Transcatheter PDA Closure Using the AMPLATZER PICCOLO OCCLUDER Device in Premature Infants Less than Two Kilograms

Real World Registry Study

Date: October 18, 2018

National Primary Investigator
Shyam Sathanandam, MD

TABLE OF CONTENTS

1 INTRODUCTION

This observational clinical study is intended to collect real world evidence (RWE) on the safety and efficacy of transcatheter device closure of patent ductus arteriosus (PDA) using the Amplatzer Piccolo Occluder in premature infants with a weight of less than 2 kg at the time of device implant. This clinical study is sponsored by Abbott.

All US clinical sites/physicians enrolling in the Congenital Cardiac Interventional Study Consortium (CCISC) are eligible to participate in the study following satisfactory completion of qualification requirements.

1.1 Study Objective

The objective of this study is to demonstrate the continued safety and efficacy in a real-world setting of transcatheter device closure of the PDA in premature infants less than 2kg in weight at the time of device implant performed at the CCISC participating centers.

1.2 Study Design

This is a multi-center, single arm, non-randomized, observational study designed to help assure continued safety and effectiveness of FDA approved Amplatzer Piccolo Occluder device for PDA closure in premature infants less than 2 kg at the time of device implant. The study will be conducted at all the CCISC participating sites.

Subjects will have transcatheter PDA closure using the Amplatzer Piccolo Occluder device as part of standard clinical practice under fluoroscopy with or without additional echocardiographic image guidance. The study involves collecting and reporting of data for the ASO II AS PDA closure procedures into the CCISC PDA Module Database. The PDA module encompasses pre-procedure, procedure, 48-hoours, 1-month and 6-months post-procedure follow-up data entry. It also encompasses an adverse event reporting system. Data entry is expected for all attempted PDA closure procedures in which the Amplatzer Piccolo Occluder device is attempted in premature infants weighing < 2 kg at the time of the procedure. It includes pre-procedural and post-procedural echocardiographic information as well as data from procedural echo guidance if utilized. Follow-up will be for a period of six months +/- 30 days after the procedure.

2. STUDYENDPOINTS

Initial data collection will be limited to 500 subjects. Additional data collection beyond the initial cohort of 500 subjects may be done on a voluntary basis by participating sites/physicians.

2.1 Primary Endpoint(s)

Safety Endpoint: Composite rate of major device- or procedure-related adverse events (AE) of interest through 6 months' post-implantation procedure. AEs of interest are broadly categorized as:

a. Vascular access complications
b. Valvular Injury
c. Device embolization
d. Pulmonary or aortic vessel stenosis

Access vessel complications include femoral arterial or femoral/jugular venous complications noted during the procedure, immediately after the procedure or delayed (>24 hours). They range from bleeding from access sites, arterial or venous thrombosis with or without the need for treatment to loss of limb secondary to arterial occlusion.

Valvular injury includes damage to the tricuspid valve or other cardiac valve resulting in immediate post-procedural valvular dysfunction.

Device embolization includes malposition of the device either during or after the procedure or delayed (>24 hours). The outcome of device embolization ranges from observation, transcatheter retrieval at time of procedure or at a separate time, surgical retrieval, other end organ damage, to mortality.

Adjacent vessel stenosis includes a narrowing of the aorta or the left pulmonary artery directly as a consequence of device implantation for PDA closure. Vessel stenosis could happen either during or after the procedure or delayed (>24 hours). The outcome of vessel stenosis ranges from no intervention needed to repeated transcatheter and surgical therapies.

For details of each AEs and definitions, refer to **Appendix A**.

Effectiveness Endpoint: The effectiveness endpoint is the rate of effective closure of the PDA using a transcatheter device within six months post procedure. If more than one attempt is required, or multiple devices are required during the same procedure, it is still considered effective if there is Grade 0 or Grade 1 shunt, as defined below, at follow-up (within six months) by transthoracic echocardiography (TTE) or if a second procedure is not required following the initial attempt. If there is device embolization, adjacent vessel stenosis that required retrieval of the device and replacement during the same procedure with less than Grade 1 shunt during follow-up, it is still considered effective. Conversely, if an AE is noted after the procedure that requires a second procedure for treatment that results in greater than Grade 1 shunt, then the procedure is considered not effective, even if the initial attempt was effective.

PDA shunt definition:

Grade 0—none;

Grade 1—trivial (narrow jet adjacent to the device via the PDA). Note: the presence of flow via existing or newly formed aortopulmonary collaterals should not be considered as representing a shunt via the PDA. (See references in **Appendix B** by Skinner and Acherman)

Grade 2—mild (broader jet filling proximal left pulmonary artery branch and extending to main pulmonary artery);

Grade 3/4—moderate to severe (wide jet filling the main pulmonary artery and extending to pulmonary valve or distal pulmonary artery branches, which also may be accompanied with the presence of flow reversal in the abdominal aortic Doppler pattern during diastole)

2.2 Secondary Endpoints

The secondary endpoint is the rate of significant obstruction of the pulmonary artery or aorta during follow-up (within 6 months) per the following definitions:

1. Significant obstruction of the left pulmonary artery is defined as less than 30% flow to the left lung by lung perfusion scan or a peak instantaneous gradient in left pulmonary artery
≥35 mmHg by echocardiogram if lung perfusion scan is not available. OR

2. Significant obstruction of the aorta is defined as a gradient of ≥20 mmHg in the aortic isthmus by invasive aortic catheterization or a mean gradient ≥20 mmHg in the aortic isthmus by echocardiogram if invasive aortic catheterization is not available.

2.3 Additional Data

Demographics and baseline characteristics, procedure information, and adverse events. For additional information, refer to the PDA Module in **Appendix C.**

3 STUDY POPULATION

Participating subjects includes infants born prematurely (<37 weeks' gestation) with a weight less than 2 kg at the time of device implant. The decision to close the PDA is entirely at the discretion of the referring/primary cardiologist or neonatologist.

3.1 Inclusion Criteria

To participate in this clinical study, subjects must meet all of the following inclusion criteria:

a. Diagnosis of a PDA
b. Clinical indication for transcatheter PDA closure (discretion of the physician)
c. Weight < 2 kg at the time of device implant

All participating study sites must obtain center specific IRB approval to enter patient data in the case reporting form (CRF) which will be called the PDA module. Individual consents from the subjects (or legally authorized representative) is not required unless local laws and governing IRB requirements require obtaining informed consent for data entry to this registry. No deviation of standard clinical practice is expected for participating in this study. No special pre-procedure, post-procedure, and follow-up testing is required for the purpose of this clinical study.

3.2 Exclusion Criteria

Subjects who meet any of the following exclusion criteria must be excluded from the clinical investigation:

a. Weight <700 gm or $\geq$ 2kg at the time of device implant
b. Age < 3 days at the time of device implant
c. Pre-existing coarctation of the aorta
d. Pre-existing left pulmonary artery stenosis
e. Cardiac output that is dependent on right to left shunt through the PDA due to pulmonary hypertension
f. Intracardiac thrombus that interferes with device implant
g. Active infection requiring treatment at the time of implant

The indication to choose transcatheter PDA closure is at the discretion of the referring and the implanting physician. Though the above stated exclusion criteria are standard for most patients undergoing transcatheter PDA closures, clinical discretion is advised for each subject selection.

4 STUDY PROCEDURES

The indication to choose transcatheter PDA closure is at the discretion of the referring and implanting physician. No deviation of standard clinical practice is expected to participate in this study. No special pre-procedure, post-procedure, and follow-up testing is required for the purpose of this clinical study.

Enrolled subjects (as defined in section 3.1) will undergo a PDA closure procedure with the appropriate device size deemed suitable for that particular patient. Post-procedure, the subject will need a follow-up within 48-hoours, 1-month and 6-months after the procedure. The Principal Investigator should arrange for appropriate care of subjects following study completion.

This will be a prospective data input Registry. Screen fail subjects who do not have a PDA closure attempt or those who have the Amplatzer Piccolo Occluder device introduced but do not retain an

Amplatzer Piccolo Occluder PDA closure device at the end of the procedure will be noted in the Registry and followed for 48 hours post procedure.

The following sections provide a detailed description of procedures required by this clinical study.

4.1 Informed Consent

The Principal Investigator or his/her authorized designee will conduct the Informed Consent for performing the procedure – transcatheter PDA closure as per their hospital policy. No special consents are required for the purpose of this clinical study. All participating study sites must obtain center specific IRB approval to enter patient data in the PDA Module. Individual consents from the subjects or legally authorized representative (LAR) is not required unless local laws and governing IRB requirements require obtaining informed consent for data entry to this registry. No deviation of standard clinical practice is expected to participate in this study. No special pre-procedure, post-procedure, and follow-up testing is required for the purpose of this clinical study.

Patients with a weight less than 2 kg will be undergoing transcatheter PDA closures and their protected health information (PHI) will be entered into the PDA module. If there are local IRB rules that involves the need for individual consents from the LAR for sharing PHI, then a separate Informed consent must be obtained using the local IRB approved informed consent in accordance with IRB requirements. The patient under the age of 18 will also be informed about the clinical study within his/her ability to understand. Per state, local, and/or IRB requirements, processes will be followed and documented to collect assent for minor children. The consent will allow for the sharing and transfer of raw patient level data to the sponsor.

4.2 Pre-catheterization Clinical Assessment

The following assessments, diagnostic tests and evaluations and must be included in the PDA module, please see Appendix C for the CRF to be used:

a. Demographics- including subject's age, gender, ethnicity, birth weight, gestational age
b. Medical History-

   o Indicate subject's primary symptom, associated heart defects and co-morbidities, genetic syndromes if any, ongoing medical support, current medications, history of prior attempted medical or surgical therapy for the PDA

c. Transthoracic echo (TTE) -

   o PDA measurements, color and spectral Doppler findings, estimates of pulmonary hypertension, left ventricular function and dimensions, pulmonary and aortic flow and dimensions, aortic arch sidedness, presence of other heart defects, and pulmonic and tricuspid valve regurgitation

Baseline assessments must be obtained within 2 weeks of the procedure

4.3 Implant/Procedure

The Amplatzer Piccolo Occluder device can be implanted either transvenously via the femoral vessels. To minimize complications in small infants (< 2 kg) it is recommended to utilize the anterograde transvenous approach via the femoral vein as the preferred approach. The use of invasive hemodynamic measurements and angiograms are not required in this study to minimize complications, and instead whenever possible hemodynamic assessments and visualization of the anatomy may be performed using intra-operative echocardiography. The recommended use of Heparin is considered optional, and not required if the subject is at high risk for bleeding complications, including children
< 2kg.

The following procedural data must be recorded in the PDA module:

a. Demographics- including subject's age and procedure weight
b. Procedure data-

   o Primary indication for the procedure, anesthesia type, image guidance techniques used, access vessels, hemodynamic assessment, sheath/catheter sizes, PDA morphologic types, intra-procedural PDA measurement by angiography, heparin administration, device delivery technique, contrast and radiation doses, adverse events

c. Device/implant data-

   o Device(s) implanted, device size, residual shunting by angiography, grade of residual shunting, peak/mean gradient across left pulmonary artery and aorta (optional)

d. Intra-procedure Transthoracic echo (optional)-

   o Baseline PDA size, residual PDA shunting post device implantation, peak/mean gradient across left pulmonary artery and aorta, left ventricular function and dimensions, pericardial effusion, increased tricuspid or pulmonary valve regurgitation.

4.4 Post-Procedure Follow-up

The follow-up assessment must be obtained within 48-hoours, 1-month and 6-months after the procedure. The schedule of all assessments is provided in Appendix E. The following post-procedure follow-up assessments, diagnostic tests and evaluations and must be included in the PDA module:

a. Demographics- including subject's age, weight
b. Transthoracic echo (TTE) – including checking for the presence of the device within the PDA, degree of residual shunting if any, spectral Doppler findings, estimates of pulmonary

hypertension, left ventricular function and dimensions, pulmonary and aortic flow and dimensions, pulmonic and tricuspid valve regurgitation

Subjects should be on appropriate endocarditis prophylaxis according to the American Heart Association recommendations for prophylaxis.

5 ADVERSE EVENTS

Risks associated with the procedure are managed in accordance with ISO 14971. The risk analysis included an objective review of published and available unpublished medical and scientific data. The sections below provide an overview of residual risks identified in the risk management report and anticipated benefits of the medical device. The additional tests and assessments required by the clinical investigation were analyzed for additional risks to subjects of this clinical investigation, and are incorporated in the sections below.

5.1 Adverse Event Definitions

For details of each adverse events (AE) and definitions, refer to **Appendix A**.

5.2 AE Reporting Requirements (Adverse Event Form)

Procedural adverse events must be documented carefully. If there is an adverse event that arises directly as a result of the procedure or the device, or noted during follow-up, an Adverse Event Form (**Appendix D, G**) must be filled out separate from the PDA Module and reported to their IRB and Industry Sponsor.

5.3 Specific Adverse Events

The adverse event form includes specific risks associated with transcatheter device closures that needs to be followed. They include:

a. Access complications: Include site, timing and type of complication, and outcome
b. Valvular injury: Include site, timing and type of complication, and outcome
c. Device embolization: Include timing of embolization, embolization site and outcome
d. Vessel stenosis: Include timing of vessel stenosis, site of vessel stenosis and outcome

5.4 Other Adverse Events

Other risks associated with the implant procedure are similar to those of other cardiac catheterization procedures in infants and children and are documented below:

Air embolism	Allergic drug reaction	Apnea
Allergic dye reaction	Anesthesia reactions	Arrhythmia

Arteriovenous fistulae

Air embolism

Bacterial endocarditis

Bleeding at the access site

Brachial plexus injury

Bruising

Cardiac perforation

Cardiac tamponade

Chest pain

Death

Deep venous thrombosis

Device erosion

Dissection

Embolism

Fever

Headache/migraine

Hematoma

Hemodynamic compromise

Hemolysis

Hypertension

Hypotension

Infection

Myocardial infarction

Nickel sensitization

Nickel toxicity

Palpitations

Partial obstruction of the Aorta

Partial obstruction of the Pulmonary Artery

Perforation

Pericardial effusion

Pericarditis

Peripheral embolism

Peripheral pulse loss

Pleural effusion

Pseudoaneurysm

Reintervention for device removal

Radiation injury/burn

Respiratory distress

Stroke

Transient ischemic attack

Thrombosis

Valve damage

Vascular occlusion

Vessel damage/perforation

Thrombus formation

5.5 Risk Minimization

Every possible effort should be taken to minimize risks. This begins with physician training and proctoring. In addition, each site is encouraged to follow their routine clinical strategies to minimize procedural risks. These guidelines are merely to help physicians to prevent adverse events, recognize risks especially is very small children and treat appropriately.

5.5.1 Standard Risk Minimization Strategies

Standard risk minimization strategies include:

I. Cardiologists with training and education in pediatric cardiology and with expertise in using the Amplatzer Piccolo Occluder device to close PDAs
II. Prior experience with transcatheter closure procedures using similar devices with a minimum of 10 cases in subjects < 2 kg.
III. Institutions will have the necessary infrastructure to support study procedures:

a. Cardiac catheterization lab or NICU bedside capability to perform intra-procedural echocardiography and fluoroscopy
b. Anesthesiology support, as needed
c. Catheterization laboratory, operating room, post anesthesia recovery, intensive care and step down unit spaces to accommodate cases with and without complications
d. On-site emergency cardiac surgery services
e. Adequate monitoring for each clinical investigation site
f. Conducting the clinical investigation in accordance with the study, all applicable laws and regulations and any conditions of approval imposed by the appropriate IRB or applicable regulatory authorities where the clinical investigation is performed
g. Preparation of the device and implant procedure in accordance with the device IFUs
h. Training of Investigators both on the study protocol and implant procedure
i. All site staff will participate and complete a raining module
j. Implanting physicians with no prior successful transcatheter PDA closure experience in small infants (<2 kg) will receive proctoring for a minimum on one case.
k. Assessment of continuing safety of subjects in the clinical investigation by an independent Clinical Events Committee (CEC).
l. Physicians are required to follow The American Heart Association Recommendations for endocarditis prophylaxis during the clinical study.
m. Sites should follow patients per their standard of care for any reported adverse events.

5.5.2 Specific Risk Minimization Strategies for Subjects < 2kg

The following measures should also be taken to reduce the risks at the time of the procedure:

a. The use of heparin is optional in children < 2 kg in order to decrease the risk of bleeding.
b. Implanting physicians with no prior successful transcatheter PDA closure experience in children< 2 kg will be trained on the Amplatzer Piccolo Occluder device, specifically device size selection and placement, to reduce the risk of device embolization, partial obstruction of the aorta or pulmonary artery and hemolysis which could be potentially caused by the device.
c. The physicians will be instructed to use their clinical judgement to monitor subjects for potential adverse events related to nickel and to report such events with the goal of protecting the welfare of the subject if the root cause of the adverse event is determined to be nickel related, paying special attention to subjects weighing < 2 kg.
d. Physicians are encouraged to utilize an anterograde implant approach, while avoiding the need for arterial access in children < 2 kg.
e. Acquisition of invasive hemodynamic measurements is not required in children < 2 kg unless there is suspicion for pulmonary hypertension in order to minimize complication and shorten procedure time.

f. Device implant is recommended to be performed based on echocardiographic and fluoroscopic guidance with judicious utilization of intravenous contrast agents as necessary for best imaging of the PDA.

5.5.3 Aortic or Pulmonary Artery Stenosis

If stenosis of the aorta or pulmonary artery is suspected or noted during the procedure or during follow-up, the following measures are recommended:

a. Perform aortic catheterization to obtain invasive measurement of the gradient if the mean gradient by echocardiogram in the aortic isthmus is ≥ 20mmHg.
b. If aortic catheterization is contraindicated, then an alternative imaging study, such as computed tomography (CT) aortic angiography imaging or magnetic resonance (MR) aortic angiography imaging may be utilized.
c. CT aortic angiography or MR aortic angiography may be used to confirm a significant aortic obstruction whenever there is ≥ 50% diameter narrowing at the aortic isthmus.
d. Alternatively, a clinical exam may be used to confirm aortic obstruction.
e. Exam criteria = 1) Diminished lower extremity pulses or a blood pressure discrepancy of ≥ 20mmHg between the upper and lower extremities AND 2) an abnormal abdominal aortic Doppler pattern (blunted profile with diminished upstroke, holo-diastolic antegrade flow, or flow reversal during diastole).
f. If a new significant gradient in the pulmonary artery or the aorta is identified on follow-up echocardiograms, a lung perfusion scan or CT/MR/aortic catheterization will be required to determine if the result meets the secondary endpoint.

5.6 Risk-to-Benefit Rationale

Risks associated with participating in this clinical study are not anticipated to be any different from risks associated with participating in any other large web-based registry. There is a small risk of a loss of confidentiality and every effort will be made to prevent this type of breach. The potential benefit of participating in this clinical study will allow for a large data registry to be compiled. Advantage of having this registry will include the possibility of future prospective, observational and cohort studies. The PDA module, though initially for the Amplatzer Piccolo Occluder device, will also provide a method for tracking and oversight for all PDA device procedures in the United States.

5.7 Precautions Taken for Web-Based Access

All paper research records will be stored in locked file cabinets and will be accessible only to research personnel. All electronic research records will be computer password protected and accessible only to research personnel. All research records will be transmitted to CCISC, will be labeled with a code, and will not contain any identifiable information about the subjects. A m a s t e r

key/list which links with the subject's PHI, such as the patient's name with the code on the research records and specimens will be maintained at individual participating institutions. Information about any subject's participation in this study or the results of procedures performed in this study will be placed in the subjects' medical record; as such, this information could be made available to your employer or insurer. While individual details about a particular case might be provided in publications or presentations, they will not be discussed in a way that would allow any subject to be individually identified as a participant.

Protecting data and patient privacy is of great importance to this study. All research records will be saved in a password protected computer at individual participating centers. Access to the records will be limited to research personnel alone. Anti-virus software will be used to protect every computer network. Several different hardware and software solutions will be used to ensure that unauthorized users cannot access our computer systems. Data Encryption will be used that transposes the PHI which is sent from each participating sited to our server and browser into a code that cannot be understood or altered without using a "key". The "key" deciphers the information from our server to be able to display on any browser. Data transmitted between participating sites will be protected using Message Authentication Codes (MACs). The MAC will be based on the actual data itself, and provides a quick way to verify that the data wasn't changed or tampered with in route.

6 Study Completion

Subject participation in the clinical investigation will conclude upon completion of the follow-up visit at 6 months' post device implantation procedure. If a subject misses the scheduled follow-up visit within the 6-month window, the subject will be considered as having missed the visit (which will be deemed a deviation from the clinical study protocol and the applicable form will be completed).

A subject will be considered 'Lost to Follow-up' after two missed scheduled visits within the 6-month window, a minimum of two unsuccessful phone calls from investigational site personnel to the subject. These two phone calls must be documented in the subject's research records. If the subject is deemed lost to follow-up, a certified letter will be sent to the subject's last known address or to the subject's general practitioner (GP). A copy of the letter must be maintained in the subject's research records.

6.1 Subject Death

Subject deaths will be documented and reported to the CCISC PDA Module PI as soon as possible (but no later than 3 business days) after becoming aware of the event via the applicable case report form (CRF) within the PDA module. In the event an autopsy is performed whenever possible data on the histopathology of the Amplatzer Piccolo Occluder device should be submitted within the case report form including any photographs of the gross and microscopic findings.

6.2 Unanticipated Adverse Events

If an unanticipated adverse event occurs, the investigator must notify the CCISC PDA Module PI and the IRB immediately, but no later than 10 working days of the investigator's knowledge of the event, as required by 21 CFR §812.150. CCISC Scientific Committee will perform a Root Cause Analysis (RCA)to investigate the cause of the event, and, as appropriate, will be responsible for notifying FDA and all other participating IRBs and investigators.

6.3 Core Laboratory

A Core Lab will not be used to review and adjudicate patient's clinical information, angiograms and transthoracic echocardiography. However, the CCISC will randomly audit up to ten percent of the patients' data entered in the PDA module from each institution. Service details are previously outlined in the applicable Service Agreement between the CCISC participating site and the CCISC.

6.4 Study Committees

6.4.1 Publication Committee

A Publication Committee may be established to oversee study publications. Publication Committee membership may include the national coordinating investigator, Principal Investigators, a representative of CCISC, and a statistician. The Publication Committee will be responsible for identifying, selecting and approving publication proposals and determining authorship according to a Publication Plan. A Publication Committee charter will define membership of the committee and outline the roles and responsibilities of the committee, as well as rules to define authorship.

6.4.2 Clinical Events Committee (CEC)

An independent CEC will be responsible for providing review and adjudication of pre-defined clinical events, including major and minor complications, deaths, or other events or endpoints as outlined in the CEC Charter. The CEC is responsible for reviewing all reportable Adverse Events as defined in section 5.

The CEC will also advise the site PIs on the continuing validity and scientific merit of the clinical study. CEC members could be investigators in the clinical study. At any time during the study, the CEC may offer opinions or provide formal recommendations concerning aspects of the study that impact subject safety (e.g. safety-related protocol changes or input regarding study-related adverse event rates).

The primary function, responsibilities and membership of the CEC will be described in detail in a CEC charter.

7 STATISTICAL CONSIDERATIONS

The following section describes the statistical methods for the clinical investigation and justification of the clinical study protocol.

7.1 Primary Safety Endpoint

The primary safety endpoint is the rate of major adverse events through up to six-months after an attempted device implant (refer to **Appendix A** for definition).

The proportion of subjects experiencing a major AE through up to six-months will be estimated. The 95% confidence interval for the percent of major AE will be calculated using the exact binomial method. The numerator for the event rate is the number of subjects who experienced an event through up to six-months. The denominator is the number of subjects in the analysis population (As detailed in Section 7.4). The primary safety endpoint rate will be descriptively compared with the rate reported in the Amplatzer Piccolo Occluder IDE and Continued Access Protocol studies. The overall estimated rate for major complications based on published literature ranges between 4.0 to 10.0%.

7.2 Primary Effectiveness Endpoint

The primary effectiveness endpoint is the rate of effective closure of the PDA among subjects with a successful device implant as assessed by the presence of either a Grade 0 or Grade 1 shunt (see **Appendix A** for definition) at the 6 month follow-up visit by transthoracic echocardiography.

The proportions of subjects who have effective closure of the PDA at follow-up will be calculated along with the 95% confidence interval. The numerator for the event rate is the number of subjects who have effective closure of the PDA at follow-up. The denominator is the number of subjects in the analysis population (As detailed in Section 7.4). The primary effectiveness endpoint will be compared with the rate reported in the ADO II AS and Continued Access Protocol studies.

Among subjects successfully implanted with any device, the PDA occlusion rate is estimated to be approximately 99%.

7.3 Secondary Endpoints

The secondary endpoint is the rate of significant obstruction of the pulmonary artery or aorta through the follow-up visit per the following definitions:

1. Significant obstruction of the left pulmonary artery is defined as less than 30% flow to the left lung by lung perfusion scan or a peak instantaneous gradient in left pulmonary artery ≥35 mmHg by echocardiogram if lung perfusion scan is not available. OR

2. Significant obstruction of the aorta is defined as a gradient of ≥20 mmHg in the aortic isthmus by invasive aortic catheterization or a mean gradient ≥20 mmHg in the aortic isthmus by echocardiogram if invasive aortic catheterization is not available.

The proportions of subjects experiencing an obstruction of the pulmonary artery or aorta through the of low-up visit will be calculated along with the 95% confidence interval. The numerator for the event rate is the number of subjects who experience an event by the follow-up visit. The denominator is the number of subjects in the analysis population (As detailed in Section 7.4).

7.4 Analysis Population

The analysis of the primary and secondary endpoints will include all subjects who achieve a successful implant, which is defined as leaving the catheterization lab with a device implanted in the PDA. If a subject has multiple devices attempted during the same procedure, but leaves procedure with at least one device within the PDA the procedure is considered successful. Subjects without an implanted device in the PDA will be excluded. Additionally, subjects who had no follow- up visits up to the six-months +/- one-month window, or lost to follow-up will be excluded.

7.5 Other Endpoints

The following endpoints will be summarized using descriptive statistics.

a. **Implant success:** The frequency and percentage of implant success (defined in Section 7.4) will be reported. This analysis will include all subjects entered in the PDA module.

b. **PDA shunt status at follow-up visit**: The frequency and percentage of PDA shunt status at the 6 month follow-up visit, as assessed by the TEE, will be reported. Shunt sizes categories are: Grade 0/1, 2, and Grade 3/4. This analysis will include subjects who achieve a successful implant.

c. **Obstruction measurements at follow-up visit**: The frequency and percentage of significant obstruction of the left pulmonary artery and the frequency and percentage of significant aortic obstruction (defined in Section 7.3) at the 6 month follow-up visit will be reported. Both analyses will include subjects who achieve a successful implant.

d. **Major and Minor Complications**: The frequency and percentage of major and minor complications (refer to **Appendix A** for definition) from the time of the implant procedure will be reported.

e. **Death**: The frequency and percentage of death will be reported.

f. **Additional data**: Demographics and baseline characteristics, procedure information, left ventricular function and dimensions, pulmonic and tricuspid regurgitation, adverse events, subjects lost to follow-up will also be summarized.

7.6. Justification of Clinical Study Design

Based on the IMPACT registry, there are over 6000 transcatheter device closures of PDA that occurs in the United States annually. However, there are no comprehensive data collection tools for this procedure. The current databases do not include multiple data points, or follow-up data, or a section for specific adverse events to be documented. Moreover, until now, there has been no approved devices for PDA closure in children < 2kg. This clinical study is the first of its kind to collect data from all transcatheter device closure of PDA in children < 2kg performed at the CCISC participating centers. This study will be limited to children between 700 to 2000 grams who are the most vulnerable population undergoing this procedure. This will allow us to understand the real world experience (efficacy and safety) of using the Amplatzer Piccolo Occluder device in an extremely vulnerable, yet highly underserved population. The study will allow for standardization of this procedure throughout the country for the small children (<2 kg) with a PDA. This is a multi-center, single arm, observational data collection study. This will be a large population study to help analyze outcomes in subjects <2 kg. The trial has two primary endpoints for safety and effectiveness without formal hypothesis. The safety and effectiveness results will be compared with data reported in the Amplatzer Piccolo Occluder IDE and Continued Access Protocol studies.

8 REQUIREMENTS FOR INVESTIGATOR RECORDS AND REPORTS

8.1 Deviations from Clinical Study Protocol (CSP)

A deviation is defined as an instance(s) of failure to follow, intentionally or unintentionally, the requirements of the CSP. The investigator should not deviate from the CSP. In some cases, failure to comply with the CSP may be considered failure to protect the rights, safety and well-being of subjects; such non-compliance exposes subjects to unreasonable risks. Examples: failure to adhere to the inclusion/exclusion criteria, failure to safeguard protected health information (PHI) failure to perform safety assessments intended to detect adverse events. Investigators should seek to minimize such risks by adhering to the CSP.

If certain assessments such as details of the echocardiogram, RSS, etc., is not performed or completed within the CRF, it may not be considered as a deviation as determined by the National PI. The PI must maintain accurate, complete, and current records, including documents showing the date of and reason for each deviation from the CSP. Relevant information for each deviation will be documented as soon as possible on the applicable CRF within the PDA module. The site will submit the CRF to the CCISC PDA Module PI. The PI is required to adhere to local regulatory requirements for reporting deviations to IRB. An investigator shall notify the CCISC PDA Module PI and the reviewing IRB of any deviation from the investigational plan to protect the life or physical well- being of a subject in an emergency. Such notice shall be given as soon as possible, but in no event later than10 working days after the emergency occurred. The protocol deviation reporting form and a log are provided in Appendix F.

8.2 Safety reporting

Safety surveillance within this study (and the safety reporting performed by the investigator), starts as soon as the subject is referred for PDA closure. The safety surveillance and the safety reporting will continue until the follow-up visit has been performed, the subject is deceased, the subject/investigator concludes his/her participation into the clinical study or the subject is deemed lost to follow-up. All adverse event data required to be reported will be collected throughout the clinical study and will be reported to the CCISC PDA Module PI.

For the purposes of this clinical study the following events will be reported (see **Appendix A** for definitions):

a. Unanticipated adverse device effects
b. All adverse events viewed/interpreted by investigator to be potentially related to either i) the implant procedure or ii) the device regardless of seriousness

Note – If relatedness is unknown or cannot be determined, then the event must be reported.

Note – if a procedure is abandoned and surgical ligation is used to close the PDA, adverse events associated with the surgical ligation will not be reported.

Records relating to the subject's subsequent medical course must be maintained and submitted (as applicable) to the CCISC PDA Module PI until the event has subsided or, in case of permanent impairment, until the event stabilizes and the overall clinical outcome has been ascertained. Adverse events will be monitored until they are adequately resolved. The status of the subject's condition should be documented at periodic intervals.

Subject deaths will be documented and reported to the CCISC PDA Module PI as soon as possible (but no later than 3 business days) after becoming aware of the event via the applicable CRF. If an unanticipated adverse device effect occurs, the investigator must notify the CCISC PDA Module PI and the IRB immediately, but no later than 10 working days of the investigator's knowledge of the event, as required by 21 CFR §812.150. The CCISC will take any steps necessary to investigate the event, and, as appropriate, will be responsible for notifying FDA and all other participating IRBs and investigators.

8.3 Source records

Source documents will be created and maintained by the investigational site team throughout the clinical study. The data reported on the PDA module will be derived from, and be consistent with, these source documents, and any discrepancies will be explained in writing.

8.4 Records retention

The CCISC PDA Module coordinator and Principal Investigators will maintain the clinical study documents as required. Measures will be taken to prevent accidental or premature destruction of these documents. The Principal Investigator or the CCISC may transfer custody of records to another person/party and document the transfer at the investigational site or the CCISC site, as appropriate. These documents must be retained by the investigational site for a period of 2 years after the conclusion of the clinical study and made available for monitoring or auditing by the CCISC or representatives of the applicable regulatory agencies. All original source documents must be stored for the maximum time required by the regulations at the hospital, research institute, or practice in question. If original source documents can no longer be maintained at the site, the investigator will notify the CCISC PDA Module PI.

9 Clinical Data Handling

The CCISC PDA Module will be responsible for the data handling. The CCISC and/or its affiliates will be responsible for compiling and submitting all required reports to governmental agencies. Data will be analyzed by the CCISC and maybe transferred to the any other worldwide regulatory authority in support of a market-approval application. CCISC will have the ability to send raw data and data analysis scrubbed of all PHI and institution information to industry, government agency or other worldwide regulatory authorities.

9.1 Protection of Personally Identifiable Information

The CCISC respects and protects personally identifiable information collected or maintained for this clinical study. The privacy of each subject and confidentiality of his/her information will be preserved in reports and when publishing any data. Confidentiality of data will be observed by all parties involved at all times throughout the clinical investigation. All data will be secured against unauthorized access.

9.2 Data Management Plan

A Data Management Plan (DMP) will describe procedures used for data review, database cleaning, and issuing and resolving data queries. If appropriate, the DMP may be updated throughout the clinical investigation duration. All revisions will be tracked and document controlled. Subject data will be captured in a validated electronic data capture (EDC) system hosted by the CCISC. Only authorized site personnel will be permitted to enter the CRF data through the EDC system deployed by CCISC. An electronic audit trail will be used to track any subsequent changes of the entered data.

9.3 Document and Data Control

9.3.1 Traceability of Documents and Data

The investigator will ensure accuracy, completeness legibility and timeliness of the data reported to the CCISC PDA Module on the CRFs and in all required reports.

9.3.2 Recording Data

The CRF will be reviewed by the authorized site personnel. An appropriate comment will be provided to explain changes to data reported on the CRF.

10 Monitoring

It is the responsibility of the CCISC PDA Module PI to ensure the clinical study is conducted, recorded and reported according to the approved CSP, subsequent amendment(s), applicable regulations and guidance documents. Monitoring will be conducted according to CCISC's Clinical Monitoring work instruction. Prior to beginning the clinical investigation, the CCISC will contact the

Investigator or designee to discuss the clinical study and data requirements. A designated monitor will periodically review the subject records and associated source documents. The investigator of each site shall make subject and clinical study records available to the clinical monitor. The percentage of data that the monitor decides to verify will be according to the discretion of the monitor. The CCISC will randomly audit ten percent of the patients entered in the PDA module from each institution. Service details are previously outlined in the applicable Service Agreement between the CCISC participating site and the CCISC.

11 Compliance Statement

11.1 Statement of Compliance

In addition to applicable regional or local laws and regulations, this clinical study will be conducted in compliance with the most current version of the World Medical Association (WMA) Declaration of Helsinki and 21 CFR Parts 50, 54, 56 and 812. In the event of any conflicts, local laws and regulations will have precedence and in such cases, good faith efforts will be made to adhere to the intent of the other documents. Each participating site will sign a Clinical Study Agreement by appropriate personnel and agree to be compliant with it. Sites will not start entering data on subjects undergoing PDA closures prior to obtaining IRB approval and relevant Regulatory Authority approval, if applicable, and authorization from the CCISC in writing for the clinical study. If additional requirements are imposed by the IRB or relevant Regulatory Authority, those requirements will be followed. If any action is taken by an IRB or a relevant Regulatory Authority with respect to the clinical study, that information will be forwarded to the CCISC.

11.2 Quality Assurance audits and Regulatory Inspections

The investigator and/or delegate should contact the CCISC immediately upon notification of a regulatory authority inspection at the site. A monitor or designee will assist the investigator and/or delegate in preparing for the audit. The CCISC may perform quality assurance audits, as required.

The Principal Investigator or institution will provide direct access to source data during and after the clinical investigation for monitoring, audits, IRB review and regulatory authority inspections, as required. The Principal Investigator or institution will obtain permission for direct access to source documents from the subject, hospital administration and national regulatory authorities before starting the clinical study.

11.3 Repeated and Serious Non-Compliance

In the event of repeated non-compliance or a one-time serious non-compliance, as determined by the CCISC, a monitor or designee will attempt to secure compliance by one or more of the following actions:

a. Visiting the investigator,
b. Contacting the investigator by telephone,
c. Contacting the investigator in writing,

d. Retraining of the investigator.

If an investigator is found to be repeatedly non-compliant with the signed agreement, the CSP or any other conditions of the clinical investigation, the CCISC will either secure compliance or, at its sole discretion, terminate the investigator's participation in the clinical investigation. In case of termination, the CCISC will inform the responsible regulatory authority, as required, and ensure that the IRB is notified, either by the Principal Investigator or by the CCISC.

12 Suspension or premature termination of the clinical investigation

The CCISC reserves the right to terminate the clinical investigation at any stage, with appropriate written notice to the investigators, IRB and relevant regulatory authorities, if required.

A Principal Investigator, IRB or regulatory authority may suspend or prematurely terminate participation in a clinical study at the investigational sites for which they are responsible. The investigators will follow the requirements specified in the Clinical Study Agreement.

If suspicion of an unacceptable risk to subjects arises during the clinical study or when so instructed by the IRB or regulatoryauthority, the CCISC may suspend the clinical study while the risk is assessed. The CCISC will terminate the clinical study if an unacceptable risk is confirmed. If the CCISC completes an analysis of the reasons for the suspension, implements the necessary corrective actions, and decides to lift the temporary suspension, the CCISC will inform the Principal Investigators, IRB, or regulatory authority, where appropriate, of the rationale, providing them with the relevant data supporting this decision. Approval from the IRB or regulatory authority, where appropriate, will be obtained before the clinical study resumes. If the CCISC suspends or prematurely terminates the clinical study at an individual investigational site in the interest of safety, the CCISC will inform all other Principal Investigators.

13 Clinical Study Conclusion

Initial data collection will be limited to 500 subjects. Additional data collection beyond the initial cohort of 500 subjects may be done on a voluntary basis by participating sites/physicians. It is anticipated to take a minimum of three years to have the 500 Subjects needed for the conclusion of the study.

14 Publication Policy

Publications or presentations of clinical study methods or results will adhere to CCISC's publication policy, which is based on Good Publication Practices and International Committee of Medical Journal Editors (ICMJE) guidelines. A copy of the policy will be provided upon request of the investigator.

Publication planning and authorship determinations will be overseen by the Publications Committee (see section 6.4.1), and investigators will be notified via email about the dissemination of study data and opportunities for involvement as authors on publications/presentations.

APPENDIX A: DEFINITIONS

NON-STUDY SPECIFIC DEFINITIONS

Adverse Event (AE)

Any untoward medical occurrence, unintended disease or injury or untoward clinical signs (including abnormal lab findings) in subjects, users, or other persons, whether or not related to the device under clinical investigation. This definition includes events related to the device as well as events related to the procedure.

Serious Adverse Event (SAE)

An adverse event that led to:

a. Death
b. A serious deterioration in the health of the subject that either resulted in:
    i. A life threatening illness or injury
    ii. A permanent impairment of body structure or function
    iii. Prolonged hospitalization
    iv. A medical or surgical intervention to prevent life threatening illness or injury
    v. A malignant tumor
c. Fetal distress, fetal death or a congenital abnormality or birth defect
d. A planned hospitalization for a pre-existing condition or a procedure required by the CSP

Adverse Device Effect (ADE)

An adverse event related to the use of an investigational medical device. This definition includes adverse events resulting from insufficient or inadequate implantation, installation or operation, or any malfunction of the investigational medical device. This definition includes any event resulting from the use error or from intentional misuse of the investigational medical device.

Serious Adverse Device Effect (SADE)

Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

Unanticipated Adverse Device Effect (UADE)

As defined in 21 CFR§812.3, Unanticipated Adverse Device Effect (UADE) are defined as any serious adverse effect on health or safety or any life threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the CSP or application (including supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

STUDY SPECIFIC DEFINITIONS

Related

The adverse event is related to the study device/procedure – i.e. an event that follows a reasonable temporal sequence from administration of the study intervention, follows a known or expected response pattern to the suspected intervention, that is confirmed by improvement on stopping and reappearance of the event on repeated exposure and that could not be reasonably explained by the known characteristics of the subject's clinical state.

In summary, the AE is related to any study device or procedure if the event satisfies all of following criteria:

a. Has a reasonable temporal relationship to intervention (e.g. device implant)
b. Could not readily have been produced or explained by the subject's clinical state or have been due to environmental or other interventions
c. Follows a known pattern of response to intervention
d. Disappears or decreases with reduction in dose or cessation of intervention and recurs with re-exposure

Major Complication

Major complications are defined as device or procedure-related adverse events resulting in any of the following:

a. Death
b. Life-threatening adverse event,
c. Persistent or significant disability/incapacity, and/or
d. A major open surgical intervention which is performed by a surgeon under general anesthesia

Examples of Major Complications:

a. Device or procedure related events leading to death
b. Cardiac perforation requiring percutaneous (e.g., pericardiocentesis) or open surgical intervention
c. Cardiac tamponade
d. Embolization requiring open surgical procedure (e.g., open heart surgery or femoral vessel cut down procedure) to retrieve the device
e. Persistent hemodynamic instability requiring emergency cardioversion/defibrillation therapy or emergency blood transfusion and/or institution of inotropic therapy
f. Excessive blood loss or hemolysis requiring transfusion > 20 cc/kg
g. Persistent or worsening respiratory instability
h. Cerebral or pulmonary embolism
i. Persistent cardiac arrhythmia requiring a pacemaker
j. Arteriovenous fistula requiring open surgical intervention
k. False aneurysm of the femoral artery requiring surgical intervention
l. Femoral vessel thrombophlebitis treated with intravenous antibiotics
m. Infection of the device (bacterial endocarditis)

Minor Complication

Minor complications are defined as device or procedure-related adverse events that do not fit the definition of a major complication. These will include adverse events which may require medical intervention but are not life threatening, are not likely to have long-term (> 6 months) sequelae, and do not require long term (> 6 months) therapy. The following are examples of adverse events considered to be minor complications:

a. Embolization that occurs intra-operatively where the device is retrieved using a transcatheter approach (e.g., using a snare) without needing to perform an open surgical procedure, such as open heart surgery or an open femoral vessel cut down procedure.
b. Reduced peripheral pulse (reversible) that can be managed with anti-thrombotic therapy (e.g., heparin, Aspirin)
c. Cardiac perforation not requiring percutaneous (e.g., pericardiocentesis) or open surgical intervention
d. Transient cardiac arrhythmia that is managed successfully with cardioversion or medication
e. Hematoma of the groin not requiring open surgical intervention

PDA Residual Shunt Grades Definitions

Grade 0—none;

Grade 1—trivial (narrow jet adjacent to the device via the PDA). Note: the presence of flow via existing or newly formed aortopulmonary collaterals should not be considered as representing a shunt via the PDA. (see references in Appendix B by Skinner and Acherman)

Grade 2—mild (broader jet filling proximal left pulmonary artery branch and extending to main pulmonary artery);

Grade 3/4—moderate to severe (wide jet filling the main pulmonary artery and extending to pulmonary valve or distal pulmonary artery branches, which also may be accompanied with the presence of flow reversal in the abdominal aortic Doppler pattern during diastole)

Definitions of significant adjacent vessel stenosis (narrowing/obstruction)

1. Significant obstruction of the left pulmonary artery is defined as less than 30% flow to the left lung by lung perfusion scan or a peak instantaneous gradient in left pulmonary artery ≥35 mmHg by echocardiogram if lung perfusion scan is not available. OR

2. Significant obstruction of the aorta is defined as a gradient of ≥20 mmHg in the aortic isthmus by invasive aortic catheterization or a mean gradient ≥20 mmHg in the aortic isthmus by echocardiogram if invasive aortic catheterization is not available.

APPENDIX B: BIBLIOGRAPHY

1. Tashiro, Jun, Eduardo A. Perez, and Juan E. Sola. "Reduced Hospital Mortality with Surgical Ligation of Patent Ductus Arteriosus in Premature, Extremely Low Birth Weight Infants: A Propensity Score-matched Outcome Study."Annals of surgery (2015).

2. Schneider, Douglas J. "The patent ductus arteriosus in term infants, children, and adults." In Seminars in perinatology, vol. 36, no. 2, pp. 146-153. WB Saunders, 2012.

3. Mahoney LT, Coyell KG, Laurer RM: The Newborn Transitional Circulation: Two-dimensional Doppler Echocardiographic Study. J Am Coll Cardiol 1985;6:623.

4. Philip, Ranjit, B. Rush Waller, Vijaykumar Agrawal, DenaWright, Alejandro Arevalo, David Zurakowski, and Shyam Sathanandam. "Morphologic characterization of the patent ductus arteriosus in the premature infantand the choice of transcatheter occlusion device." Catheterization and Cardiovascular Interventions (2015).

5. Krichenko A, Benson LN, Burrows P, et al: Angiographic classification of the isolated, persistently patent ductus arteriosus and implications for percutaneous catheter occlusion. *Am J of Card* 1989;63:877-80.

6. Pass R: AMPLATZER Duct Occluder Device: A New Technologyfor the Closure of the Moderate- to-large-sized Patent Ductus Arteriosus. *Expert Rev Med Devices* 2006;3:291-296.

7. Schneider, Douglas J. "The patent ductus arteriosus in term infants, children, and adults." In Seminars in perinatology, vol. 36, no. 2, pp. 146-153. WB Saunders, 2012.

8. Moore JW, Levi DS, Moore SD, Schneider DJ, Berdjis F. Interventional Treatment of Patent Ductus Arteriosus in 2004. Catheter Cardiovasc Interv 2005;64:91-101.

9. Perlo f, Joseph K.*The Clinical Recognition of Congenital Heart Disease*. Philadelphia: Saunders. Print.

10. Gross RE, Hubbard JP. Surgical ligation of a patent ductus arteriosus: report of first successful case. Congenital Heart Disease, Hutchinson Ross Pub Co., 1982, p 253.

11. Kabra,Nandkishor S., etal. "Neurosensory impairment after surgical closure of patent ductus arteriosus in extremely low birth weight infants: results from the Trial of Indomethacin Prophylaxis in Preterms." The Journal of pediatrics 150.3 (2007): 229-234.

12. Chorne, Nancy, etal. "Patent ductus arteriosus and its treatment as risk factors for neonatal and neurodevelopmental morbidity." Pediatrics 119.6 (2007): 1165-1174.

13. Teixeira, L. S., et al. "Postoperative cardiorespiratory instability following ligation of the preterm ductus arteriosus is related to earlyneed forintervention." Journal of Perinatology 28.12 (2008): 803-810.

14. Portsmann W, Wierny L, Warnke H, etal: Catheter closure of patent ductus arteriosus: 62 cases treated without thoracotomy. Radiol Clin North Am 1971;9:203-218.

15. Weisz, Dany E., and Patrick J. McNamara. "Patent ductus arteriosus ligation and adverse outcomes: causality or bias?." Journal of clinical neonatology 3.2 (2014): 67.

16. Philip, Ranjit, B. Rush Waller, Vijaykumar Agrawal, DenaWright, Alejandro Arevalo, David Zurakowski, and Shyam Sathanandam. "Morphologic characterization of the patent ductus arteriosus in the premature infantand the choice of transcatheter occlusion device." Catheterization and Cardiovascular Interventions (2015).

17. 17. Gruenstein, Daniel H., et al. "Transcatheter closure of patent ductus arteriosus using the AMPLATZER™ duct occluder II (ADO II)." Catheterization and Cardiovascular Interventions 89.6 (2017): 1118-1128.Agnoletti, Gabriella, D. Marini, A. M. Villar, R. Bordese, and F. Gabbarini. "Closure of thepatent ductus arteriosus with the new duct occluder II additional sizes device." Catheterization and Cardiovascular Interventions 79, no. 7 (2012): 1169-1174.

18. Kenny, Damien, Gareth J. Morgan, James R. Bentham, Neil Wilson, Robin Martin, Andrew Tometzki, Paul Oslizlok, and Kevin P. Walsh. "Early clinical experience with a modified Amplatzer ductal occluder for transcatheter arterial duct occlusion in infants and small children." Catheterization and Cardiovascular Interventions 82, no. 4 (2013): 534-540.

19. Sungur, Metin, Cemsit Karakurt, Nazan Ozbarlas, and Osman Baspinar. "Closure of patent ductus arteriosus in children, small infants, and premature babies with Amplatzer duct occluder I additional sizes: multicenter study."Catheterization and Cardiovascular Interventions 82, no. 2 (2013): 245-252.

20. Bruckheimer, Elchanan, Max Godfrey, Tamir Dagan, Michael Levinzon, Gabriel Amir, and Einat Birk. "The Amplatzer duct occluder I additional sizes device for transcatheter PDA closure: Initial experience." Catheterizationand Cardiovascular Interventions 83, no. 7 (2014): 1097-1101.

21. Baspinar, Osman, Derya Aydin Sahin, Ayse Sulu, Ahmet Irdem, Gokhan Gokaslan, Ercan Sivasli, and Metin Kilinc. "Transcatheter Closure of Patent Ductus Arteriosus in Under 6 kg and Premature Infants." Journal ofinterventionalcardiology 28, no. 2 (2015): 180-189.

APPENDIX C: PDA MODULE/CASE REPORTING FORM (CRF)

Patent Ductus Arteriosus Module

CLINICAL PRE-CATHETERIZATION DATA (To be obtained within 2 weeks of the procedure)

Patient ID: _____

Date of Birth: _____/_____/_____
MM /DD/YYYY

Date of Clinical Assessment: _____/_____/_____
MM /DD/YYYY

Sex: Male ☐ Female ☐

Ethnicity: White ☐ African American or Black ☐ Hispanic or Latino ☐ Asian ☐

Pacific Islander ☐ Native American ☐ Other ☐

Current weight: _____.___ kg **Birth weight:** _____.___ kg

Height: _____.___ cm

Gestational age at birth: _____ weeks

Other associated congenital heart defects: Left-to-right shunt lesions ☐
Right-to-left shunt lesions ☐
Other (Specify) _____

Other associated co-morbidities: (Mark all that are present)
Pulmonary hypertension ☐
Necrotizing enterocolitis ☐ Grade_____
Current ☐ Resolved ☐
Intraventricular hemorrhage ☐ Grade_____
Retinopathy of prematurity ☐
Chronic lung disease ☐
Renal insufficiency ☐
History of sepsis ☐
Other (Specify) _____

Genetic syndrome: _____

Ongoing medical support: Mechanical respiratory support ☐ Supplemental oxygen ☐

Conventional Ventilator ☐ Oscillator ☐ Non-inavasive ☐ CPAP ☐

Nasal Cannula ☐ None ☐

Inotropic support ☐

1

Tube feedings ☐ Parenteral nutrition ☐ Other (Specify) _____ None ☐

Current Medications: Diuretics ☐ ACE-Inhibitors ☐ Digoxin ☐ Antiplatelet ☐
Anti-pulmonary Hypertensive ☐ Anticoagulation ☐ None ☐

History of pharmacotherapy for PDA closure: Yes ☐ No ☐ N/A ☐

History of prior surgical ligation of PDA: Yes ☐ No ☐ N/A ☐

Number of attempts at pharmacologic closure of PDA:

One ☐ Two ☐ Three ☐ More than three ☐

Pre-procedure chest X-Ray: Date _____/_____/_____
(If available. Optional) MM / DD / YYYY

Cardiomegaly ☐ Increased pulmonary vascular markings ☐

Other ☐ (Specify) _____ N/A ☐

PRE-CATHETERIZATION ECHOCARDIOGRAM (To be obtained within 2 weeks of the procedure)

Pre-procedure Echo: Date _____/_____/_____
MM / DD / YYYY

PDA size by 2D Imaging: Aortic end ___.___mm

Pulmonary artery end ___.___mm

Minimum luminal diameter ___.___mm

Length ___.___mm

Color Doppler: Left-to-right ductal shunting ☐ Right-to-left ductal shunting ☐

Bi-directional shunting ☐ Other aorto-pulmonary shunting ☐

Spectral Doppler: Peak gradient across PDA ___.___ mmHg

Peak gradient across aortic isthmus ___.___ mmHg

Peak gradient across left pulmonary artery ___.___ mmHg

Left ventricular enlargement: Yes ☐ No ☐ N/A ☐

Patent Ductus Arteriosus Module

Estimates of pulmonary hypertension:
Tricuspid Regurgitation: ___.___m/s Right ventricular pressure estimate (+RA): _____

Interventricular septal flattening in systole:
Normal septal curvature ☐ Mild septal flattening ☐ Moderate septal flattening ☐
Ventricular septal inversion ☐

Left ventricular ejection fraction: _____ %

Other echo findings: Left aortic arch ☐ Right aortic arch ☐ Unknown arch sidedness ☐

Abdominal aorta diastolic flow reversal ☐ Coarctation of aorta ☐

Ventricular septal defect ☐ Atrial septal defect ☐ Pericardial effusion ☐

Mitral Valve Regurgitation: None/Trivial ☐ Mild ☐ Moderate ☐ Severe ☐

Tricuspid Valve Regurgitation: None/Trivial ☐ Mild ☐ Moderate ☐ Severe ☐

Pulmonary Valve Regurgitation: None/Trivial ☐ Mild ☐ Moderate ☐ Severe ☐

Other congenital heart defects ☐ (Specify) _____

CATHETERIZATION DATA

Date of Catheterization: _____/_____/_____
MM / DD / YYYY

Weight: _____.___ kg **Height:** _____.___ cm **BSA:** _____.___ m^2

Indication for PDA closure: Left heart enlargement ☐ Pulmonary hypertension ☐
Prematurity ☐ SBE prevention ☐ Frequent respiratory infection ☐ Failure to thrive ☐
Ventilator dependence ☐ Other ☐ (Specify) _____

Pre-Procedure **Respiratory Severity Score** (Mean airway pressure x FiO_2): _____

Anesthesia:
General endotracheal anesthesia ☐ Moderate sedation ☐ Monitored anesthesia care ☐
Was Patient Specifically Intubated for the Procedure Yes ☐ No ☐

Guidance:
Fluoroscopy only ☐ Trans-thoracic echo only ☐ Combination of Fluoroscopy and Echo ☐

Location:
Cardiac Cath Lab ☐ Bedside ☐ Other Location ☐
Started in another location but completed in the cath lab ☐

Access: Venous access only ☐ Arterial access only ☐ Venous and arterial access ☐

Right femoral vein ☐ Left femoral vein ☐ Right femoral artery ☐ Left femoral artery ☐

Use of Ultrasound for vascular access:
Ultrasound was primarily used for access ☐
Ultrasound was used after failed attempted access without ultrasound ☐
Ultrasound was not used for vascular access ☐

Hemodynamics: Not performed ☐

Qp:Qs _____ Pulmonary artery pressure _____ mmHg

Pulmonary vascular resistance_____WU*m^2

Largest venous sheath size: _____ French **Largest arterial sheath size:** _____ French

PDA Morphology

Patent Ductus Arteriosus Module

Type A (Conical) ☐ Type B (Window) ☐ Type C (Short tubular) ☐ Type D (Complex) ☐ Type E (Elongated) ☐ Type F (Fetal type) ☐

Intra-Procedure PDA measurements:

If Angiographic measurements were performed	*If measurements were performed only by Intra-procedural trans-thoracic echo*
Aortic end ___.___mm	Aortic end ___.___mm
Pulmonary artery end ___.___mm	Pulmonary artery end ___.___mm
Minimum luminal diameter ___.___mm	Minimum luminal diameter ___.___mm
Length ___.___mm	Length ___.___mm

Heparin administration: Yes ☐ **No** ☐ **If Yes, highest ACT** _____ **secs**

Device delivery: Antegrade ☐ Retrograde ☐

Contrast:
No contrast was used ☐ Total contrast volume _____.___ mL/kg

Radiation:
Total Fluoroscopy time: _____.___ minutes

Cumulative DAP: _____.___

DAP Units: Gy-cm2 ☐ dGy-cm2 ☐ cGy-cm2 ☐ mGy-cm2 ☐ mcgGy-m2 ☐

Device (s):

Device count	Device	Device outcome		
1		Implanted, not released ☐	Implanted, released ☐	Implanted, released, and retrieved ☐
2		Implanted, not released ☐	Implanted, released ☐	Implanted, released, and retrieved ☐
3		Implanted, not released ☐	Implanted, released ☐	Implanted, released, and retrieved ☐
4		Implanted, not released ☐	Implanted, released ☐	Implanted, released, and retrieved ☐

Patent Ductus Arteriosus Module

Implanted device # 1 size: _____ mm X _____mm **Device type:** _____

Implanted device # 2 size: _____ mm X _____mm **Device type:** _____

Implanted device # 3 size: _____ mm X _____mm **Device type:** _____

Implanted device # 4 size: _____ mm X _____mm **Device type:** _____

Residual shunting by angiography: Grade 0 (None) ☐ Grade 1 (Trivial) ☐
Grade 2 (Mild) ☐ Grade 3 (Moderate) ☐ Grade 4 (Severe) ☐

Residual shunting by intra-procedural echo if utilized (Optional):
Grade 0 (None) ☐ Grade 1 (Trivial) ☐
Grade 2 (Mild) ☐ Grade 3 (Moderate) ☐ Grade 4 (Severe) ☐

Gradient across the proximal left pulmonary artery (Cath/Echo – Optional):
Pre-procedure peak gradient ☐ Pre-procedure mean gradient ☐
Post-procedure peak gradient ☐ Post-procedure mean gradient ☐

Gradient across the distal aortic arch (Cath/Echo – Optional):
Pre-procedure peak gradient ☐ Pre-procedure mean gradient ☐
Post-procedure peak gradient ☐ Post-procedure mean gradient ☐

Other echo findings (optional):

Increased tricuspid regurgitation compared to baseline: Yes ☐ No ☐

Increased pulmonary valve regurgitation from baseline: Yes ☐ No ☐

Left ventricular ejection fraction: _____ % Pericardial effusion: Yes ☐ No ☐

Other echo findings ☐ (Specify) _____

Date Patient Extubated Following Procedure:_____/_____/_____
MM / DD / YYYY

Date of Hospital Discharge: _____/_____/_____
MM DD YYYY

Adverse Events:

Where there any Adverse Events during the procedure: Yes ☐ No ☐
(If Yes, complete the AE Form)

FOLLOW-UP CLINICAL EXAM

(All patients need a post-procedure follow-up within 48 hours, one month ± 7 days and at six months ± 30 days post procedure)

Date of follow-up: _____/_____/_____
MM DD YYYY

Weight: _____.____ (kg) Height:_____.___ (cm)

Blood pressure (optional): Upper extremity ___ /___ mmHg Lower extremity ___ /___ mmHg

Pulses: Equal upper and lower extremity pulses ☐ Weak lower extremity pulses ☐

Lower extremity pulses not palpable ☐

Ongoing medical support: Mechanical respiratory support ☐ Supplemental oxygen ☐

Conventional Ventilator ☐ Oscillator ☐ Non-inavasive ☐ CPAP ☐

Nasal Cannula ☐ None ☐

Inotropic support ☐

Respiratory Severity Score (Mean airway pressure x FiO_2): _____

Tube feedings ☐ Parenteral nutrition ☐ Other (Specify) _____ None ☐

FOLLOW-UP ECHOCARDIOGRAPHY

Date of echocardiogram: _____/_____/_____
MM DD YYYY

Weight: _____.____ (kg) Height:_____.___ (cm)

Device within PDA: ☐

Presence of residual PDA shunting:

Grade 0 (None) ☐ Grade 1 (Trivial) ☐ Grade 2 (Mild) ☐
Grade 3 (Moderate) ☐ Grade 4 (Severe) ☐

Spectral Doppler: Peak gradient across aortic isthmus ___.___ mmHg

Peak gradient across left pulmonary artery ___.___ mmHg

Other echo findings:

Increased tricuspid regurgitation compared to baseline: Yes ☐ No ☐

Increased pulmonary valve regurgitation from baseline: Yes ☐ No ☐

Left ventricular ejection fraction: _____ %

Pericardial effusion: Yes ☐ No ☐

Evidence for Pulmonary Hypertension: Yes ☐ No ☐

Other echo findings ☐ (Specify) _____

FOLLOW-UP CHEST X-RAY (Optional)

Post-procedure chest X-Ray: Date _____/_____/_____
MM / DD / YYYY

Cardiomegaly ☐ Increased pulmonary vascular markings ☐

Device malposition ☐

Other ☐ (Specify) _____

APPENDIX D: ADVERSE EVENT REPORTING FORM

ADVERSE EVENT FORM

Type of adverse event:

Device embolization ☐ Access complications ☐ Vessel stenosis ☐ Valve injury ☐ Other ☐

Device embolization:

During the procedure (In the cath lab): Yes ☐ No ☐
After the procedure (In recovery): Yes ☐ No ☐
Delayed embolization (>24 hours later): Yes ☐ No ☐

Embolization site:

Left pulmonary artery ☐ Right pulmonary artery ☐
Aorta/systemic artery ☐ Right ventricle ☐ Other site ☐ (Specify) _____

Outcome of embolization:

Observation only ☐
Successful transcatheter retrieval with PDA occlusion with another device ☐
Successful transcatheter retrieval, PDA not occluded with another device ☐
Successful transcatheter retrieval, PDA surgically ligated ☐
Unsuccessful transcatheter retrieval, PDA occlusion with another device ☐
Unsuccessful transcatheter retrieval, PDA not occluded with another device ☐
Unsuccessful transcatheter retrieval, PDA surgically ligated ☐
Device embolization led to initiation of inotropic suport ☐
Device embolization led to initiation of mechanical circulatory support ☐
Device embolization led to patient mortality ☐

Access complications:

During the procedure (In the cath lab): Yes ☐ No ☐
After the procedure (In recovery): Yes ☐ No ☐
Delayed access complication (>24 hours later): Yes ☐ No ☐

Arterial access complication:

Transient loss of pulse with spontaneous recovery without intervention ☐
Transient loss of pulse with recovery following intervention ☐
Non-occlusive arterial thrombus – No intervention needed/performed ☐
Non-occlusive arterial thrombus – Requiring intervention ☐
Medical ☐ Surgical ☐
Occlusive arterial thrombus – Requiring intervention ☐
Medical ☐ Surgical ☐
Loss of limb secondary to vascular access complication ☐

Venous access complication:

Venous thrombosis – anticoagulation/antiplatelet therapy performed ☐
Venous thrombosis – anticoagulation/antiplatelet therapy not performed ☐

Vessel stenosis:

- Noted during the procedure (In the cath lab): Yes ☐ No ☐
- Noted after the procedure (In recovery): Yes ☐ No ☐
- Delayed finding (>24 hours later): Yes ☐ No ☐

Left pulmonary artery stenosis:

- No intervention was required ☐
- Intervention performed during the same catheterization ☐
- Intervention performed within 24 hours ☐
- Intervention performed > 24 hours ☐
- Re-intervention on the left pulmonary artery is unlikely ☐
- Re-intervention on the left pulmonary artery is likely ☐

Type of intervention for the left pulmonary artery stenosis:

- Retrieval of device with no further intervention ☐
- Retrieval of device with repositioning of the same device ☐
- Retrieval of device with use of a different device ☐
- Balloon angioplasty of the left pulmonary artery ☐
- Stent implantation for left pulmonary artery stenosis ☐
- Surgical repair ☐

Descending aorta stenosis:

- No intervention was required ☐
- Intervention performed during the same catheterization ☐
- Intervention performed within 24 hours ☐
- Intervention performed > 24 hours ☐
- Re-intervention on the aorta is unlikely ☐
- Re-intervention on the aorta is likely ☐

Type of intervention for the descending aorta stenosis:

- Retrieval of device with no further intervention ☐
- Retrieval of device with repositioning of the same device ☐
- Retrieval of device with use of a different device ☐
- Balloon angioplasty of the descending aorta stenosis ☐
- Stent implantation for descending aorta stenosis ☐
- Surgical repair ☐

Valve Injury:

Noted during the procedure (In the cath lab): Yes ☐ No ☐
Noted after the procedure (In recovery): Yes ☐ No ☐
Delayed finding (>24 hours later): Yes ☐ No ☐

Injured Valve:

Tricuspid valve ☐
Pulmonary valve ☐
Mitral valve ☐
Aortic valve ☐

Degree of regurgitation:

Mild ☐
Moderate ☐
Severe ☐

Mechanism of regurgitation:

Avulsion of chordae ☐
Central non-coaptation of the valve ☐
Valve leaflet injury ☐
Injury to valve annulus ☐

Outcome:

Observation only ☐
Medical therapy ☐
Surgical intervention ☐

Other complications:

Bleeding into:

Pericardium ☐ Pleura ☐ Peritoneum ☐ Retroperitoneum ☐ External hemorrhage ☐

Vessel perforation ☐ Cardiac arrest ☐ Arrhythmias including AV heart blocks ☐

Stroke ☐ Death ☐ Infection including suspected endocarditis and sepsis ☐

Post PDA ligation syndrome ☐

APPENDIX E: SCHEDULE OF ASSESSMENTS

	Pre-Catheterizatio	Device Implan	Follow up within 48 hours	Follow up at 30 ± 7 days	Follow up at 6 ± 1 months
Demographic Data	X				
Physical Exam Data	X		X	X	X
Medical History Data	X				
Procedure Data		X			
Device Data		X			
Transthoracic Echocardiogram Data	X	X *	X	X	X
Adverse Event Data		X	X	X	X
Death Data		X	X	X	X
	* optional Intra-procedure Transthoracic Echocardiogram				

APPENDIX F

PROTOCOL DEVIATION REPORTING FORM

Report Date:		**Title:**	
Sponsor:		**Principal Investigator:**	
Date of Deviation/ Violation:		**Subject Identifier: (if available)**	

Reporting Deviations to IRB

***Sites must report violations that affect the safety and welfare of the subject to be submitted within 10 working days from the date the Investigator becomes aware of the event.**

- Minor Deviations that do not affect the safety and welfare of the subject may be submitted at the time of continuing review. Please note that the sponsor's requirement may differ from IRB's reporting requirements; contact the sponsor and your institutional IRB to confirm if you have any questions regarding their policy.

- FDA 21 CFR 56.108(a)(4) and ICH 3.3.7 state that planned protocol deviations require prior approval of the IRB except when necessary to eliminate apparent immediate hazards to human subjects. Please submit this form to the CCISC as soon as possible after receiving sponsor approval for the planned deviation and prior to the deviation occurring.

Protocol Deviation/Violation Assessment

Did the protocol deviation/violation affect the safety and welfare of the subject? ☐ Yes* ☐ No

Has the Sponsor been notified of this event? ☐ Yes ☐ No

Will the subject continue his/her participation in the study? ☐ Yes ☐ No

Was the deviation planned or unplanned? ☐ Planned** ☐ Unplanned

(**please provide prior approval of Sponsor)

Protocol Deviation/Violation Description and Reason

Please provide a description of the deviation/violation:

Please explain the reason for the deviation/violation:
Corrective Action
Please describe what action(s) you have taken to prevent recurrence of this deviation/violation in the future:

Principal Investigator Signature: _____ Date: _____

Protocol Deviation Tracking Log

Tool:	Protocol Deviation Tracking Log
Purpose:	To record all protocol deviations that occur at a study site
User:	Study coordinators, principal investigators (PIs), other site staff, clinical monitor
Details:	This tracking log should provide a comprehensive list of all protocol deviations that occur at a study site. This tool is complementary to, and does not replace, the form reporting individual protocol deviations to the institutional review board (IRB). Deviations should be reported to the IRB and others, as required.

Best Practice Recommendations:

- Record protocol deviations in the tracking log as they occur, to ensure completeness and accuracy of the data.
- The site PI should sign each form after it has been completed within 10 working days. If it has been signed with fewer than five deviations entered into it, the next identified deviation should be reported on a new page to ensure that all deviations have been reviewed by the PI.
- Number each page and maintain this log in the Essential Documents Binder, behind the Protocol Deviations tab. (Synonyms for this binder include Investigator Binder, Regulatory Binder, Investigator Site File [ISF], and Study File.)
- Store pages in reverse chronological order, with the newest pages of the log placed at the front of the section.
- At the conclusion of the study, identify the final page of the log by checking the box in the footer.
- Remove this Tool Summary Sheet before use of the log.

Protocol Deviation Tracking Log

Protocol ID/Number:		**Site Name/Number:**	
Protocol Title (Abbreviated):			
Principal Investigator:		**Page number [1]:**	

Ref No.	Subject ID	Date of Deviation	Date Identified	Deviation Description	Dev. Type [2]	Resulted in AE?	Did Subject Continue in Study?	Meets IRB Reporting Req. (Yes/No)	IRB Reporting Date
1									
2									
3									
4									
5									
6									
7									

Investigator Signature: _____ **Date:** _____

Form Instructions:

[1] Each page should be separately numbered to allow cross-referencing (e.g., deviation #2 on p. 7)

[2] Deviation Type: (A-I) See codes below—enter the appropriate deviation code from the list.

Protocol Deviation Codes:

A – Consent Procedures
B – Inclusion/Exclusion Criteria
C – Concomitant Medication/Therapy
D – Laboratory Assessments/Procedures
E – Study Procedures
F – Serious Adverse Event Reporting/Unanticipated Adverse Device Effect
G – Visit Schedule/Interval
H – Efficacy Ratings
I – Other

APPENDIX G

Serious Adverse Event (SAE) Report Form

For CCISC Office Use:
Date received: _____ *(mm/dd/yyyy)*
Application Reference No.: _____

1. Basic Information

Study title			
IRB Ref. No.		Protocol no.	

2. Study Site(s) Involved

☐ Overseas site(s)

☐ Local site(s) Name of study site: ☐

3. Subject Outcome at Time of Report

☐ Complete recovery ☐ Recovery with sequelae ☐ Events not yet resolved

☐ Unknown ☐ Death; cause: ☐

4. Serious Adverse Events

Subject reference: Code ☐ Initials ☐ Age ☐ Sex ☐

Relevant medical history & current treatments: ☐

Nature of SAE: *(Describe temporal relationship with intervention & other concomitant therapies)* ☐

SAE start date ☐ SAE stop date ☐ /not resolved*

Type of SAE ☐ initial ☐ follow up

Frequency ☐ One episode ☐ Intermittent ☐ Continuous

Seriousness	☐ Death	☐ Life threatening
	☐ Significant disability/incapacity	☐ Required hospitalisation
	☐ Persistent disability/incapacity	☐ Prolonged hospitalisation
	☐ Congenital anomaly/birth defect	☐ None of the above
	☐ Other medically important condition	

5. Suspected relationship to Study

☐ Definite ☐ Probable ☐ Possible ☐ Not related ☐ Not assessable

6. Remedial actions

On the affected subject:	☐ None	☐ Protocol deviation form submitted
	☐ Interrupted temporarily	☐ Discontinued/ terminated study
Details:		

Report by	Name	Signature	Date