Preliminary Percutaneous Intervention Versus Observational Trial of Arterial Ductus in Low-weight Infants

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PROTOCOL TITLE: PIVOTAL Pilot Study **Version 1**

STUDY SITES: **Nationwide Children's Hospital (NCH)**
University of Tennessee Health Sciences Center (UTHSC)

PRINCIPAL INVESTIGATOR (NCH):

Name: Carl Backes, MD
Department / Center: Cardiology and Center for Perinatal Research
Telephone Number: 614-264-6374
E-mail Address: carl.backesjr@nationwidechildrens.org

PRINCIPAL INVESTIGATOR (UTHSC):

Name: Mark Weems, MD
Department / Center: Department of Pediatrics
Telephone Number: 901-448-5950
E-mail Address: mweems@uthsc.edu

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REVISION HISTORY:

Revision #	Version Date	Summary of Changes	Consent Change?

1.0 Study Summary

Study Title:	PIVOTAL Pilot Study
Study Design:	Randomized + Prospective
Primary Objective	Collect preliminary data to be used for a large multi-site randomized study proposal
Secondary Objective	Provide inside into parental willingness for randomization regarding treatment interventions to be used
Research Intervention(s) / Investigational Agents	1) Percutaneous (catheter-based) closure of patent ductus arteriosus [active intervention], 2) Conservative management of patent ductus arteriosus [non-intervention] 3) "Rescue" intervention (if medically necessary for conservative management group [rescue intervention]
IND/IDE #	N/A
Study Population	Premature infants born at <28 weeks gestation with hemodynamically significant patent ductus arteriosus (PDA) at days of life 14 – 28.
Sample Size	10 each for interventions 1) and 2) for a total of 20 enrolled at NCH. 20 additional infants will be enrolled at the collaborating institution (University of Tennessee Health Sciences Center) *Unknown additional for non-randomized prospective data collection (see protocol narrative)*
Study Duration for individual participants	From birth to hospital discharge.
Study Specific Abbreviations / Definitions	PDA ≡ patent ductus arteriosus; ECHO ≡ echocardiography; HSPDA ≡ hemodynamically-significant patent ductus arteriosus; NCH ≡ Nationwide Children's Hospital; UTHSC ≡ University of Tennessee Health Sciences Center

2.0 Objectives

This pilot study is intended to collect preliminary data for a large, multi-site study proposal: *Percutaneous Intervention Versus Observational Trial of Arterial ductus in Low-weight infants (PIVOTAL)*. Not only will this pilot trial serve to collect preliminary data, but it will also provide critical information with regards to parental willingness to have their infants randomized to a particular intervention, which may affect recruitment strategies for a larger endeavor. The underlying hypothesis is that percutaneous closure will reduce the incidence and severity of bronchopulmonary dysplasia (BPD) in these infants, as evidenced by need for supplemental oxygen and ventilator support.

3.0 Background

Patent ductus arteriosus (PDA) is the most common cardiovascular complication among preterm infants, and there is ongoing debate regarding if intervention is required, when intervention is warranted or necessary, and how best to intervene. Treatment strategies for PDA vary markedly among institutions, with some centers aggressively pursuing intervention (closure), based on evidence that a PDA is associated with greater rates of mortality and linked to harmful longer-term outcomes, including chronic lung disease and heart failure. Other centers prefer a conservative approach, with no active intervention, in the hopes that the PDA will close naturally. This approach is based upon evidence that all forms of deliberate ductal closure have the potential for adverse side effects and that no studies have shown that treating all preterm infants with a PDA improves outcomes. These two very different approaches frame the ongoing debate and controversy regarding PDA patient management and treatment, and will form the two different treatment “arms” for the pilot study. Both the current, pilot study and the later multicenter trial will be centered around two widely accepted methods for treating PDA in preterm infants, both of which are considered “standard of care” at Nationwide Children’s Hospital (NCH). An additional item frequently debated among cardiologists and neonatologists is the definition of “Hemodynamically-significant” when it comes to PDA. To avoid confusion, we have elected to define a number of both clinical and echocardiographic criteria for evaluating whether or not a PDA would be considered “hemodynamically significant” (HSPDA). These criteria are shown in **Table 1**.

4.0 Study Endpoints

Discharge from the hospital.

5.0 Study Intervention/Investigational Agent

At NCH, the interventional method of choice is percutaneous (catheter-based) closure, in which a catheter is run to the heart and a device is implanted within the PDA of the patient in an effort to close it. Surgical ligation of the ductus is only performed at NCH under very unusual circumstances where catheter intervention is contraindicated. For the purposes of this study, the closure device that will be implanted is sized based upon measurements taken during the procedure. It is anticipated that most, if not all of the infants in this arm of the study will receive the Ampatzer Piccolo Occluder (formerly the Amplatzer Duct Occluder II Additional Sizes), which received FDA approval in January of this year. The second method is conservative

treatment (aka – “watchful waiting”), in which fluid intake is restricted and the patient is administered diuretic medications, but no physical intervention is applied in the hopes that the ductus will close naturally.

We recognize that parents may be reluctant to permit randomization to one treatment or the other (ie – leaving the treatment approach up to chance). For this reason, we have introduced a purely observational second “arm” to the study (**Figure 1**). Parent(s) who decline randomization, and therefore, enrollment in the randomized pilot trial will be given the option to approve prospective data collection, if they are willing to do so. A second consent document has been prepared for this purpose.

6.0 Procedures Involved

Echocardiography (ECHO): All possible participants will receive a research ECHO as a “qualifying” or “screening” step. This will occur at any point during the 14 – 28 postnatal day time period once informed consent for participation has been obtained. Patients meeting criteria for hemodynamic significance (**Table 1**) will qualify. Patients with a closed PDA or a PDA not meeting the criteria as hemodynamically-significant on this qualifying ECHO will be excluded from further participation. There will be an additional research ECHO performed at 36 weeks corrected gestational age. Additional echocardiographic studies during hospitalization will be at the discretion of the attending treatment team(s).

ECHO studies will be obtained via standard practice at NCH and UTHSC for neonatal subjects. Pre-warmed coupling gel will be placed on the chest of the subject, and the "wand" will be placed in contact with the chest under minimal pressure. The wand will then be carefully moved and positioned to obtain the appropriate viewing angles for optimum image and data acquisition. Clinical ECHOs from NCH will be stored on a secured server (EchoIMS) for later analysis; research ECHOs will be stored initially on the secure Merge database. ECHO data and reports are currently scheduled to be moved to the secure Siemens Syngo system in July of 2019. ECHOs at UTHSC will be stored and analyzed per institutional protocol, but PHI will be removed from ECHO reports prior to sharing with NCH (see *Data Sharing Between External Entities*).

Percutaneous PDA Closure:

Briefly, femoral venous access will be used exclusively. A coronary guidewire will be advanced under fluoroscopic guidance through the right heart, across the PDA, and into an ileac artery. A 4-F hydrophilic sheath (Flexor, Cook Medical, Bloomington, Indiana) will be advanced over the

wire into the descending aorta, and the ADO-II AS device implanted through the sheath using a combination of fluoroscopic and echocardiographic guidance. Prior to release from the delivery cable, the left pulmonary artery (LPA) and descending aorta will be carefully evaluated by echocardiography with 2-dimensional imaging and color and spectral Doppler and compared with the pre-procedural imaging. If vascular stenosis related to the device is observed, as defined by a maximal instantaneous gradient >15 mm Hg or an "obstructed" pattern with persistent antegrade diastolic flow, the device will be recaptured and either repositioned or removed and replaced with another device of a different size. If on repeat attempt(s) there was persistent stenosis, the patient was converted to surgical ligation. Following release of the device, echocardiographic evaluation of all pertinent structures will be repeated. Per protocol, patients will be administered a single intraprocedural and 2 post-procedural doses of antibiotics (cefazolin 25 mg/kg) and a single procedural dose of intravenous heparin (100 U/kg) unless contraindicated.

Conservative Treatment: For this approach, both medication (primarily diuretics) and fluid restriction may be used in the hopes of limiting PDA-related complications while allowing time for natural closure. Under this protocol, healthcare decisions will be made at the discretion of the treatment team, while the infant is carefully monitored for any decline in status that may be attributed to the presence of PDA. In this case, "Rescue" Intervention (below) may be considered.

"Rescue" Intervention: It is recognized that some infants randomized to the conservative management arm will continue to have a HSPDA, which may be hindering clinical improvement or worse yet, be an underlying or secondary cause for continued clinical decline. If deemed medically necessary by the treating physicians, and additional criteria are met, these infants will be assigned to "Rescue" intervention by percutaneous closure. These "additional" criteria are noted below (*please refer to **Table 1**, also*):

RESCUE CRITERIA #1

- Receipt of dopamine or dobutamine at ≥10 mcg/kg/minute or epinephrine or norepinephrine at ≥0.01 mcg/kg/min for systemic hypoperfusion, as determined by attending Neonatologist in the absence of non-PDA related etiologies

  OR

- Increase in FiO_2 >20% from baseline value for >24 hours in the absence of atelectasis or worsening interstitial lung disease

  OR

- Increase in baseline creatinine >30% *and* creatinine >1 mg/dL
  AND
- ≥3 large ECHO criteria
- ≥1 large ECHO criteria AND mitral regurgitation (annular dilatation of the valve)

RESCUE CRITERIA #2

- Moderate OR severe clinical criteria AND ≥1 criteria for large ECHO criteria
  AND
- mitral regurgitation (annular dilatation of the valve)

Data to be Collected: Clinical echocardiographic data for NCH-enrolled patients will be obtained from ECHO reports on the EchoIMS server. Research ECHO data will be stored initially on the secure Merge database. ECHO data and reports are currently scheduled to be moved to the secure Siemens Syngo system in July of 2019. Catheterization data (Percutaneous intervention arm) and information will be obtained from the reports found under the "Cardiology" tab in EPIC. All other data will be obtained from the patient's electronic medical record. Data collected at UTHSC will similarly involve the patient's electronic medical records, and ECHO data retrieved from local, secure databases, if not embedded within the medical records.

Demographics (Patient): Date of birth, Gender, Gestational age, Birth weight, Birth length, Weight and length at procedure (if applicable), Study arm assignment

Echocardiographic (ECHO): Date of ECHO study, Results of ECHO studies - including all cardiac and major blood vessel measurements and performance evaluations, PDA size, PDA flow direction (All clinical ECHO studies, as well as research-specific ECHO studies), and any ECHO contraindications for percutaneous closure

Procedural (Percutaneous closure arm): Date of procedure, Type of implant / device used, Number of implant attempts, Procedural complications, Time of procedure start, Time of procedure end, Medications and anesthetics administered, flucoroscopic data (contrast dose, timing), receipt of transfusion (if applicable), Post-operative complications (if applicable), All hemodynamic measurements obtained – including size and type of PDA per angiography, Any catheter-based finding that would contraindicate percutaneous closure (ex – previously

undiagnosed aortic coarctation or narrowing of the left pulmonary artery), Any adverse events reported

Conservative treatment arm: Medication(s) administered (with focus upon diuretics), Doses of medications, Date(s) of medications, Fluid intake restriction volumes, Referral(s) for percutaneous closure and procedural data as noted above (if applicable, for “Rescue” cases)

Hospitalization: Date of admission, Diagnosis and severity of known preterm morbidities (necrotizing enterocolitis, intraventricular hemorrhage, retinopathy of prematurity, bronchopulmonary dysplasia), Body weight, Length/Height, Treatment with supplemental oxygen – including dates, ventilatory support, and % oxygen, Dates on IV fluids, Date of full PO intake, Date of discharge, Length of stay

7.0 Data and Specimen Banking

Clinical data will be kept on the secure and limited-access patient database at Nationwide Children’s Hospital, EPIC for NCH patients. Clinical echocardiography scans and reports will be stored on a secure and limited-access database, EchoIMS. Research ECHO data will be stored initially on the secure Merge database, but are currently scheduled to be moved to the secure Siemens Syngo system in July of 2019. Data that is collected at NCH for analysis from these sources will be stored on secure, limited-access shared storage locations (R:) as Excel files. Clinical and ECHO data collected at UTHSC will be stored in accordance to local protocols. PHI will be removed from UTHSC-collected data and ECHO reports prior to sharing with NCH (see *Data Sharing Between External Entities*). No specimens will be collected and stored for this study.

8.0 Sharing of Results with Subjects

The procedural outcomes for the infants in the percutaneous intervention arm will be shared with the parents, either by the interventional cardiologist or a representative. The parents of infants in the conservative management arm will likewise be aware of the outcomes, as the PDA will either be 1) open at discharge – requiring Cardiology follow up, or 2) closed at discharge – not requiring Cardiology follow-up. Similarly, infants who qualify for Rescue Intervention will be consulted regarding the procedure, as consent to perform said procedure (including discussion

of risks) must be obtained prior to the intervention, and the outcomes of the procedure discussed as previously noted. The procedural reports will be placed in the patient's electronic medical record, which may be shared at a later date with a patient's primary care physician, if requested. Pilot study results will be posted on ClinicalTrials.gov.

9.0 Study Timelines

Prior to 14 days postnatal, up to 28 postnatal days of age: Obtain informed consent / informed consent process

14 – 28 postnatal days of age: Qualifying ECHO and randomization (if permitted) for all patients that qualify for participation in the study.

Within 72 hours of randomization (Percutaneous arm ONLY): Catheter-based closure of PDA

Otherwise (Conservative arm ONLY): Treatment per institutional guidelines for conservative management of PDA

Continuous: Data collection on clinical status, including clinical ECHO studies, ventilatory support, need for supplemental oxygen, and other complications. For Conservative arm ONLY – clinical and treatment team evaluations to determine if Rescue Intervention is warranted.

36 weeks corrected gestational age: Follow-up ECHO study.

Discharge: Study exit; if randomized to conservative arm and no Rescue Intervention is required, status of PDA (open / closed) and size, if known at time of discharge.

Post-Discharge analysis: 1 year after discharge of the final patient enrolled to either the percutaneous intervention arm OR conservative management arm (based upon randomization order; it is currently unknown which treatment the final randomized patient will be assigned to).

10.0 Inclusion and Exclusion Criteria

Study Inclusion Criteria:

1. Premature infants born at <28 weeks gestation
2. HSPDA (criteria, **Table 1**) verified by treating cardiologist and echocardiographic imaging

Study Exclusion Criteria:

1. Patients meeting criteria initially, but with a non-hemodynamically-significant PDA or closed PDA at postnatal age of 14 days (ex. – a patient with a large PDA and echocardiographic signs of fluid overload and/or cardiac remodeling at day of life 7, which decreased in size to small with a reduction in symptomology by day of life 14)
2. Life-threatening congenital abnormalities, including congenital heart disease (excluding patent ductus arteriosus and atrial septal defects (ASDs) / ventricular septal defects (VSDs)). Infants with evidence of coarctation of the aorta or left pulmonary artery stenosis will be excluded
3. Infants with evidence of pulmonary hypertension, as defined by ductal right to left shunting for more than 33% of the cardiac cycle.
4. Infants likely to require surgical treatment (ex. – congenital diaphragmatic hernia, omphalocele, gastroschisis), abnormalities of the upper and lower airways (Pierre-Robin sequence, pulmonary hypoplasia), and neuromuscular disorders.
5. Infants for whom treatment withdrawal or limitation of intensive care treatment is being considered.

11.0 Vulnerable Populations

This research involves children (neonates) who are not of legal age to provide informed consent themselves. Thus, the parent(s) of the patients will be approached to obtain informed consent for their child or children (in the case of multiple gestation infants) to participate. Regarding cases of uncertain viability of neonates, as noted above, infants for whom treatment withdrawal or limitation is considered or mandated will be excluded from participation in the study.

12.0 Number of Subjects

The objective is to have 10 subjects per treatment arm (Percutaneous closure, Conservative management) for a total of 20 in the randomized intervention study. An additional 20 patients (10 per treatment arm) will be recruited at the University of Tennessee Health Sciences Center. The number of non-randomized, prospective data collection participants remains uncertain, and cannot be predicted.

13.0 Recruitment Methods

Potential participants will be identified from the neonatal intensive care unit (NICU) patient pool at Nationwide Children's Hospital, Main Campus and similarly at The University of Tennessee Health Sciences Center. Potential subjects will include all infants born at <28 weeks who do not meet any of the exclusion criteria. This will include infants with a previously-identified, open PDA on a clinical echocardiography (ECHO) study, or infants who have had no ECHO study performed prior to transfer to NCH or UTHSC. Parental informed consent will be obtained prior to a qualifying echocardiography study being performed. Face-to-face contact will be the primary method; however, telephone consents will be allowed for cases in which an infant was transferred from an outside institution and the parents are otherwise unavailable. During the consenting process, the randomized nature of the study interventions will be clearly defined. Parents who express a preference to one specific option, or are uncomfortable with the idea of randomization will be excluded from the randomized trial, and will be asked to provide consent for prospective data collection only. A second consent form has been prepared for this purpose.

14.0 Withdrawal of Subjects

Subjects will be free to withdraw from the study at any time. Additionally, subjects may be excluded / withdrawn by the study team if previously undiagnosed conditions are found after consent has been obtained (ex. – a previously undiagnosed aortic coarctation, which is a contraindication to percutaneous closure).

15.0 Risks to Subjects

The risks to the percutaneous closure arm participants would be complications and/or adverse events associated with the closure procedure, up to and including death, which is rare. Some of the more common adverse events would include a need for transfusion due to blood loss, hematoma at the catheter access site, thrombosis, and embolization of the implant. For the latter, embolization during the procedure may be possible to resolve using percutaneous re-capture of the embolized device. However, if this fails, emergent surgery may be required, which is an additional risk. For the conservative management group, the risks involve failure to improve clinical status, or a depreciation in clinical status due to increased shunting of deoxygenated blood into the primary circulation. Volume overload due to the shunt also frequently causes ventricular remodeling and distension, affecting cardiac performance.

16.0 Potential Benefits to Subjects

The potential benefits to the arm receiving percutaneous closure would be a reduction in risks to develop morbidities or additional complications associated with PDA, as well as reduction in supplemental oxygen or ventilator support. For the conservative management arm, the benefits would be not having an invasive procedure with its affiliated risks and/or complications.

17.0 Data Management and Confidentiality

Clinical data from Nationwide Children's Hospital will be kept on the secure and limited-access patient database, EPIC. Echocardiography scans and reports will be stored on a secure and limited-access database, EchoIMS. Data that is collected for analysis from these two sources will be stored on secure, limited-access shared storage locations (R:) as Excel files. Only the study team (C. Backes, D. Berman, B. Rivera, B. Richardson) will have access to the collected data files containing confidential information and protected health information. Should significant biostatistical analyses be required (unanticipated at this time), only limited data sets will be used for this purpose after identifying information is removed. Data storage for patients at the University of Tennessee Health Sciences Center will be via their secure electronic medical records and other databases. PHI will be removed from ECHO reports and data collected at each institution prior to sharing of data files, which will be restricted to limited data sets (see *Data Sharing Between External Entities*).

18.0 Provisions to Monitor the Data to Ensure the Safety of Subjects

No DSMB is planned as both options are considered standard of care at NCH and the University of Tennessee Health Sciences Center.

19.0 Provisions to Protect the Privacy Interests of Subjects

All protected health information and confidential information will be stored on password-protected, limited access databases and computer systems. Only personnel appropriately trained and listed as members of the study team will be permitted to access any data files assembled for this research. Only limited data sets will be shared between collaborating institutions (see *Data Sharing Between External Entities*).

20.0 Compensation for Research-Related Injury

There are no plans to compensate for research-related injury, as all procedures are considered standard-of-care at Nationwide Children's Hospital, with known risks being discussed in detail with the patient's parents prior to conducting any procedure. For patients at UTHSC, compensation (if any) will be according to institutional protocols.

21.0 Economic Burden to Subjects

As all procedures are considered standard-of-care, parents and/or their health insurance carrier are expected to absorb all costs associated with the patient's care during their hospital stay. Research-specific echocardiographic studies, however, that are not part of routine care (qualifying / screening ECHO) will be paid by the research team.

22.0 Consent Process

Informed consent will be obtained by Dr. Carl Backes or Dr. Darren Berman, both cardiologists at Nationwide Children's Hospital and co-investigators for this study. Consent at The University of Tennessee Health Sciences Center will be obtained by Dr. Mark Weems or a designated member of his team. Face-to-face contact will be the primary method to obtain informed consent; however, telephone consents will be allowed for cases in which an infant was transferred from an outside institution and the parents are otherwise unavailable. Both treatment arms (intervention vs. non-intervention) will be clearly defined, and the randomized nature of the study will be clearly defined, as will the risks for each study arm. The provision of "Rescue intervention" will also be presented, if deemed clinically necessary, for those that may quality from the non-intervention arm of the study if randomized to this arm. As noted previously, parents will also have the option to consent to prospective data collection only, if they refuse to permit randomization to one treatment arm or the other.

23.0 Process to Document Consent in Writing

After appropriate consultation and sufficient time has been provided to allow the parent(s) to make an informed decision regarding the study, they will be asked to sign a written consent form. They will also be asked to indicated whether or not they will permit randomization to a

specific treatment arm. If they decline, the consent will only be to allow prospective data collection.

24.0 Settings

Nationwide Children's Hospital, Main Campus (Columbus, OH)

University of Tennessee Health Sciences Center (Memphis, TN)

25.0 Resources Available

Nationwide Children's Hospital and The University of Tennessee Health Sciences Center have all resources necessary for the conduct of this study, with an exceptional neonatal intensive care unit (NICU) with specialists trained in neonatal care, echocardiography technicians trained and skilled in neonatal cardiac studies, and a specialized catheterization laboratory suite for percutaneous procedures staffed by pediatric cardiologists, anesthesiologists, technicians, and nurses.

26.0 Multi-Site Research

This pilot study will enroll patients at Nationwide Children's Hospital Main Campus in Columbus, OH and The University of Tennessee Health Sciences Center in Memphis, TN.

27.0 Protected Health Information Recording

1.0 Indicate which subject identifiers will be recorded for this research.

- ☒ Name
- ☐ Complete Address
- ☐ Telephone or Fax Number
- ☐ Social Security Number (do not check if only used for ClinCard)
- ☒ Dates (treatment dates, birth date, date of death)
- ☐ Email address , IP address or url
- ☒ Medical Record Number or other account number
- ☐ Health Plan Beneficiary Identification Number
- ☐ Full face photographic images and/or any comparable images (x-rays)
- ☐ Account Numbers

☐ Certificate/License Numbers
☐ Vehicle Identifiers and Serial Numbers (e.g. VINs, License Plate Numbers)
☒ Device Identifiers and Serial Numbers
☐ Biometric identifiers, including finger and voice prints
☐ Other number, characteristic or code that could be used to identify an individual
☐ None (Complete De-identification Certification Form)

2.0 Check the appropriate category and attach the required form* on the Local Site Documents, #3. Other Documents, page of the application. (Choose one.)

☐ Patient Authorization will be obtained. (Include the appropriate HIPAA language (see Section 14 of consent template) in the consent form OR attach the HRP-900, HIPAA AUTHORIZATION form.)
☒ Protocol meets the criteria for waiver of authorization. (Attach the HRP-901, WAIVER OF HIPAA AUTHORIZATION REQUEST form.)
☐ Protocol is using de-identified information. (Attach the HRP-902, DE-IDENTIFICATION CERTIFICATION form.) (Checked "None" in 1.0 above)
☐ Protocol involves research on decedents. (Attach the HRP-903, RESEARCH ON DECEDENTS REQUEST form.)
☐ Protocol is using a limited data set and data use agreement. (Contact the Office of Technology Commercialization to initiate a Limited Data Use Agreement.

***Find the HIPAA forms in the IRB Website Library, Templates.**

Attach the appropriate HIPAA form on the "Local Site Documents, #3. Other Documents", page of the application.

3.0 How long will identifying information on each participant be maintained?

Identifying information will be kept until all of the desired data related to all participating patients has been collected.

4.0 Describe any plans to code identifiable information collected about each participant.

Should specialist biostatistical analysis be required (unanticipated at this time), identifying information (names, MRNs) will be removed from files shared with the biostatisticians, and the patients will be coded as subject 1, 2, 3, etc. Only limited data sets will be exchanged in this manner (due to possible need for date/timing information). Files with the links to this information will be kept on the computers of the local study PIs (C. Backes, Nationwide Children's Hospital; M. Weems, University of Tennessee Health Sciences Center).

5.0 Check each box that describes steps that will be taken to safeguard the confidentiality of information collected for this research:

☒ Research records will be stored in a locked cabinet in a secure location

☒ Research records will be stored in a password-protected computer file

☒ The list linking the assigned code number to the individual subject will be maintained separately from the other research data

☒ Only certified research personnel will be given access to identifiable subject information

6.0 Describe the provisions included in the protocol to protect the privacy interests of subjects, where "privacy interests" refer to the interest of individuals in being left alone, limiting access to them, and limiting access to their information. (This is not the same provision to maintain the confidentiality of data.)

Patients and their parent(s) will be afforded privacy in accordance with NCH and UTHSC standards for care. Contact with the parent(s) will be required in order to obtain consent. They will be asked by consenting personnel if they are open to the idea of having their child participate in a research study. Further contact would only be if they were willing to consider it or for further discussion during the process. Those that refuse will no longer be approached. Follow up for those who are "thinking about it" or "considering it" will be limited, as well. Additional contact with the parent(s) will be required prior to the interventional procedure (for patients randomized to the percutaneous intervention arm), in order to obtain consent for said procedure. This will be done by a member of the interventional cardiology team.

The qualifying ECHO scan is a research-specific scan, separate from any that would otherwise be performed for clinical purposes, and is recognized as an additional instance in which contact with the infant occurs, but is necessary for the purposes of the study to ensure that appropriate inclusion criteria are meet, and that exclusion criteria are not present. This would include findings of non-hemodynamically-significant PDA, for which intervention would not be warranted.

All data obtained through the study will be stored in either a locked file in the research office (paper consent forms) or stored on a secured shared drive accessible only by password-protected computer systems behind the NCH firewall. Similar data security practices are in place at UTHSC. Prior to sharing data, PHI will be removed from data sources at NCH and UTHSC. Generic "identifiers" will be used for each case ("1", "2", "3") in place of names and/or MRNs. (see *Data Sharing Between External Entities*).

Confidential Health Information

1.0 Please mark all categories that reflect the nature of health information to be accessed and used as part of this research.

☒ Demographics (age, gender, educational level)
☒ Diagnosis
☐ Laboratory reports
☒ Radiology reports
☐ Discharge summaries
☒ Procedures/Treatments received
☒ Dates related to course of treatment (admission, surgery, discharge)
☐ Billing information
☒ Names of drugs and/or devices used as part of treatment
☐ Location of treatment
☐ Name of treatment provider
☒ Surgical reports
☒ Other information related to course of treatment
☐ None

2.0 Please discuss why it is necessary to access and review the health information noted in your response above.

Several of the items indicated will be used as qualifying criteria for the study. This includes age / gestational age, diagnosis, and radiology (echocardiography) reports which are used to

determine final eligibility to participate in the study (see Inclusion Criteria). Date information is used to track the age at the time either intervention is applied, and how long a PDA remains open (in the conservative management group). Procedural data, surgical / procedural reports, and the device names all appear on the cardiac catheterization reports, which will be accessed for procedural data in the percutaneous treatment group. “Other information” may include incidence of adverse events in the percutaneous arm patients, treatments for adverse events, and all affiliated complications and morbidities experienced by both groups during the hospital stay, as well as respiratory therapy, ventilatory support required, and level of supplemental oxygen required during the hospital stay.

3.0 Is the health information to be accessed and reviewed the minimal necessary to achieve the goals of this research? ☒ Yes ☐ No

4.0 Will it be necessary to record information of a sensitive nature? ☐ Yes ☒ No

5.0 Do you plan to obtain a federally-issued Certificate of Confidentiality as a means of protecting the confidentiality of the information collected? ☐ Yes ☒ No

Data Sharing Between External Entities

1.0 Will it be necessary to share human subjects’ data with a colleague or another person or entity not associated with Nationwide Children’s Hospital (Ohio State University employees are considered external entities). ☒ Yes ☐ No

- List the intended external recipient(s) (institutions/entities) of such data:

  University of Tennessee Health Sciences Center

2.0 Will it be necessary to receive human subjects’ data from a colleague or an entity not associated with Nationwide Children’s Hospital (Ohio State University employees are considered external entities). ☒ Yes ☐ No

- List the intended external sender(s) (institutions/entities) of such data:

  University of Tennessee Health Sciences Center

3.0 Check the type of data shared:

a. De-identified: ☐

b. Limited Data Set ☒

- List the specific PHI elements (see **Protected Health Information Recording**) to be shared:

  Diagnoses, dates of studies, and findings, dates of catheter closure (if applicable), type of implant used (if applicable) and any device-related adverse events and treatments

received, dates and detail on ventilatory and supplemental oxygen support, dates and detail of medications used to treat PDA-related cardiopulmonary symptoms, discharge date.

c. Identifiable data with consent ☐

- List the specific PHI elements (see **Protected Health Information Recording**) that will be obtained:

4.0 Briefly describe the manner in which data will be shared/transmitted between sites (such as via REDCap, Dropbox, etc).

Limited data sets may be shared via secure exchange of password-protected Excel files.

Table 1: Clinical and echocardiographic criteria that will be used to define a "hemodynamically-significant patent ductus arteriosus" (HSPDA) for the purposes of this pilot study.

	CLINICAL		ECHOCARDIOGRAPHIC	
Non-HSPDA	**Asymptomatic**	Room air, no positive airway pressure	**None**	No PDA
Non-HSPDA	**Mild**	• CPAP (NIPPV) FiO_2 <0.30 OR • Any nasal cannula (including high-flow nasal cannula)	**Small**	• <1.5 mm diameter • DA flow Vmax >2.5 m/s • LA:Ao ratio <1.5:1 (LVEDD [cm] <1.2)* • LVO (ml/kg/min) <250
HSPDA	**Moderate**	• CPAP (NIPPV) FiO_2 0.30-0.50**	**Moderate**	• ≥1.5-3 mm diameter • DA flow Vmax 1.5-≤2.5 m/s • LA:Ao ratio ≥1.5 to 2:1 (LVEDD [cm] ≥1.2-1.5)* • LVO (ml/kg/min) ≥ 250-430 • Decreased or absent end-diastolic flow in DA
HSPDA	**Severe**	• CPAP (NIPPV) FiO_2 >0.50** OR • Mechanical ventilation (conventional or high frequency)**	**Large:**	• ≥3 mm diameter • DA flow V_{max} ≤1.5 m/s • LA:Ao ratio >2:1 (LVEDD [cm] ≥1.5)* • LVO (ml/kg/min) ≥ 430 • Reversed end-diastolic flow in the DA

*Infants with an atrial septal defect or ventricular septal defect might have altered LA:Ao dimensions, wherein LVEDD (left ventricular end diastolic dimension) will also be used to assess PDA characteristics

**Composite risk of death or moderate or severe BPD must be >50% (Laughon *et al.* Prediction of Bronchopulmonary Dysplasia by Postnatal Age in Extremely Premature Infants. Am J Respir Crit Care Med. 2011)

DA= Descending aorta; LVO= Left ventricular output will be calculated as follows: [(Velocity time integral) × (Heart rate) × (Aortic cross-sectional area)] indexed to body weight

Figure 1: PIVOTAL pilot trial flowsheet