Abbott	Clinical Investigation Plan Cover Page

NCT Number: 03055858
ADO II AS
AMPLATZER Duct Occluder II Additional Sizes (ADO II AS) Clinical Study
Study Document No: SJM-CIP-10171
Version D
Date: 02-AUG-2018

Sponsor

St. Jude Medical, Inc.
Global Clinical Affairs
5050 Nathan Lane North
Plymouth, MN 55442 USA

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AMPLATZER Duct Occluder II Additional Sizes (ADO II AS) Clinical Study
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[redacted]

Table of Contents

1 Introduction

This document is a clinical investigation plan (CIP) for the AMPLATZER Duct Occluder II® Additional Sizes (ADO II AS) clinical investigation. This clinical investigation is intended to demonstrate the safety and effectiveness of St. Jude Medical's ADO II AS in subjects with a patent ductus arteriosus (PDA). This clinical investigation will be conducted under an investigational device exemption (IDE) and is intended to support market approval of the ADO II AS device in the United States and other countries. This clinical investigation is sponsored by St. Jude Medical (SJM).

This clinical investigation will be conducted in accordance with this CIP. All parties involved in the conduct of the clinical investigation will be qualified by education, training, or experience to perform their tasks and this training will be documented appropriately.

1.1 Continued Access Protocol (CAP) Enrollment

[redacted]

1.2 Scope and Description of CAP Enrollments

[redacted] pertaining only to CAP subjects are organized as sub-sections of their corresponding protocol section. These sub-sections are labeled 'for CAP Subjects' and are underlined for identification. For these subjects, the content of these sub-sections replaces the corresponding content of the associated protocol section. If sections of this protocol are not accompanied by a section specified for CAP subjects, then the original IDE section will be followed for all subjects.

[redacted]

2 Background and justification for clinical investigation

2.1 Disease to be treated

In the fetus, 85% of the blood bypasses the unexpanded lungs. The blood flows from the right ventricular outflow tract through the ductus arteriosus to the aorta. At birth, the increase in oxygen tension leads to inhibition of local prostaglandins and causes functional closure of the ductus, followed by anatomic closure. A patent ductus arteriosus (PDA) is a persistence of the fetal connection (ductus arteriosus) between the aorta and pulmonary artery after birth, resulting in a persistent left-to-right shunt. PDA is the most common congenital heart lesion in newborns and accounts for approximately 5 to 10% of all congenital heart defects. The incidence of a PDA is approximately 1 in 2,000 term newborns and this incidence increases to >50% in premature babies, and >80% in severely premature low birth weight infants (<1200 gm) [1]. PDA is more commonly seen in female infants, with a female-to-male ratio of 2:1 for PDA [2].

Typically the PDA will close in the first 10-18 hours of life, and anatomically, it is generally closed within six weeks [3]. PDA anatomy varies considerably both in diameter, length and configuration. Krichenko et al

provided angiographic classification of the different PDA configurations labeled as A-type through E-type, which recently has been expanded by Philip et al [4] to also include the tubular and longer F-type configuration commonly seen in premature born infants [5]. The PDA diameter refers to its narrowest segment, which is smaller than 4 mm in 78% of cases [6].

While this lesion may spontaneously resolve in some neonates, persistence, particularly in premature infants is a major health concern. The presence of a hemodynamically significant PDA in premature infants has been associated with an increased risk of developing necrotizing enterocolitis, chronic respiratory disease, pulmonary hemorrhage, intraventricular hemorrhage, and death [1, 7]. Should a baby survive the neonatal period with a significant PDA, this lesion can result in continued morbidity during infancy, which includes failure to thrive, chronic respiratory infections, and repeated hospital admissions.

Closure of PDA is indicated to restore hemodynamic status and to prevent congestive heart failure, pulmonary vascular disease, and, in the long-term, bacterial endocarditis [8]. The risk of endocarditis with small residual shunts remains unknown, although continued bacterial endocarditis prophylaxis is generally advocated as long as flow persists or a murmur can be auscultated [9].

2.2 Current Treatment Options

The current standard of care for a persistent patent ductus arteriosus (PDA) includes the following two treatment options: surgical ligation or closure with alternative devices.

Surgical Ligation
PDA was the first congenital cardiac heart disease to be conquered by surgeons. The first surgical ligation of a PDA was performed by Gross and Hubbard in 1939 [10]. Surgical ligation or ligation and division were the standard of care for persistent PDA until the advent of transcatheter closure. Today surgery remains the standard of care for PDA closure in preemies and infants with large hemodynamically significant PDAs. Although the standard of care, surgical ligation has been associated with the potential risk for significant procedural complications (pneumothorax, hypothermia, bleeding, phrenic nerve palsy, chylothorax, wound infection, vocal cord paralysis, and thoracic scoliosis [1, 7, 11, 12]), significant post-procedural clinical decline known as post-ligation syndrome [13], and poor long-term outcomes including neuro-developmental delay, retinopathy of prematurity and chronic lung disease (bronchopulmonary dysplasia) [11, 12]. Because a growing body of literature has suggested that surgical ligation of PDA in premature neonates may actually result in worse outcomes than no treatment at all a trend of permissive conservative observation of this lesion has developed, reserving surgery for only the most severe cases. Unfortunately, recent data suggests that this approach is associated with an increased risk for the development of chronic lung disease and death [15].

Transcatheter device closure
The first interventional closure of a PDA was performed by Portsmann in 1967 [14] and has emerged as the gold standard for treatment of this lesion in larger infants, children and adults [7]. Historically, transcatheter closure of a PDA has not been performed in infants and premature neonates for a variety of reasons including: fear of patient fragility; concerns regarding vascular access and arterial injury; unknown effects of intravenous contrast media; concerns regarding catheter manipulation; and most importantly, absence of a suitable PDA closure device. Recently, a growing body of clinical evidence has emerged suggesting that transcatheter closure of PDA can be performed safely and effectively in selected infants and premature newborns. The ADO II AS device has the ideal characteristics (size, shape, delivery system) for this unique population but its lack of availability in the USA has limited wide spread adaptation of this procedure.

2.3 AMPLATZER PDA Occluder

The AMPLATZER Duct Occluder II received PMA approval on August 15, 2013. [redacted] The AMPLATZER Duct Occluder II Additional Sizes device was designed as a line extension to ADO II to allow closure of smaller sizes of a PDA.

[redacted] The ADO II AS is designed to treat a PDA with a diameter ≤ 4.0 mm and a length ≥ 3.0 mm.

The ADO II AS is a self-expanding nitinol mesh occlusion device with a central waist and retention discs deployed on both ends. The central waist of the device ranges in diameter from 3 to 5 mm in 1 mm increments. The retention discs have a diameter 1, 1.25, or 1.5 mm larger than the waist diameter for the 3, 4, and 5 mm waist diameters, respectively. Each device size is available in 2, 4, or 6 mm length. The device can be delivered forward from a 4 French (4F) delivery catheter either by the aortic or venous route. The central waist is designed to fill the ductal lumen, and the retention discs are designed to deploy in the pulmonary and the aortic end of the ductus arteriosus. The ADO II AS comes pre-attached to a delivery cable. The delivery cable's distal tip is extremely flexible and has angiographically visible properties, which helps to achieve precise placement of the proximal disc during device placement and unscrewing. TorqueVue Low Profile Delivery Catheter has 4F outer diameter compatible with all 9 ADO II AS occluders.

[redacted] Procedural related complications associated with implanting the device in small infants may be minimized by utilizing an echocardiographic anterograde approach and avoiding invasive hemodynamic measurement and angiographic image acquisition.

Although the device is recommended for ductal diameters up to 4 mm, the largest waist diameter available is 5 mm with the retention discs only 1.5 mm larger. This leaves very little extra anchoring with this device compared to either the ADO or the ADO II, and therefore, the maximum diameter for deployment should be less than or equal to 4 mm. Tubular PDA's in young infants may stretch more easily. The small, flexible retention discs provide minimal anchoring support, meaning that the device relies heavily on constraint of the central portion for stable positioning. Careful device diameter sizing is required in larger ductal diameters to avoid embolization. The device may be implanted in ducts that are longer in length than the

length of the device, as long as the selected device diameter satisfies the specified diameter within the sizing chart.

2.4 Study Rationale (IDE and CAP)

2.4.1 Pivotal IDE Rationale

The rationale for this investigation is to offer patients a safe and effective device for closure of a small PDA (≤ 4 mm diameter) with an FDA approved device. Current treatment for smaller PDAs includes off label use of devices. Major drawbacks of current devices in terms of this unique population include: device length (too long, placing the left pulmonary artery and descending aorta at risk for obstruction), device shape (large retention disks placing the left pulmonary artery and descending aorta at risk for obstruction), and stiffness of delivery systems. Currently there is no FDA approved device for PDA closure in patients <5 kg or <6 months of age, which encompasses virtually all infants, neonates and premature neonates.

2.4.2 CAP Rationale

The rationale for the CAP is to allow current IDE study implanters to maintain their technical proficiency in ADO II AS device implantation and to allow additional implanters to gain experience with the device after enrollment completion in the pivotal cohort and while the pre-market approval (PMA) application for the ADO II AS device is being prepared and is under FDA review. Data from the CAP may be used to support post approval requirements for the ADO II AS occluder.

3 Device(s) under investigation

3.1 Identification and description of the devices under investigation

3.1.1 Identification

Figure 1: ADO II AS Device

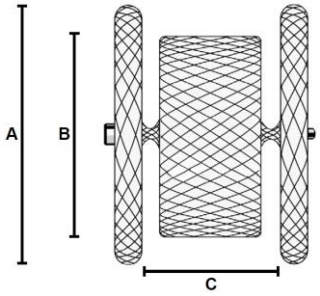

Table 1: Identification of Devices under Investigation

Device Name	Model/Type	A mm (in)	B mm (in)	C mm (in)	Investigational or Market Released
ADO II AS Occluder	9- PDA2ASIDE-03-02	4.00 (0.157)	3.00 (0.118)	2.00 (0.079)	Investigational
ADO II AS Occluder	9- PDA2ASIDE-03-04	4.00 (0.157)	3.00 (0.118)	4.00 (0.157)	Investigational
ADO II AS Occluder	9- PDA2ASIDE-03-06	4.00 (0.157)	3.00 (0.118)	6.00 (0.236)	Investigational
ADO II AS Occluder	9- PDA2ASIDE-04-02	5.25 (0.207)	4.00 (0.157)	2.00 (0.079)	Investigational
ADO II AS Occluder	9- PDA2ASIDE-04-04	5.25 (0.207)	4.00 (0.157)	4.00 (0.157)	Investigational
ADO II AS Occluder	9- PDA2ASIDE-04-06	5.25 (0.207)	4.00 (0.157)	6.00 (0.236)	Investigational
ADO II AS Occluder	9- PDA2ASIDE-05-02	6.50 (0.256)	5.00 (0.197)	2.00 (0.079)	Investigational
ADO II AS Occluder	9- PDA2ASIDE-05-04	6.50 (0.256)	5.00 (0.197)	4.00 (0.157)	Investigational
ADO II AS Occluder	9- PDA2ASIDE-05-06	6.50 (0.256)	5.00 (0.197)	6.00 (0.236)	Investigational
AMPLATZER™ TorqVue™ LP Catheter	9-TVLPC4F90/080	Not Applicable	Not Applicable	Not Applicable	Market Released

Table 2: Device Sizing Chart for subjects >2 Kg

Measured Ductus Diameter mm (in)	Minimal Measured Ductus Length mm (in)		
	3–4 (0.118–0.157)	**4.1–6 (0.161–0.236)**	**6.1–8 (0.240–0.315)**
≤2 (≤0.079)	9-PDA2ASIDE-03-02	9- PDA2ASIDE-03-04	9- PDA2ASIDE-03-06
2.1–3 (0.083–0.118)	9- PDA2ASIDE-04-02	9- PDA2ASIDE-04-04	9- PDA2ASIDE-04-06
3.1–4 (0.122–0.157)	9- PDA2ASIDE-05-02	9- PDA2ASIDE-05-04	9- PDA2ASIDE-05-06

Table 3: Device Sizing Chart for subjects ≤2 Kg

Measured Ductus Diameter mm (in)	Minimal Measured Ductus Length mm (in)	
	3–6 (0.118–0.236)	≥6.1 (≥0.240)
≤1.5 (<0.059)	9-PDA2ASIDE-03-02	9- PDA2ASIDE-03-04
1.6–2.5 (0.063–0.098)	9- PDA2ASIDE-04-02	9- PDA2ASIDE-04-04
2.6–4 (0.102–0.157)	9- PDA2ASIDE-05-02	9- PDA2ASIDE-05-04

3.1.2 Device Description and Intended Indications for Use

The AMPLATZER Duct Occluder II Additional Sizes (ADO II AS) is a percutaneous transcatheter occlusion device intended for the non-surgical closure of PDAs. The AMPLATZER TorqVue LP Delivery System is intended to facilitate the attachment, loading, delivery and deployment of the ADO II AS.

The ADO II AS is a self-expandable Nitinol mesh occlusion device for the occlusion of patent ductus arteriosus (PDA). The device configuration is a central waist with two retention disks. The central waist is designed to fill the defect and the two retention disks are designed to be deployed on the arterial and venous sides of the defect. Because of the isodiametric design of the device it may be implanted in ducts longer than the device as long as the diameter of the device is sufficiently large to constrain the device within the PDA. Devices are available in three lengths to accommodate various lengths of PDA. The ADO II AS has a screw attachment for a delivery wire and radiopaque marker bands at both ends.

The AMPLATZER TorqVue LP Catheter consists of a delivery catheter, Touhy-Borst hemostasis valve, loading device, and a self-sealing hemostasis valve. The delivery catheter was designed to facilitate attachment, loading, delivery and deployment of AMPLATZER devices pre-loaded onto a delivery wire. The TorqVue LP Catheter is not investigational.

3.1.3 Device handling and storage

Sponsor requires all investigational products be stored, according to the labeling and instructions for use, in a secure area to prevent unauthorized access or use.

3.2 Device accountability

Investigational product shall be shipped to sites or approved SJM personnel after sites receive documentation of site activation and shipping authorization is complete.

The Principal Investigator or an authorized designee must maintain records of the date of receipt, the identification of each investigational device (batch number, serial number or unique code), the subject identification, the date of use, the expiration date and final disposition.

Storage locations for the devices at investigational sites will be locked with access restricted only to investigators and authorized personnel.

Sponsor must also maintain device accountability documenting all shipments and returns of investigational devices.

4 Clinical Investigation Design

4.1 Clinical Investigation Design for Pivotal IDE Subjects

The ADO II AS IDE study is a single arm, prospective, multicenter, non-randomized clinical investigation designed to characterize the safety and effectiveness of the ADO II AS device in patients with a patent ductus arteriosus (PDA). The study will be conducted at up to 10 centers within the United States.

Subjects will be implanted with the ADO II AS device using a transcatheter femoral vessel approach under fluoroscopic and echocardiographic guidance. Clinical follow-up will be performed at 1 month, 6 months, 12 months, 24 months, and 36 months following the implant procedure. A pre-market approval (PMA) application will be submitted after 40 subjects have reached 6 months of follow-up post implant attempt. A minimum of 15 subjects will be enrolled with a weight ≤ 2 kg. In the event there is difficulty in enrolling 15 subjects with a weight of ≤ 2 kg, a PMA application will be submitted after 25 subjects with weight > 2 kg have reached 6 months of follow-up. An additional submission will be done when 15 subjects with a weight of ≤ 2 kg reach 6 months of follow-up. Follow-up after 6 months will be used to satisfy the post-approval requirements. Enrollment and follow-up occurring after the PMA is submitted will be used to satisfy post-approval requirements.

[redacted]

[redacted]

4.2 Clinical Investigation Design for CAP Subjects

[redacted]

4.3 Objective

The objective of this clinical investigation is to characterize the safety and effectiveness of the ADO II AS device to close the ductus arteriosus in subjects with a patent ductus arteriosus (PDA).

4.4 Endpoints

The safety and effectiveness endpoints of the clinical investigation are as follows:

4.4.1 Primary Endpoints (IDE and CAP)

Primary Safety Endpoint:
The primary safety endpoint is the rate of major complications through 180 days after an attempted ADO II AS device implant (refer to Appendix B for definitions).

[redacted]

Primary Effectiveness Endpoint:
The primary effectiveness endpoint is the rate of effective closure of the ductus arteriosus among patients with a successful ADO II AS implant as assessed by the presence of either a Grade 0 or Grade 1 shunt, as defined below, at the six-month follow-up by transthoracic echocardiography (TTE).

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. [redacted]
- 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)

4.4.2 Secondary Endpoint (IDE and CAP)

The secondary endpoint is the rate of significant obstruction of the pulmonary artery or aorta through the 6-month 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.

4.4.3 Descriptive Endpoints and Additional Data for Pivotal IDE Subjects

Descriptive endpoints will be reported using summary statistics.

- Implant success
- PDA shunt grade status at each follow-up visit
- Gradient measurements of the pulmonary artery and aorta at each follow-up visit
- Major and Minor Complications
- Death
- Additional data: demographics and baseline characteristics, procedure information, and left ventricular function and dimensions, pulmonic and tricuspid regurgitation, adverse events, withdrawal and protocol deviations will also be summarized at each follow-up visit.

4.4.4 Descriptive Endpoints and Additional Data for CAP Subjects

Descriptive endpoints will be reported using summary statistics.

- Implant success
- Major and Minor Complications
- Death
- Additional data:
  Demographics and baseline characteristics, procedure information, left ventricular function and dimensions and pulmonic and tricuspid regurgitation at 6 months, and adverse events, withdrawal and protocol deviations will also be summarized at each follow-up visit.

4.5 Study Population

The intended population for this clinical investigation is patients greater than 3 days of age with a PDA requiring closure.

4.5.1 Inclusion Criteria

To participate in this clinical investigation, the subject must meet all of the following inclusion criteria:

- Diagnosis of a PDA
- PDA ≤ 4mm in diameter
- PDA ≥ 3mm in length
- Subject (or legally authorized representative) is willing to comply with all pre-procedure, post-procedure, and follow-up testing requirements and provides consent to participate in the clinical study *

* This study is enrolling children and all local laws and governing IRB requirements will be followed for obtaining informed consent.

4.5.2 Exclusion Criteria

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

- Weight < 700 grams at time of the procedure
- Age < 3 days at time of procedure
- Coarctation of the aorta
- Left pulmonary artery stenosis
- Cardiac output that is dependent on right to left shunt through the PDA due to pulmonary hypertension
- Intracardiac thrombus
- Active infection requiring treatment at the time of implant
- Female subjects of child bearing potential are either pregnant or desire to become pregnant within six months post implant
- Other disease process likely to limit survival to less than six (6) months
- Participating in another study for an investigational drug and/or device that may clinically interfere with this study's endpoints

5 Procedures

Approval from the Sponsor must be received prior to initiating study procedures.

Enrolled subjects (as defined in section 5.2) will undergo a PDA closure procedure with the ADO II AS device. Post-procedure, the subject will have follow-up visits at 30 days, 6 months, 12 months, 24 months, and 36 months. Subjects who do not have a successful implant will be withdrawn upon completion of the 30-day follow-up visit. Upon completion of the 36-month follow-up visit, the subject will be considered to have completed the follow-up requirements of this clinical investigation. The Principal Investigator should arrange for appropriate care of subjects following study completion.

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

5.1 Informed Consent Process

The Principal Investigator or his/her authorized designee will conduct the Informed Consent Process, as required by applicable regulations and the center's IRB. This process will include a verbal discussion with the patient and/or patient's legally authorized representative on all aspects of the clinical investigation that are relevant to the patient's decision to participate, such as details of clinical investigation procedures, anticipated benefits, and potential risks of clinical investigation participation. During the discussion, the Principal Investigator or his/her authorized designee will avoid any improper influence on the patient's legally authorized representative and will respect patient's legal rights. The patient's legally authorized representative shall be provided with the informed consent form written in a language that is understandable to the subject's legally authorized representative and has been approved by the center's IRB. The patient's legally authorized representative shall have adequate time to review, ask questions and consider participation.

If the patient's legally authorized representative agrees to participate, the Informed Consent form must be signed and dated by the patient's legally authorized representative and by the person obtaining the consent. The signed original Informed Consent will be filed in the subject's hospital or research charts, and a copy will be provided to the subject.

The Principal Investigator or his/her authorized designee will document the informed consent process in the subject's hospital and/or research charts. The date of signature will be entered on an appropriate Case Report Form (CRF).

Failure to obtain informed consent from a subject prior to clinical investigation enrollment should be reported to Sponsor within 5 working days and to the reviewing center's IRB according to the IRB's/ EC's reporting requirements.

The Principal Investigator or his/her authorized designee will inform the subject of any important new information about the clinical investigation.

5.1.1 Special circumstances for informed consent

Patients under the age of 18 will be enrolled in this clinical investigation. Informed consent must be obtained using the IRB approved informed consent in accordance with IRB requirements.

If the patient is under the age of 18, the legally authorized representative will represent the patient during the informed consent process, which will be performed according to the requirements in section 5.1. The patient under the age of 18 will also be informed about the clinical investigation 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.

5.2 Point of Enrollment

A patient is considered enrolled in the clinical investigation from the moment the patient's legally authorized representative has provided a written Patient Informed Consent, has been confirmed to meet all inclusion criteria, meets none of the exclusion criteria, and the TorqVue™ LP Catheter (9-TVLPC4F90/080) is inserted into the vasculature of the subject. An intra-procedural echocardiogram or angiogram must be performed to confirm the sizing inclusion criteria of the PDA length (≥ 3 mm) and PDA diameter (≤ 4 mm) prior to inserting the delivery catheter into the vasculature.

The Principal Investigator or delegated study personnel will record enrollment information (name of the clinical investigation, date of consent and Inclusion/exclusion information) in the hospital records and complete and submit an Enrollment CRF in a timely manner.

Notification of enrollment to the Sponsor is considered to have occurred when the Procedure CRF has been received by the Sponsor.

5.3 Scheduled Procedures

The Principal Investigator is responsible for ensuring all clinical investigation data is collected as required per CIP scheduled procedures.

Trained Sponsor personnel may provide technical expertise and technical guidance on the use of the ADO II AS device, including training and proctored case coverage. Refer to section 5.6 for specifics.

5.3.1 Screening and Baseline for Pivotal IDE subjects

Potential subjects presenting at the investigational sites will be fully informed about the clinical investigation, following the established Informed Consent process described in section 5.1. Once a duly dated and signed Informed Consent Form is obtained, the study-specific screening procedures and assessments may begin.

The following assessments are performed as part of the screening process through medical record review or prospective tests and evaluations:

- Demographics- including subject's age and gender
- Physical examination-
  - include subject's weight, upper and lower extremity blood pressure measurements taken during visit, heart murmur evaluation, and assessment of femoral pulses.
- Medical History-
  - indicate subject's risk factors, relevant co-morbidities, neonatal ICU status, previous cardiac procedures
- Cardiovascular History (most recent information closest to baseline visit)
- Pregnancy test (required only for females of child bearing potential)
- Transthoracic echo (TTE) - within 14 days prior to the device implant procedure
  - PDA measurements, left ventricular function and dimensions (area and length), pulmonary and aortic flow and dimensions, and pulmonic and tricuspid valve regurgitation
- Electrocardiogram (ECG)
- Chest X-ray (CXR) – Anteroposterior view

Baseline assessments must be collected within 30-days prior to the procedure, unless noted differently above. Records of patients who are screened must be maintained.

In case the subject does not meet all inclusion criteria or meets any of the exclusion criteria, the subject is considered a screening failure. The Principal Investigator or the delegated study personnel will record the screening failure in the hospital records and on a screening log as required.

5.3.2 Screening and Baseline for CAP subjects

Potential subjects presenting at the investigational sites will be fully informed about the clinical investigation, following the established Informed Consent process described in section 5.1. Once a duly dated and signed Informed Consent Form is obtained, the study-specific screening procedures and assessments may begin.

The following assessments are performed as part of the screening process through medical record review or prospective tests and evaluations:

- Demographics- including subject's age and gender
- Physical examination-
  - include subject's weight, heart murmur evaluation, and assessment of femoral pulses.
- Medical History-
  - indicate subject's risk factors, relevant co-morbidities, neonatal ICU status, previous cardiac procedures
- Cardiovascular History (most recent information closest to baseline visit)
- Pregnancy test (required only for females of child bearing potential)
- Transthoracic echo (TTE) - within 14 days prior to the device implant procedure
  - PDA measurements, left ventricular function and dimensions (area and length), pulmonary and aortic flow and dimensions, and pulmonic and tricuspid valve regurgitation
- Electrocardiogram (ECG)
- Chest X-ray (CXR) – Anteroposterior view

Baseline assessments must be collected within 30-days prior to the procedure, unless noted differently above. Records of patients who are screened must be maintained.

In case the subject does not meet all inclusion criteria or meets any of the exclusion criteria, the subject is considered a screening failure. The Principal Investigator or the delegated study personnel will record the screening failure in the hospital records and on a screening log as required.

5.3.3 Implant/Procedure

The ADO II AS device is implanted either transvenously or transarterially 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 operator must complete an intra-procedural echocardiogram or angiogram to confirm the sizing inclusion criteria of the PDA length (≥ 3 mm) and PDA diameter (≤ 4 mm) prior to inserting the TorqVue™ LP Catheter into vasculature.

Proper sizing of the ADO II AS device is important in all subjects to reduce risk of complications. Refer to the Instructions for Use (IFU) [redacted] for important instructions regarding device sizing.

The recommended use of Heparin is considered optional, and not required if the subject is at high risk for bleeding complications.

Record the required information on the appropriate CRF.

- Transthoracic Echocardiogram (TTE) or angiogram – Intra-procedural
  - PDA measurements to confirm eligibility

[redacted]

- Procedural data (including access site, medications (heparin dose), hemodynamics (gradients derived from echocardiography), contrast usage (use of contrast is optional) & fluoroscopy, device deployment)
- Evaluation and data collection of any reportable adverse events

Subjects that are enrolled (i.e. have a TorqVue™ LP Catheter inserted), but do not have an ADO II AS study device implanted will be followed through the 30 day follow-up visit. Adverse events will be collected either in-person or via telephone as documented in section 8.2. Sponsor Representatives may be involved in providing support during the implant/procedure.

5.3.4 Post-Procedure

Perform the following assessments within 48 hours after the procedure and prior to discharge:

- Physical exam (PE) – including murmur evaluation
- Chest X-ray (CXR) – Anteroposterior view
- Electrocardiogram (ECG)
- Transthoracic echo (TTE)
- Evaluation and data collection of any reportable adverse events

At the post-procedure visit, the following additional procedures may be required (refer to Table 6 for criteria):

- Lung Perfusion scan
- Aortic Catheterization (or other confirmatory testing such as cardiac CT/MRI)

Table 4: Post-Procedure Visit Window

Visit	Window
Post-procedure	Within 48 hours after procedure and prior to discharge

Subjects should be on appropriate endocarditis prophylaxis according to the American Heart Association recommendations for prophylaxis (**Appendix E**).

5.3.5 Scheduled Follow-ups for Pivotal IDE Subjects

Follow-up visits are scheduled at 1 month, 6 months, 12 months, 24 months, and 36 months after the device implant/procedure. The scheduled visit windows are calculated from the enrollment date (procedure date).

Table 5: Follow-up Windows

Visit	Window
1 month	30 days +/- 7 days
6 months	180 days +/- 20 days
12 month	+/- 30 days
24 month	+/- 60 days
36 month	+/- 60 days

At each follow-up visit, the following procedures must be completed:

- Physical exam (PE) – including weight, murmur, femoral pulse, and upper/lower extremity blood pressure evaluation
- Transthoracic echo (TTE)
- Evaluation and data collection of any reportable adverse events

At each follow-up visit, the following additional procedures may be required (refer to Table 6 for criteria):

- Electrocardiogram (ECG)
- Lung Perfusion scan
- Aortic Catheterization (or other confirmatory testing such as cardiac CT/MRI)

Sponsor Representatives may be involved in providing support during the Follow-up procedures.

5.3.6 Scheduled Follow-ups for CAP Subjects

After implant, the subject will return to the clinic at 1 and 6 months. The following procedures must be completed:

- Physical exam (PE) – including weight, murmur, and femoral pulse
- Evaluation and data collection of any reportable adverse events
- TTE (TTE is not required at the 1 month visit for subjects weighing > 2kg at time of enrollment)

The following additional procedures may be required (refer to Table 7 for criteria):

- Lung Perfusion scan
- Aortic Catheterization (or other confirmatory testing such as cardiac CT/MRI)

If the ductus arteriosus is not effectively closed (Grade 0 or Grade1 shunt) at 6 months, as assessed by the Echo Core Lab, the site will be notified of the finding and the TTE must be repeated at the 12 month visit.

Subjects will have a 12 month follow-up and annually thereafter through the 36 month follow-up via telephone. Assessments completed at these follow-ups include:

- Adverse Event Assessment – sites should follow patients per their standard of care for any reported adverse events.

5.4 Study Flow Chart

The Study Flow Chart (Figure 1) and Table 6, Pivotal IDE subjects or Table 7, CAP subjects, below summarize subject flow and requirements of this clinical investigation.

Figure 2: Study Flow Chart

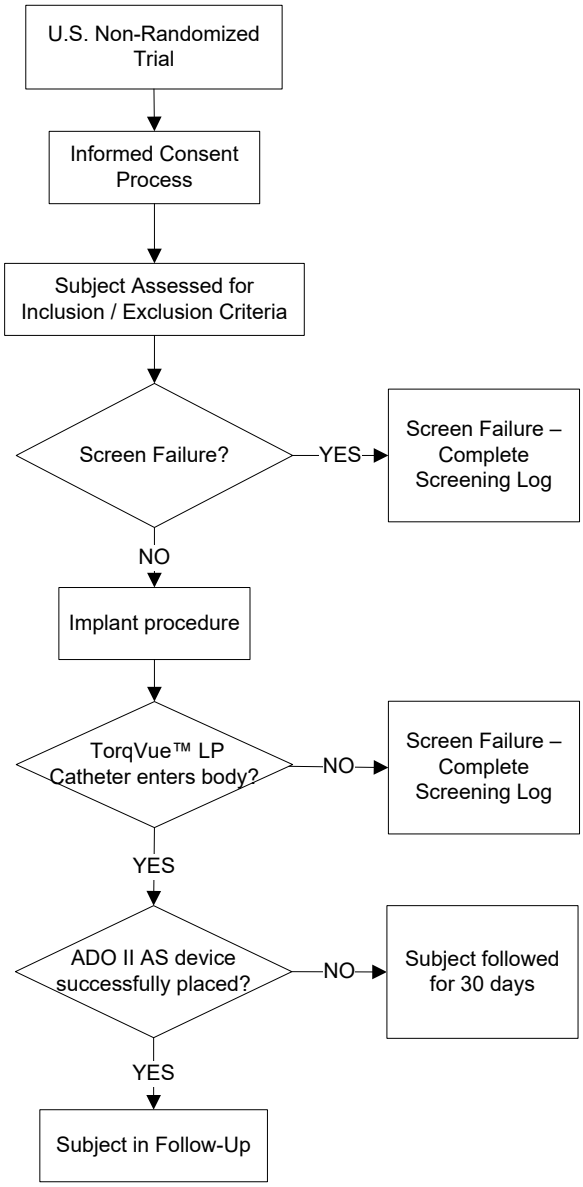

Table 6: Schedule of Assessments for Pivotal IDE Subjects

Visit Study Activity	Baseline	Procedure	Post-Procedure [5]	1 month (30 days +/- 7 days)	6 Month (180 days +/- 20 days)	12 Month (+/- 30 days)	24 Month (+/- 60 days)	36 Month (+/- 60 days)
Office Visit	X		X	X	X	X	X	X
Informed Consent Process	X							
Demographics	X							
Pregnancy Test[1]	X							
Medical History	X							
Physical Examination (murmur evaluation)	X		X	X	X	X	X	X
Chest X-Ray (AP)	X		X					
Electrocardiogram (ECG)	X		X	X				
Echocardiogram (TTE)	X	X[6]	X[4]	X[4]	X[4]	X	X	X
Angiogram		X[6]						
Lung Perfusion Scan [2]			(X)	(X)	(X)	(X)	(X)	(X)
Aortic catheterization; or other confirmatory testing [3]			(X)	(X)	(X)	(X)	(X)	(X)
Adverse Event		(X)	(X)	(X)	(X)	(X)	(X)	(X)

(X) if applicable

[1] Required only for females of child bearing potential and must be completed prior to the implant procedure.

[2] Perform a lung perfusion scan if peak instantaneous gradient in left pulmonary artery is ≥ 35mmHg by echocardiogram.

[3] Perform aortic catheterization to obtain invasive measurement of the gradient if the mean gradient by echocardiogram in the aortic isthmus is ≥ 20mmHg. 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. Rationale for not performing aortic catheterization shall be specified on the case report form. 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.

> **NOTE -** Alternatively, a clinical exam may be used to confirm aortic obstruction. Rationale for not performing a confirmatory imaging study (aortic catheterization, MR imaging, or CT imaging) shall be specified on the case report form.
>
> 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).

[4] If the Echo Core Lab identifies a new significant gradient in the pulmonary artery or the aorta as defined in (2) or (3) during the review of the follow-up echocardiograms through six months, a lung perfusion scan or

aortic catheterization will be required to determine if the result meets the secondary endpoint. If obstruction is detected and confirmed via a lung perfusion scan or aortic catheterization (or other confirmatory testing) only an echocardiogram will be required at subsequent follow-up visits.

[5] Post-procedure visit must be within 48 hours after the procedure and prior to discharge.

[6] Either an intra-procedure echocardiogram (TTE) or angiogram will be allowed to confirm the sizing inclusion criteria of the PDA length (≥ 3 mm) and PDA diameter (≤ 4 mm) prior to inserting the TorqVue™ LP Catheter into vasculature.

Table 7: Schedule of Assessments for CAP Subjects

Visit / Study Activity	Baseline	Procedure	Post-Procedure [5]	1 month (30 days +/- 7 [illegible])	6 Month (180 days +/- 20 [illegible])	12 Month (+/- 30 days)	24 Month (+/- 60 days)	36 Month (+/- 60 days)
Office Visit	X		X	X	X			
Telephone Visit						X[8]	X	X
Informed Consent Process	X							
Demographics	X							
Pregnancy Test[1]	X							
Medical History	X							
Physical Examination (murmur evaluation)	X		X	X	X			
Chest X-Ray (AP)	X		X					
Electrocardiogram (ECG)	X		X					
Echocardiogram (TTE)	X	X[6]	X[4]	X[4, 7]	X[4]	(X)[8]		
Angiogram		X[6]						
Lung Perfusion Scan [2]			(X)	(X)	(X)			
Aortic catheterization; or other confirmatory testing [3]			(X)	(X)	(X)			
Adverse Event		(X)	(X)	(X)	(X)	(X)	(X)	(X)

(X) if applicable

[1] Required only for females of child bearing potential and must be completed prior to the implant procedure.

[2] Perform a lung perfusion scan if peak instantaneous gradient in left pulmonary artery is ≥ 35mmHg by echocardiogram.

[3] Perform aortic catheterization to obtain invasive measurement of the gradient if the mean gradient by echocardiogram in the aortic isthmus is ≥ 20mmHg. 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. Rationale for not performing aortic catheterization shall be specified on the case report form. 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.

NOTE - Alternatively, a clinical exam may be used to confirm aortic obstruction. Rationale for not performing a confirmatory imaging study (aortic catheterization, MR imaging, or CT imaging) shall be specified on the case report form.

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).

[4] If the Echo Core Lab identifies a new significant gradient in the pulmonary artery or the aorta as defined in (2) or (3) during the review of the follow-up echocardiograms through six months, a lung perfusion scan or aortic catheterization will be required to determine if the result meets the secondary endpoint. If obstruction is detected and confirmed via a lung perfusion scan or aortic catheterization (or other confirmatory testing) only an echocardiogram will be required at subsequent follow-up visits.

[5] Post-procedure visit must be within 48 hours after the procedure and prior to discharge.

[6] Either an intra-procedure echocardiogram (TTE) or angiogram will be allowed to confirm the sizing inclusion criteria of the PDA length (≥ 3 mm) and PDA diameter (≤ 4 mm) prior to inserting the TorqVue™ LP Catheter into vasculature.

[7] If the subject weighed > 2kg at the time of enrollment, the 1 month TTE is not required.

[8] If the Echo Core lab determines that the ductus arteriosus is not effectively closed (Grade 0 or Grade1 shunt) at the 6 month visit, the TTE must be repeated at the 12 month visit.

5.5 Description of activities performed by Sponsor Representatives

Trained Sponsor personnel will provide technical expertise and technical guidance on the use of the ADO II AS device, including training and proctored case coverage.

While Sponsor representatives may perform these activities, the Principal Investigator remains responsible for ensuring all clinical investigation data is collected as required per CIP.

5.6 Subject Study Completion

Subject participation in the clinical investigation will conclude upon completion of the 36-month visit. Upon completion of subject participation in the clinical investigation, the subject will return to standard of care.

5.7 Subject Withdrawal

Subjects must be informed about their right to withdraw from the clinical investigation at any time and for any reason without sanction, penalty or loss of benefits to which the subject is otherwise entitled. Withdrawal from the clinical investigation will not jeopardize their future medical care or relationship with the investigator. Subjects will be requested to specify the reason for the request to withdraw. The investigator must make all reasonable efforts to retain the subject in the clinical investigation until completion of the clinical investigation.

If a subject misses one or more of the scheduled follow-up visits (i.e., does not have a scheduled follow-up within the assigned visit windows) without being lost to follow-up, the subject will be considered as having

missed the visit (which will be deemed to be a deviation from the CIP and the applicable form should be completed). If the subject has missed a visit, the subject shall return for subsequent follow-up visits.

A subject will be considered 'Lost to Follow-up' after two missed visits, a minimum of two unsuccessful phone calls from investigational site personnel to the subject or contact to schedule the next follow-up visit. These two phone calls must be documented in the subject's hospital records. If the subject is deemed lost to follow-up, a letter should 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 hospital records.

When subject withdrawal from the clinical investigation is due to an adverse event the subject will be followed outside of the clinical investigation until resolution of that adverse event or determination that the subject's condition is stable. The status of the subject's condition should be documented at the time of withdrawal.

In case of subject withdrawal, the site should make attempts to schedule the subject for a final study visit. At this final study visit, the subject will undergo the following assessments:

- Physical exam (PE)
- Evaluation and data collection of any reportable adverse events

5.8 Requirements for Clinical Laboratories

An independent Core Lab will be used to review and adjudicate the transthoracic echocardiography (TTE). Service details will be outlined in the applicable Service Agreement.

5.9 Study Committees

5.9.1 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 St. Jude Medical, 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.

5.9.2 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 8.2.

The CEC will also advise the Sponsor regarding the continuing safety of subjects and those yet to be recruited, as well as the continuing validity and scientific merit of the clinical investigation. CEC members will not be investigators in the clinical investigation. At any time during the investigation, 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.

6 Statistical Considerations

The following section describes the statistical methods for the clinical investigation and justification of the design. For the Primary and Secondary Endpoints, pivotal IDE subjects will be analyzed separately from CAP subjects.

6.1 Endpoints

6.1.1 Primary Safety Endpoint (IDE and CAP)

The primary safety endpoint is the rate of major complications through 180 days after an attempted ADO II AS device implant (refer to Appendix B for definition).

6.1.1.1 Analysis Methodology

The proportion of subjects experiencing a primary safety endpoint through 180 days will be estimated. The 95% confidence interval for the proportion of subjects experiencing a primary safety endpoint will be calculated using the exact binomial method. [redacted]

6.1.2 Primary Effectiveness Endpoint (IDE and CAP)

The primary effectiveness endpoint is the rate of effective closure of the ductus arteriosus among subjects with a successful ADO II AS implant as assessed by the presence of either a Grade 0 or Grade 1 shunt (see Section 4.4.1) at the six-month follow-up by transthoracic echocardiography.

6.1.2.1 Analysis Methodology

The proportions of subjects who have effective closure of the ductus arteriosus at the 6-month follow-up will be estimated. The 95% confidence interval for the rate of effective closure of the ductus arteriosus will be calculated using the exact binomial method. [redacted]

[redacted]

6.1.3 Secondary Endpoint (IDE and CAP)

The secondary endpoint is the rate of significant obstruction of the pulmonary artery or aorta through the 6-month 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.

6.1.3.1 Analysis Methodology

The proportions of subjects experiencing a secondary endpoint through the 6-month follow-up visit will be estimated. The 95% confidence interval for the proportion of subjects experiencing a secondary endpoint will be calculated using the exact binomial method. [redacted]

[redacted]

6.1.4 Descriptive Endpoints and Additional Data for Pivotal IDE Subjects

The following endpoints will be summarized using descriptive statistics.

- Implant success:
  The frequency and percentage of implant success (defined in Section 6.1.3.2) will be reported. This analysis will include enrolled subjects.
- PDA shunt status at each follow-up visit:
  The frequency and percentage of PDA shunt status at each follow-up visit, as assessed by the Echo Core Lab, 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.
- Obstruction measurements at each 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 6.1.3) at each follow-up visit will be reported. Both analyses will include subjects who achieve a successful implant.
- Major and Minor Complications:
  The frequency and percentage of major and minor complications (refer to Appendix B for definition) from the time of the implant procedure will be reported.
- Death:
  The frequency and percentage of death will be reported.

- Additional data:
  Demographics and baseline characteristics, procedure information, left ventricular function and dimensions, pulmonic and tricuspid regurgitation, adverse events, withdrawal and protocol deviations will also be summarized.

6.1.5 Descriptive Endpoints and Additional Data for CAP Subjects

The following endpoints will be summarized using descriptive statistics.

- Implant success:
  The frequency and percentage of implant success (defined in Section 6.1.3.2) will be reported. This analysis will include enrolled subjects.
- Major and Minor Complications:
  The frequency and percentage of major and minor complications (refer to Appendix B for definition) from the time of the implant procedure will be reported.
- Death:
  The frequency and percentage of death will be reported.
- Additional data:

Demographics and baseline characteristics, procedure information, left ventricular function and dimensions and pulmonic and tricuspid regurgitation at 6 months, and adverse events, withdrawal and protocol deviations will also be summarized at each follow-up visit.

[redacted]

[redacted]

6.7 Deviations from Statistical Plan

If any deviations from the original statistical plan occur, such deviations will be documented in the clinical study report or statistical report containing the analysis results.

7 Risks and Benefits

Risks associated with the device 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.

7.1 Risks associated with the Device under Investigation

7.1.1 Anticipated Adverse Device Effects

The risks associated with the implant procedure are similar to those of other cardiac catheterization procedures in infants and children and are documented below. Radiation risks associated with the procedure are comparable to a diagnostic catheterization procedure.

- Air embolism
- Allergic reaction
- Arrhythmia
- Arteriovenous fistulae
- Bleeding at the access site
- Brachial plexus injury
- Bruising
- Cardiac tamponade
- Death
- Deep venous thrombosis
- Dissection
- Embolism
- Endocarditis
- Hematoma
- Hemodynamic compromise
- Infection
- Myocardial infarction
- Perforation
- Peripheral pulse loss
- Pseudoaneurysm
- Respiratory distress
- Stroke/transient ischemic attack
- Thrombosis
- Valve damage
- Vascular access site injury
- Vascular occlusion
- Vessel damage

[redacted]

The following is a list of the anticipated adverse device effects associated with the ADO II AS device under investigation:

- Air embolism
- Allergic dye reaction
- Allergic drug reaction
- Anesthesia reactions
- Apnea
- Arrhythmia
- Bacterial endocarditis
- Bleeding
- Cardiac perforation
- Cardiac tamponade
- Chest pain
- Device embolization
- Device erosion
- Death
- Fever
- Hemolysis
- Headache/migraine
- Hypertension
- Hypotension
- Myocardial infarction
- Nickel sensitization
- Nickel toxicity
- Palpitations
- Partial obstruction of the Aorta
- Partial obstruction of the Pulmonary Artery
- Pericardial effusion
- Pericarditis
- Peripheral embolism
- Pleural effusion
- Pulmonary embolism
- Reintervention for device removal
- Stroke
- Transient ischemic attack
- Thrombus
- Valvular regurgitation
- Vascular access site injury
- Vessel perforation
- Carcinogenicity

Potential carcinogenicity risk. The ADO II AS device consists of a nickel-titanium alloy. In vitro testing has demonstrated that that nickel is released from this device for a minimum of 60 days. Some forms of nickel have also been associated with carcinogenicity (ability to cause cancer) in animal models. In humans, carcinogenicity has been demonstrated only through an inhalation route (breathing nickel in), which will not occur with this procedure.

7.1.1 Risks associated with Clinical Investigation Assessments

The risks associated with the ADO II AS device implant procedure are similar to those of other cardiac catheterization procedures. Radiation risks associated with the procedure are comparable to a diagnostic catheterization procedure.

The risks associated with the ADO II AS device are similar to other implantable cardiac occlusion devices.

Additional study required procedures are listed below with the associated risks/discomforts.

Blood Draw
There may be some minor discomfort and/or anxiety associated with drawing blood including pain or bruising associated with the needle from the blood draw. Fainting and local infection can also occur.

Aortic Catheterization
Aortic catheterizations have a risk for injury to the vessel, allergic reaction to dye, anesthesia reaction irregular heartbeat, infection, poisonous products in the bloodstream, loss of blood flow to the extremities from the catheter placement, damage or injury to the heart, lungs, valves or vessels from the catheter or wire advancement, air or blood clot formation in a vessel or heart which may cause temporary or complete blockage of blood flow to the heart, brain, or extremities, irregular blood pressure, fever, injury to the nerves that control the arm or shoulder, kidney dysfunction due to exposure to contrast media (liquid used for imaging) and death.

Lung Perfusion Scan
Lung perfusion scans expose the patient to a small dose of radiation (about as much radiation as natural exposure over a year). There is always a slight risk from being exposed to radiation.

Computed Tomography (CT) Aortic Angiography
There may be risks due to the radiation used during the CT imaging. There is also a risk for an allergic response to the contrast media/dye used during the CT imaging procedure.

Magnetic Resonance (MR) Aortic Angiography
MR imaging use magnetic and radio waves to generate images of the vasculature. The risk from these waves is no greater than experienced in daily life. There is also a risk for an allergic response to the contrast media/dye used during the MRI procedure.

Echocardiogram
The electrodes placed on subject's chest may cause discomfort such as redness or itching. The subject may feel slight pressure from the transducer or probe that the technician utilizes to take measurements.

Chest X-ray
The risks of chest x-rays include exposure to small doses of radiation (about as much radiation as natural exposure over 10 days). There is always a slight risk from being exposed to any radiation.

Electrocardiogram
The electrodes placed on subject's chest can sometimes cause discomfort such as redness or itching.

7.2 Possible interactions with concomitant treatments

The risks from intra-procedural medications administration upon undergoing ADO II AS implant are no different from the risks associated with medications prescribed during a cardiac catheterization procedure or implant of commercially available transcatheter PDA occluder device.

7.3 Risk Control Measures

Every possible effort will be taken to minimize the risks, including:

- Careful selection of experienced Investigators for the clinical investigation
  - Cardiologists with training and education in pediatric cardiology and experience using transcatheter techniques to close PDAs
  - Prior experience with transcatheter closure procedures using devices such as ADO, ADO II or other similar devices with a minimum of 60 cases
  - Institutions will have the necessary infrastructure to support trial procedures:
    - Cardiac catheterization lab or NICU bedside capability to perform intra-procedural echocardiography and fluoroscopy
    - Anesthesiology support, as needed
    - Catheterization laboratory, operating room, post anesthesia recovery, intensive care and step down unit spaces to accommodate cases with and without complications
    - On-site emergency cardiac surgery services
- Adequate monitoring for each clinical investigation site
- Conducting the clinical investigation in accordance with the CIP, 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
- Preparation of the ADO II AS device and implant procedure in accordance with the device IFUs
- Training of Investigators both on the CIP and ADO II AS implant procedure
  - All site staff will participate and complete a training module on the CIP
  - All implanting physicians must complete an implanter training module
  - Implanting physicians with no prior successful transcatheter PDA closure experience with ADO II AS in small infants (≤2 kg) will receive proctoring for a minimum on one case.
- Assessment of continuing safety of subjects in the clinical investigation by an independent CEC

The following measures have also been taken to reduce the risks of specific study device related adverse events:

- Subject eligibility criteria include maximum diameter and minimum lengths of the PDA to be treated with the ADO II AS which should reduce the likelihood of partial obstruction of the pulmonary artery or aorta.
- Whenever possible, subjects will be given a loading dose of Heparin at the beginning of the procedure to reduce the risk of thrombus formation on the devices. The use of heparin in patients with a risk of bleeding is considered optional.
- The physicians will be trained on the procedure, 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 ADO II AS.
- 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 less than 6kg at baseline

- The physicians will be encouraged to utilize an anterograde implant approach, while avoiding the need for arterial access. Additionally, the protocol will not require the acquisition of invasive hemodynamic measurements to minimize complication and shorten procedure time. Device implant is recommended to be performed based on echocardiographic and fluoroscopic guidance without needing to utilize intravenous contrast agents and angiograms.
- Physicians are required to follow The American Heart Association Recommendations for endocarditis prophylaxis during the clinical study.

7.4 Anticipated Benefits

The ADO II AS will be implanted via transcatheter approach, therefore avoiding open heart surgery. The device has been designed to be delivered through a 4F catheter delivery system which may decrease the risk of vascular access site injuries and temporary loss of peripheral pulse compared to a 5F or larger catheter delivery system. The device has also been designed to conform to different defect lengths allowing this device to be placed in short PDAs.

7.5 Risk-to-Benefit Rationale

Risks associated with participating in this clinical study are not anticipated to be any different from risks associated with undergoing implant with commercially available transcatheter devices such as ADO II or coils. The potential benefit of participating in this clinical study is close follow-up of the subject by their treating physicians. Potential benefits of the ADO II AS device compared to currently available options are minimally invasive PDA closure with a smaller device suitable for a smaller sized PDA, and a lower rate of complications. Future neonatal patients with PDA may benefit from the results of this clinical trial.

7.6 History of device modifications or recall

There have been no recalls or field actions during the global marketing and sale of the ADO II AS device.

8 Requirements for Investigator records and reports

8.1 Deviations from CIP

A deviation is defined as an instance(s) of failure to follow, intentionally or unintentionally, the requirements of the CIP. The investigator should not deviate from the CIP.

In some cases, failure to comply with the CIP 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 perform safety assessments intended to detect adverse events. Investigators should seek to minimize such risks by adhering to the CIP.

The PI must maintain accurate, complete, and current records, including documents showing the date of and reason for each deviation from the CIP. Relevant information for each deviation will be documented as soon as possible on the applicable CRF. The site will submit the CRF to the Sponsor.

The PI is required to adhere to local regulatory requirements for reporting deviations to IRB.

An investigator shall notify the Sponsor 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 than 5 working days after the emergency occurred. Except in such an

emergency, prior approval by the Sponsor is required for changes in or deviations from a plan, and if these changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of human subjects, FDA and IRB is also required.

8.2 Adverse Event Reporting

Safety surveillance within this trial (and the safety reporting performed by the investigator), starts as soon as the subject is enrolled. The safety surveillance and the safety reporting will continue until the last investigational visit has been performed, the subject is deceased, the subject/investigator concludes his/her participation into the clinical investigation or the subject withdrawal from the clinical investigation.

All adverse event data required to be reported will be collected throughout the clinical investigation and will be reported to the Sponsor on a CRF.

Adverse events will be monitored until they are adequately resolved or the subject has ended his/her participation in the trial, whichever comes first. The status of the subject's condition should be documented at each visit.

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

- Unanticipated adverse device effects
- All adverse events viewed/interpreted by investigator to be potentially related to either a) the implant procedure or b) the study device (ADO II AS) 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 a non-study device is used to close the PDA, adverse events associated with the non-study device will not be reported.

Records relating to the subject's subsequent medical course must be maintained and submitted (as applicable) to the Sponsor 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 each visit.

<u>SAE Reporting</u>

Reportable adverse events that are deemed by the investigator to be serious should be reported to the Sponsor as soon as possible but no later than outlined below.

Clinical Site	Reporting timelines
All Sites	SAEs must be reported to the Sponsor no later than 3 calendar days from the day the site personnel became aware of the event or as per the investigative site's local requirements, if the requirement is more stringent than those outlined above.

The date the site staff became aware the event met the criteria of an SAE must be recorded in the source document. The Investigator will further report the SAE to the local IRB/EC according to the institution's IRB/EC reporting requirements.

8.2.1 Subject Death

Subject deaths will be documented and reported to the Sponsor as soon as possible (but no later than 3 calendar days) after becoming aware of the event via the applicable CRF.

8.2.2 Unanticipated Adverse Device Effect

If an unanticipated adverse device effect occurs, the investigator must notify the Sponsor and the IRB immediately, but no later than 3 calendar days of the investigator's knowledge of the event, as required by 21 CFR §812.150. St. Jude Medical 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.

8.2.3 Complaints

During the study, the investigator will be responsible for reporting all complaints. If the complaint does not involve an AE, the investigator must notify the St. Jude Medical (SJM) Postmarket Surveillance Department by emailing the information on the device to complaints_amplatzer@sjm.com or calling 651-756-5400 as soon as possible after becoming aware of the complaint.

If the complaint involves an AE, the investigator must complete an AE Case Report Form (CRF) including the information on the complaint and report to St Jude Medical as soon as possible.

Should a subject death be caused by the SJM device or the device contributed to the death, the investigator should complete a Form 3500A (MedWatch) and submit to SJM and the FDA within 10 days after becoming aware of the event.

8.3 Source records

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

8.4 Records retention

The Sponsor and the Principal Investigators will maintain the clinical investigation documents as required. Measures will be taken to prevent accidental or premature destruction of these documents. The Principal Investigator or the Sponsor may transfer custody of records to another person/party and document the transfer at the investigational site or the Sponsor's facility, as appropriate.

These documents must be retained by the investigational site for a period of 2 years after the conclusion of the clinical investigation and made available for monitoring or auditing by the Sponsor's representative 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 Sponsor.

9 Clinical Data Handling

The Sponsor will be responsible for the data handling. The Sponsor and/or its affiliates will be responsible for compiling and submitting all required reports to governmental agencies. Data will be analyzed by the Sponsor

and may be transferred to the Sponsor's locations worldwide and/or any other worldwide regulatory authority in support of a market-approval application.

9.1 Protection of Personally Identifiable Information

St. Jude Medical respects and protects personally identifiable information collected or maintained for this clinical investigation. 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 Sponsor.

Only authorized site personnel will be permitted to enter the CRF data through the EDC system deployed by St. Jude Medical. 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 Sponsor 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 Sponsor to ensure the clinical investigation is conducted, recorded and reported according to the approved CIP, subsequent amendment(s), applicable regulations and guidance documents.

Monitoring will be conducted according to St. Jude Medical's Clinical Monitoring work instruction.
Prior to beginning the clinical investigation, the Sponsor will contact the investigator or designee to discuss the clinical investigation and data requirements. A designated monitor will periodically review the subject records and associated source documents. The investigator shall make subject and clinical investigation records available to the clinical monitor for monitoring.

11 Compliance Statement

11.1 Statement of Compliance

In addition to applicable regional or local laws and regulations, this clinical investigation 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.

The investigator will sign a Clinical Trial Agreement and agrees to be compliant with it. The investigator will not start enrolling subjects or requesting informed consent from any subject prior to obtaining IRB approval and relevant Regulatory Authority approval, if applicable, and authorization from the Sponsor in writing for the clinical investigation. 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 investigation, that information will be forwarded to the Sponsor.

11.2 Quality Assurance audits and Regulatory Inspections

The investigator and/or delegate should contact the Sponsor 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 Sponsor 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 investigation.

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 Sponsor, a monitor or designee will attempt to secure compliance by one or more of the following actions:

- Visiting the investigator,
- Contacting the investigator by telephone,
- Contacting the investigator in writing,
- Retraining of the investigator.

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

12 Suspension or premature termination of the clinical investigation

The Sponsor 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 investigation at the investigational sites for which they are responsible. The investigators will follow the requirements specified in the Clinical Trial Agreement.

If suspicion of an unacceptable risk to subjects arises during the clinical investigation or when so instructed by the IRB or regulatory authority, the Sponsor may suspend the clinical investigation while the risk is assessed. The Sponsor will terminate the clinical investigation if an unacceptable risk is confirmed. If the Sponsor completes an analysis of the reasons for the suspension, implements the necessary corrective

actions, and decides to lift the temporary suspension, the Sponsor 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 investigation resumes. If subjects have been informed of the suspension, the Principal Investigator or authorized designee will inform them of the reasons for resumption.

If the Sponsor suspends or prematurely terminates the clinical investigation at an individual investigational site in the interest of safety, the Sponsor will inform all other Principal Investigators.

If suspension or premature termination occurs, the Sponsor will remain responsible for providing resources to fulfill the obligations from the CIP and existing agreements for following up the subjects enrolled in the clinical investigation, and the Principal Investigator or authorized designee will promptly inform the enrolled subjects at his/her investigational site, if appropriate.

13 Clinical Investigation Conclusion

The clinical investigation will be concluded when:

- All sites are closed AND
- The final report has been provided to investigators or the Sponsor has provided formal documentation of clinical investigation closure.

14 Publication Policy

Publications or presentations of clinical investigation methods or results will adhere to St. Jude Medical'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 5.10.1), and investigators will be notified via email about the dissemination of study data and opportunities for involvement as authors on publications/presentations.

15 Reporting Results on ClincalTrials.gov Website

Upon receiving IDE approval from the FDA, this clinical investigation will be registered on ClinicalTrials.gov. A full report of the pre-specified outcomes, regardless of the results, will be made public through the ClinicalTrials.gov website no later than 12 months after clinical investigation completion, as required by section 801 of the FDA Amendments Act. If this clinical investigation is terminated early, the Sponsor will make every effort to hasten the release of the pre-specified outcomes through the ClinicalTrials.gov website.

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Appendix B: Definitions

Non-study Specific Definitions

Adverse Event (AE)
Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device under clinical investigation.

This definition includes events related to the investigational medical device (ADO II AS) as well as events related to the procedures involved in the clinical protocol.

Serious Adverse Event (SAE)
An adverse event that led to:

- Death
- A serious deterioration in the health of the subject, that either resulted in:
  - A life-threatening illness or injury OR
  - A permanent impairment to a body structure or a body function OR
  - An in-patient or prolonged hospitalization OR
  - A medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function OR
  - A malignant tumor
- Fetal distress, fetal death or a congenital abnormality or birth defect
- A planned hospitalization for a pre-existing condition, or a procedure required by the CIP is not considered a serious adverse event.

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 instructions for use, deployment, 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 effects (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 CIP or application (including a 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 the study device (ADO II AS) or procedure if the event satisfies all of following criteria:

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

Attempted ADO II AS Device Implant
Insertion of the TorqVue™ LP Catheter (9-TVLPC4F90/080) into the vasculature of the subject.

Major Complication
Major complications are defined as device (ADO II AS) or procedure-related adverse events resulting in any of the following:

- death,
- life-threatening adverse event,
- persistent or significant disability/incapacity, and/or
- a major open surgical intervention which is performed by a surgeon under general anesthesia

Examples of Major Complications:

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

Minor Complication

Minor complications are defined as device (ADO II AS) 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:

Examples of Minor Complications:

- 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 cutdown procedure.
- Reduced peripheral pulse (reversible) that can be managed with anti-thrombotic therapy (e.g., heparin, Aspirin)
- Cardiac perforation not requiring percutaneous (e.g., pericardiocentesis) or open surgical intervention
- Transient cardiac arrhythmia that is managed successfully with cardioversion or medication
- Hematoma of the groin not requiring open surgical intervention

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Appendix D: Bibliography

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Appendix E: American Heart Association Recommendations for Prophylaxis

PREVENTION OF BACTERIAL ENDOCARDITIS
Wallet Card

This wallet card is to be given to patients (or parents) by their physician. Healthcare professionals: Please see back of card for reference to the complete statement.

Name: _____

needs protection from **BACTERIAL ENDOCARDITIS** because of an existing heart condition.

Diagnosis: _____
Prescribed by: _____
Date: _____

You received this wallet card because you are at increased risk for developing adverse outcomes from infective endocarditis, also known as bacterial endocarditis (BE). The guidelines for prevention of BE shown in this card are substantially different from previously published guidelines. This card replaces the previous card that was based on guidelines published in 1997.

The American Heart Association's Endocarditis Committee together with national and international experts on BE extensively reviewed published studies in order to determine whether dental, gastrointestinal (GI), or genitourinary (GU) tract procedures are possible causes of BE. These experts determined that there is no conclusive evidence that links dental, GI, or GU tract procedures with the development of BE.

The current practice of giving patients antibiotics prior to a dental procedure is no longer recommended **EXCEPT** for patients with the highest risk of adverse outcomes resulting from BE (see below on this card). The Committee cannot exclude the possibility that an exceedingly small number of cases, if any, of BE may be prevented by antibiotic prophylaxis prior to a dental procedure. If such benefit from prophylaxis exists, it should be reserved **ONLY** for those patients listed below. The Committee recognizes the importance of good oral and dental health and regular visits to the dentist for patients at risk of BE.

The Committee no longer recommends administering antibiotics solely to prevent BE in patients who undergo a GI or GU tract procedure.

Changes in these guidelines do not change the fact that your cardiac condition puts you at increased risk for developing endocarditis. If you develop signs or symptoms of endocarditis – such as unexplained fever – see your doctor right away. If blood cultures are necessary (to determine if endocarditis is present), it is important for your doctor to obtain these cultures and other relevant tests **BEFORE** antibiotics are started.

Antibiotic prophylaxis with dental procedures is recommended only for patients with cardiac conditions associated with the highest risk of adverse outcomes from endocarditis, including:

- Prosthetic cardiac valve
- Previous endocarditis
- Congenital heart disease only in the following categories:
  - –Unrepaired cyanotic congenital heart disease, including those with palliative shunts and conduits
  - –Completely repaired congenital heart disease with prosthetic material or device, whether placed by surgery or catheter intervention, during the first six months after the procedure*
  - –Repaired congenital heart disease with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibit endothelialization)
- Cardiac transplantation recipients with cardiac valvular disease

*Prophylaxis is recommended because endothelialization of prosthetic material occurs within six months after the procedure.

Dental procedures for which prophylaxis is recommended in patients with cardiac conditions listed above.

All dental procedures that involve manipulation of gingival tissue or the periapical region of teeth, or perforation of the oral mucosa*

***Antibiotic prophylaxis is NOT recommended for the following dental procedures or events:** routine anesthetic injections through noninfected tissue; taking dental radiographs; placement of removable prosthodontic or orthodontic appliances; adjustment of orthodontic appliances; placement of orthodontic brackets; and shedding of deciduous teeth and bleeding from trauma to the lips or oral mucosa.

Antibiotic Prophylactic Regimens Recommended for Dental Procedures

Situation	Agent	Regimen – Single Dose 30-60 minutes before procedure	
		Adults	Children
Oral	Amoxicillin	2 g	50 mg/kg
Unable to take oral medication	Ampicillin **OR**	2 g IM or IV*	50 mg/kg IM or IV
	Cefazolin or ceftriaxone	1 g IM or IV	50 mg/kg IM or IV
Allergic to penicillins or ampicillin – Oral regimen	Cephalexin**†	2 g	50 mg/kg
	OR		
	Clindamycin	600 mg	20 mg/kg
	OR		
	Azithromycin or clarithromycin	500 mg	15 mg/kg
Allergic to penicillins or ampicillin and unable to take oral medication	Cefazolin or ceftriaxone†	1 g IM or IV	50 mg/kg IM or IV
	OR Clindamycin	600 mg IM or IV	20 mg/kg IM or IV

*IM – intramuscular; IV – intravenous
**Or other first or second generation oral cephalosporin in equivalent adult or pediatric dosage.
†Cephalosporins should not be used in an individual with a history of anaphylaxis, angioedema or urticaria with penicillins or ampicillin.

Gastrointestinal/Genitourinary Procedures: Antibiotic prophylaxis solely to prevent BE is no longer recommended for patients who undergo a GI or GU tract procedure, including patients with the highest risk of adverse outcomes due to BE.

Other Procedures: BE prophylaxis for procedures of the respiratory tract or infected skin, tissues just under the skin, or musculoskeletal tissue is recommended **ONLY** for patients with the underlying cardiac conditions shown above.

Adapted from *Prevention of Infective Endocarditis: Guidelines From the American Heart Association,* by the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease. *Circulation,* e-published April 19, 2007. Accessible at www.americanheart.org/presenter.jhtml?identifier=3004539.

Healthcare Professionals – Please refer to these recommendations for more complete information as to which patients and which procedures need prophylaxis.

ADA ACCEPTED American Dental Association

The Council on Scientific Affairs of the American Dental Association has approved this statement as it relates to dentistry.

American Heart Association. | American Stroke Association.
Learn and Live.

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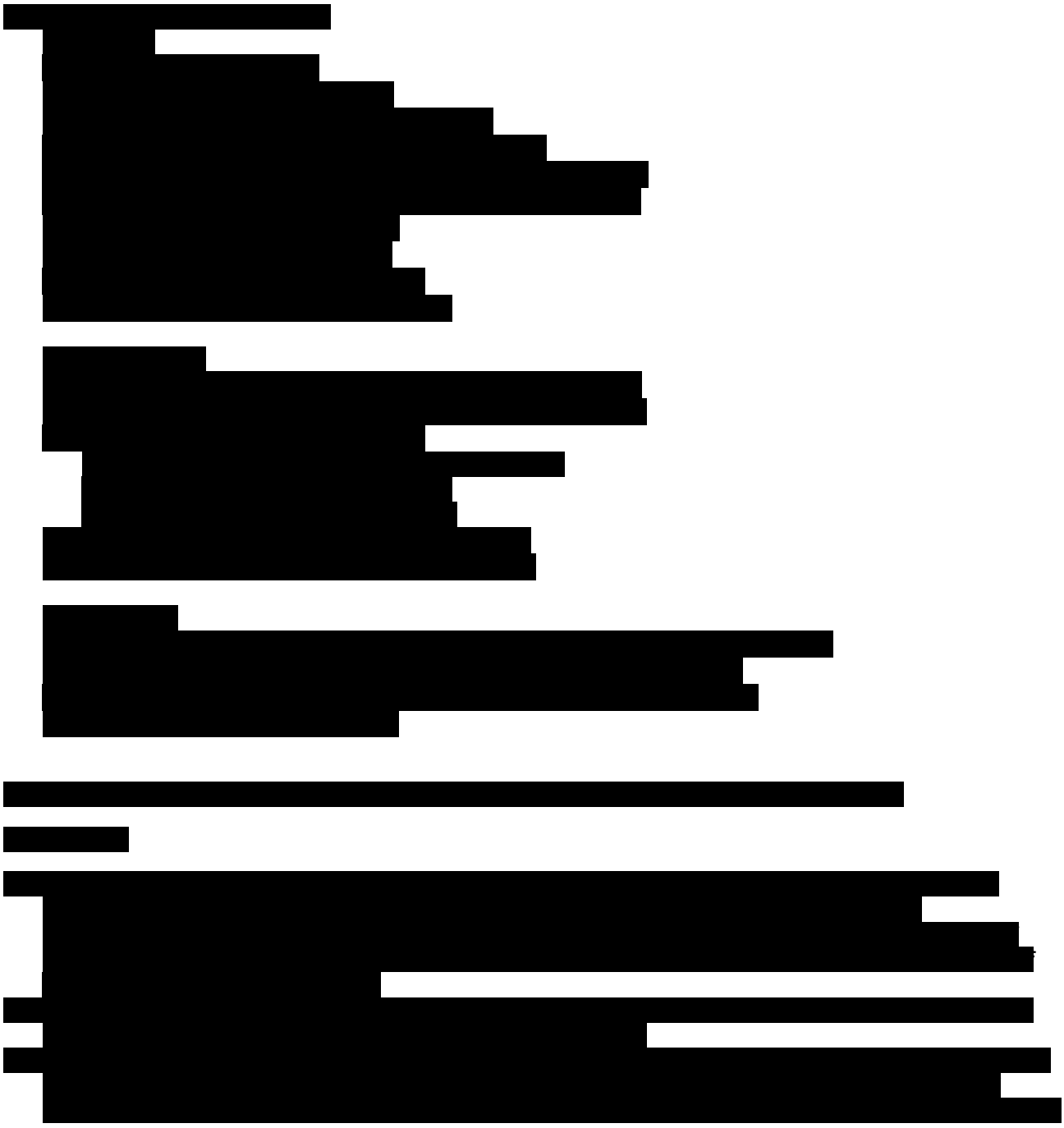

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