39
Interim Looks: 2.5%	0.025	21
Total Sample Size		836

**Note:* assumes two sample proportions (0.5 and 0.4 or 0.6 and 0.5), 80% power, and alpha of 0.05

Justification of measure of effect (10% risk difference in incidence proportion): We justify this risk difference because the risk difference for the "before-after" study design ranged from -14% to +11%. Clinicians are unlikely to change practice without at least a 10% difference in study groups.

4.3. AVAILABLE POPULATION

With consultation from RTI, we identified ~1800 infants/year in 2014/2015 that meet the 22-28 weeks GA inclusion criteria. Of these, 802 infants in 2015 and 751 infants in 2014 were diagnosed with a symptomatic (non-protocol defined) PDA.

4.4. PROJECTED RECRUITMENT TIME

Based on 2015 GDB, approximately 802 patients are eligible in the NRN/year. Assuming enrollment of 30%, we will enroll about 240/year once all sites are activated and screening; recruitment would occur over 4.5 years, with 2 years of follow-up; total duration=6.5 years. Assuming enrollment of 40%, we will enroll about 321/year; recruitment would occur over ~3.5 years, with 2 years of follow-up; total duration=5.5 years. Enrollment will be monitored monthly per normal NRN monthly reports, reviewed by the PDA Trial subcommittee on conference calls, and presented to the SC by the PI quarterly. If patient enrollment does not meet expected, the reasons for the problem will be analyzed. Study forms will be constructed to include reasons for lack of enrollment to assist in this process. After 100% of NRN centers

have been IRB-approved and screening, subject accrual will be reviewed formally at one year by the PDA Trial subcommittee with recommendations to the Steering Committee and the NRN DSMC. If enrollment is <110 participants then the recommendation will likely be to discontinue the study. Decisions about continuation of the trial will be based on recruitment and safety data.

4.5. STUDY MONITORING PLAN

4.5.1. Reporting Adverse Events

All potential Adverse Events (AEs) will be reported on the Adverse Events form and entered in the electronic data capture system (EDC). Potential adverse events include:

a. NEC (Bell's Stage II or higher)
b. Intestinal Perforation
c. Renal Insufficiency
d. Other events resulting in death or classified as a Serious or Related (to study procedures).

All serious adverse events (SAEs) that are at least possibly related and unexpected will be reported promptly (within 24 hours of knowledge) to NICHD and the Data Coordinating Center (DCC). These events will be forwarded to the Chair of the Data Monitoring and Safety Committee (DSMC). An initial SAE form must be as complete as possible, including details of the current serious adverse event, and provide an Investigator assessment of the causal relationship between the event and study procedures. Information not available at the time of the initial report must be documented on a follow-up SAE form

4.5.2. Data Monitoring Plan and Stopping Rules

The study subcommittee will review protocol adherence to treatment assignment (i.e., the % crossover) after 50 subjects have been enrolled and reached 36 weeks PMA. The independent NRN Data Safety Monitoring Committee (DSMC) will have overall responsibility for interim data monitoring, and operate based on the NICHD NRN charter for the DSMC. The DSMC will formally review interim safety and efficacy data in a sequential fashion using interim monitoring boundaries after approximately 25% (279), 50% (558), and 75% (837) of the subjects reach the primary outcome at 36 weeks. Treatment groups will be compared statistically using the analysis methods planned for the final analysis (as specified in Section 4.1).

4.5.2.1. Safety

Safety outcomes include incidence of mortality up through 36 weeks PMA, NEC, and ROP. Longer term safety outcomes, if relevant, will include mortality and NDI at 2 years corrected age. The DSMC may request other outcomes at their prerogative. Formal statistical testing for an imbalance of mortality or NEC in either treatment arm at GDB status or at 36 weeks PMA, whichever occurs first, will be based on a comparatively liberal Lan DeMets Pocock boundary at the 3 interim safety looks to guard against any occurrence of false positives while at the same time allowing for stopping at reasonable levels of evidence. Thus, at each interim, an increased incidence of death in either treatment group with $p < 0.0179$ (for 4 total tests) will be considered as statistically significant evidence of harm that the Data Safety and Monitoring

Committee can use to recommend suspension of the trial for safety reasons. In addition to the formal safety outcome, the DSMC will examine other safety outcomes, including all reported serious adverse events by treatment group in considering a recommendation to suspend the trial for safety reasons.

4.5.2.2. Efficacy

Formal interim testing will assess for early overwhelming efficacy in either the active or expectant management treatment group. To control for the inflation of Type I error associated with sequential testing, Lan-DeMets O'Brien-Fleming stopping boundaries will be calculated for the efficacy look at the primary outcome, based on the 3 planned interim looks. Thus, an increased incidence of the primary outcome (Death or BPD at 36 weeks PMA) in either treatment group with $p < 0.000015$ at interim 1, $p < 0.0030$ at interim 2, or $p < 0.01830$ at interim 3 will be considered as statistically significant evidence of efficacy that the Data Safety and Monitoring Committee can use to recommend suspension of the trial for efficacy reasons.

4.5.2.3. Futility

The DSMC can also make a recommendation for stopping the trial at an interim analysis if there is a very low probability that the study will find any difference between treatment groups in the primary outcome at the end of the study. Statistical interim futility monitoring will be conducted after 50% and 75% of subjects reach the primary outcome. At each of these two looks, we will estimate conditional power, i.e., the probability to detect a statistically significant treatment benefit of either treatment group, given the observed data. The Data Safety and Monitoring Committee may recommend suspension of the trial for futility if this probability is less than 15%. In addition to the conditional power analysis, the Data Safety and Monitoring Committee may also consider other pertinent aspects included in the interim report such as the quality of the data, protocol violations and treatment adherence, rate of enrollment, and rate of attrition in its recommendation to stop for futility.

SECTION 5. DATA SHARING

Data collected for this study will be analyzed and stored at the Data Coordinating Center, RTI International. After the study is completed, the de-identified, archived data will be transmitted to the NICHD Data and Specimen Hub (DASH), for use by other researchers including those outside of the study. Permission to transmit data to DASH will be included in the informed consent.

SECTION 6. REFERENCES

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